INCORPORATING TUMOUR MARKERS WITHIN A PHARMACEUTICAL CARE PLAN

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To my family

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Abstract

The availability of tumour markers in managing oncology patients contributes to developing personalised pharmacotherapy. The aim of this research was to develop a personalised pharmaceutical approach through the design and implementation of a pharmaceutical care plan (PCP) incorporating tumour markers for patients suffering from ovarian, pancreatic or prostate cancer. Guidelines, recommendations and standards of care for the management of ovarian, pancreatic and prostate cancer were reviewed. The classification systems for drug therapy problems developed and validated by Cipolle et al. (2004)[1] and the Pharmaceutical Care Network Europe version 6.2[2] were considered. These classifications were used in the development of a newly designed PCP template, which presented specific pharmaceutical oncology care requirements and trending of tumour marker results. The developed PCP, which was implemented at Sir Anthony Mamo Oncology Centre consists of two sections. The first section records patient's details, carer's details, diagnosis, past medical history, previous cancer treatments, current medications including non-oncologic therapy, chemotherapy cycles prescribed, relevant laboratory investigations and tumour marker results. The second section of the PCP categorises individualised pharmaceutical care issues (PCIs) identified. The pharmacist's actions are documented in this section. A total of 67 patients (35 male, 32 female) were enrolled in this study. The mean age was 65 ± 10.4 years. The range was 26 to 83 years. Forty-five patients had a family history of cancer while 22 did not. Patients suffering from ovarian, pancreatic and prostate cancer were 19, 27 and 21 respectively. A total of 238 PCIs were identified, ranging from 2 to 5 PCIs per patient. The most common PCIs identified were classified as counselling needs (65), adverse drug reactions (65) and additional medication needs (47). There was statistical correlation ($p < 0.05$) between age and cancer type and between pre- and post-treatment tumour marker results. The developed

individualised PCP was developed as a helpful tool for the clinical pharmacist who can update patient pharmaceutical care records according to the PCIs identified whilst at the same time taking into consideration relevant tumour marker trends as well as other laboratory investigations.

Keywords: clinical oncology pharmacists, oncology medications, pharmaceutical care issues, pharmaceutical care plan, solid tumours, tumour markers

1. Cipolle RJ, Strand LM, Morely PC. Pharmaceutical Care Practice. USA: McGraw Hill Co; 2004.
2. Pharmaceutical Care Network Europe (PCNE) Foundation: PCNE Classification for drug related problems. V6.2. 2010. Available from: http://www.pcne.org/upload/files/11_PCNE_classification_V6-2.pdf

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List of Abbreviations

5-HT_3 RAs	5-hydroxytryptamine receptor antagonists
A&E	Accident & emergency department
AA	Abiraterone acetate
ACB	The Association for Clinical Biochemistry and Laboratory Medicine
ACBI	The Association of Clinical Biochemists in Ireland
ADR	Adverse drug reaction
AFP	α-fetoprotein
AlkP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASCO	The American Society of Clinical Oncology
AVR	Automated voice response
β-HCG	Beta-human chorionic gonadotrophin
BSA	Body surface area
CA 125	Cancer antigen 125
CA 19-9	Cancer antigen 19-9
CEA	Carcinoembryonic antigen
CHF	Congestive heart failure
CINV	Chemotherapy-induced nausea and vomiting
CML	Chronic myeloid leukaemia
COPD	Chronic obstructive pulmonary disease
CPGT	Clinical pharmacist-led guidance team
CPOE	Computerized physician/provider order entry

CPP	Clinical pharmacist practitioner
CPS	Clinical pharmacy service
CRC	Colorectal cancer
CT	Chemotherapy
CTX	Cyclophosphamide
DC	Dosing calculations
DD	Drug duplication
DDI	Drug-drug Interaction
DH	Drug history
DM	Dexamethasone
DO	Drug order
DRP	Drug-related problem
DVT	Deep vein thrombosis
ED	Emergency department
EGTM	The European Group on Tumour Markers
EMR	Electronic medical record
ENZ	Enzalutamide
ESMO	European Society for Medical Oncology® Oncology Clinical Practice Guidelines®
FIGO	International Federation of Gynaecology and Obstetrics
FMEA	Failure modes and effects analysis
GCIG	The Gynecological Cancer Intergroup
GGT	Gamma glutamyl transferase
GORD	Gastro-oesophageal reflux disease

Hb	Haemoglobin
HCP	Health care professional
HCT	Health care team
HFS	Hand-foot syndrome
IHD	Ischaemic heart disease
ITS	The Institute of Tourism Studies
LDH	Lactate dehydrogenase
MAR	Medication administration record
MCAST	Malta College of Arts, Science and Technology
MCC	Mediterranean conference centre
MCCF	Malta Community Chest Fund
MCMM	Multi professional cancer medication management
MDT	Multidisciplinary team
MEs	Medication errors
MEMS	Microelectonic monitoring system
MPR	Medication possession ratio
MR	Medication reconciliation
MSAS	Memorial symptom assessment scale
NACB	The National Academy of Clinical Biochemistry
NCCN	The National Comprehensive Cancer Network®
Neut	Neutrophils
NICE	The National Institute for Health and Care Excellence
NSAIDs	Non-steroidal anti-inflammatory drugs

OC	Ovarian cancer
ORS	Oral rehydration salt/solution
OTC	Over the counter
PBCN	Pan Birmingham Cancer Network
PCI	Pharmaceutical care issue
PCP	Pharmaceutical care plan
PCs	Pill counts
PI	Pharmaceutical intervention
PLT	Platelets
PMC	Pharmacist-managed clinic
POYC	Pharmacy of Your Choice
PPE	Palmar-plantar erythrodysesthesia
PRDL	Prednisolone
PSA	Prostate specific antigen
QOL	Quality of life
SAMOC	Sir Anthony Mamo Oncology Centre
SCP	Seamless care pharmacist
SIGN	Scottish Intercollegiate Guidelines
SMA	Shared medical appointments
SPC	Summary of product characteristics
SR	Self-report
T_4	Thyroxine
TNM	Tumour-node-metastasis

TSH	Thyroid stimulating hormone
TXT	Docetaxel
UICC	Union for International Cancer Control
VAS	Visual analog scale
WBC	White blood cell count

Chapter 1

Introduction

1.1. The role and classification of tumour markers

Tumour markers are molecules that are present in tissues or body fluids such as blood serum and urine and may be present in concentrations higher than the upper limit of the reference range. The term tumour marker "embraces a spectrum of molecules with widely divergent characteristics sharing an association with the clinical detection, management, and prognosis of cancer patients" (Crooke, 2010). In response to tumour presence, tumour markers are produced by the tumour or the host (Amayo and Kuria, 2009).

Tumour markers can be classified into tumour associated antigens also known as cellular tumour markers, and humoral tumour markers. Serum-based tumour markers which are tested in Malta include α-fetoprotein (AFP), cancer antigen 19-9 (CA 19-9), cancer antigen 125 (CA 125), carcinoembryonic antigen (CEA), beta-human chorionic gonadotrophin (β-HCG), lactate dehydrogenase (LDH) and prostate specific antigen (PSA).

An increase in the level of serum tumour markers can originate from either a presence of cancer or due to a rise in a number of benign conditions and metabolic or hormonal changes. Benign conditions include active hepatitis (AFP), liver failure (CEA), cirrhosis, cholestasis, cholangitis and pancreatitis (CA 19-9), and prostatic hypertrophy and prostatitis (PSA) (Duffy, 2013). In cases of malignancy, tumour markers might not generate elevation in tumour marker results (Sharma, 2009; Aetna, 2016). Structure or biological function of the molecule can be used to classify tumour markers (Amayo and Kuria, 2009). This scenario leads to a situation where the use of tumour markers is still questioned especially for their diagnostic value.

1.1.1. Clinical applications of tumour markers

Tumour markers have various clinical applications. These comprise screening, diagnosis, prognosis, assessment in treatment efficacy, maintaining surveillance following surgical removal of the primary tumour and monitoring response to treatment (Duffy, 2001; Duffy, 2007; Faulkner and Meldrum, 2012; Duffy, 2013; Chabner and Chabner Thompson, 2017).

Each marker has specific associations to conditions. An elevated AFP suggests the presence of either primary hepatocellular carcinoma or germ cell tumour of the ovaries or testicle (Sherman, 2011; Aetna, 2016). AFP is a significant marker for hepatocellular carcinoma, helpful in assessing problems in the management of hepatocellular carcinoma and monitoring treatment regimen (Baig et al., 2009). Serum tumour markers play a vital role in testicular cancer (Toner and MacCallum, 2004). The most commonly used serum markers for management of testicular germ cell cancer include AFP, β-HCG and LDH (Amayo and Kuria, 2009). Since these markers are not very specific, they are only detected in approximately 60% of testicular cancer (Leman and Gonzalgo, 2010).

CA 19-9 is produced by adenocarcinoma of the pancreas, stomach, gallbladder, colon, ovary and lung. Response to chemotherapy (CT) can be assessed through the use of CA 19-9 serum level trends. Oncologic patients with prolonged survival usually have showed treatment related decline in CA 19-9 serum levels (Ballehaninna and Chamberlain, 2011).

CA 125 is expressed in ovarian carcinoma. Duffy (2007) exhibited that the use of CA 125 gave better results than radiology in predicting survival during second-line CT. According to the available literature, changes in CA 125 levels can be effectively used to monitor treatment response, where a decrease in CA 125 level will indicate response to treatment and increased survival, while high levels of CA 125 pre- and post-treatment will indicate no response to

treatment or residual cancer remaining. Failure to normalise CA 125 level post-three cycles of CT will indicate residual tumour, early treatment failure and decrease in survival rate (Colyer, 2012[1]; Aetna, 2016).

Another tumour marker is CEA. CEA is over-expressed by adenocarcinomas, primarily of the colon, rectum, breast and lung. CEA is predominately used in monitoring colorectal cancer (CRC), especially in cases where the disease has metastasised. When compared to CA 19-9, a decrease in CEA level is more accurate to reflect response to treatment (Duffy, 2001; EGTM, 2014[2]; Aetna, 2016).

β-HCG levels can be used to monitor the treatment of trophoblastic disease. An increase in β-HCG levels may also result in cancer of either testis, ovary, liver, stomach, pancreas and lung. AFP and β-HCG as markers have added value since false-positive results are low when compared to other tumour markers (Excellus Health Plan, 2015).

PSA is useful for prostate cancer screening, staging, monitoring response to therapy, and detecting disease recurrence. PSA does not differentiate between benign prostate conditions and malignancy. An increase in PSA level must be followed by other tests to confirm whether malignancy is present. PSA levels are useful in monitoring treatment effectiveness and to check post-treatment recurrence (Sikaris, 2011).

Consensus is more clear regarding the use of blood tumour marker measurements as a valuable tool in the monitoring of therapeutic response in oncologic patients. Monitoring of serum tumour markers is used in the management of malignant disease as routine practice

[1] Colyer S. Association for Clinical Biochemistry (ACB). CA 125 (serum), 2012 [cited 2016 June 20]. Available from: http://www.acb.org.uk/Nat%20Lab%20Med%20Hbk/CA125.pdf

[2] egtm.eu [Internet]. Lung cancer. Europe: European Group on Tumour Markers (EGTM), Inc., c2014 [cited 2016 June 20]. Available from: http://www.egtm.eu/professionals/lung_cancer

since most tumour markers show some relation with the clinical picture of the disease, by elevation in any stage and decline after an intervention (McGinley and Kilpatrick, 2003; Crooke, 2010). Clinicians are frequently requesting tumour markers for the management of malignant diseases. Tumour markers must be used for patients with established malignancies, only if they provide benefit to the patient. Even though tumour marker tests are less expensive than radiological procedures, they are more expensive than other biological tests. Also, inappropriate use may harm the patient. An evidence-based approach should be considered to ensure that markers are used cost-effectively (Amayo and Kuria, 2009). Continuity of results can only be ensured if the same pathology laboratory is used each time. This is due to the fact that different laboratories may use different methods leading to inconsistent tumour markers results (Sturgeon and Diamandis, 2009; Faulkner and Meldrum, 2012).

The National Academy of Clinical Biochemistry (NACB) published various guidelines about tumour markers for different malignancies. Only the 'traditional' markers are used in different applications such as diagnosis, prognosis and monitoring, whilst new proposed tumour markers are less likely to be used (Faulkner and Meldrum, 2012). The reason is that the latter tumour markers lack sufficient clinical trial data. Such an example is the bladder cancer. Even though, the US Food and Drug Administration approved at least six urine tumour marker kits; Sturgeon et al. (2010) reported that not all aforementioned tumour markers kits have sufficient data on survival time and/or quality of life.

While tumour markers have various clinical applications, they also have their limitations and implications of inappropriate use (McGinley and Kilpatrick, 2003). Various audits in hospitals had been conducted in different countries to assess whether the requests for tumour markers

were appropriate (McGinley and Kilpatrick, 2003; McDonnell, 2004; Ntaios et al., 2009; Crooke, 2010).

1.1.2. Ideal tumour marker

Clinical applications of tumour markers depends on their sensitivity and specificity. Being highly specific for a particular cancer and highly sensitive for the required application makes a tumour marker more ideal. Tumour markers may not be useful for screening whilst useful for treatment monitoring (Amayo and Kuria, 2009; NIH, 2015[3]). Tumour markers are not wholly specific and hence, there is no specific tumour marker for each type of cancer (Sharma, 2009; Aetna, 2016). The ideal tumour marker must easily and reproducibly measure a positive result in oncologic patients only, whilst its quantitative levels would correspond to stage and treatment response (Crooke, 2010).

According to Duffy (2013), an ideal tumour marker should have the following characteristics:

1. possess a high positive and negative predictive value;
2. have an inexpensive, simple, standardized and automated assay with clearly defined reference limits;
3. be acceptable to subjects undergoing the test and
4. have a clinical value validated in a large prospective trial.

The Association for Clinical Biochemistry and Laboratory Medicine (ACB)[4], 2014 confirmed what the aforesaid authors stated. The author also added that not all cancers have a unique

[3] cancer.gov [Internet]. Tumour Markers. USA: National Institutes of Health (NIH) National Cancer Institute (NCI); c2015 [cited 2016 Nov 4]. Available from: http://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-fact-sheet.

[4] abc.org [Internet]. The Association for Clinical Biochemistry and Laboratory Medicine. Best practice when providing interpretative comments on laboratory medicine reports; 2014 [cited 2016 Nov 3]. Available from: http://www.acb.org.uk/docs/default-source/committees/scientific/guidelines/acb/best-practice-when-providing-interpretative-comments-for-laboratory-medicine---final.pdf?sfvrsn=2

tumour marker associated with them. Nevertheless, tumour markers can be used to provide more information in line with patient's medical history, physical exams whilst also in conjunction with laboratory and/or imaging tests[5].

As at today, no tumour marker satisfies the criteria. Tumour markers are not indicated for screening asymptomatic patients for malignancy, since patients may have an elevated result due to benign disease (lack of specificity), leading to unnecessary investigations and financial impact, or patients with malignancy will have a normal result (lack of sensitivity), leading to false reassurance (Crooke, 2010).

1.2. Serial monitoring of tumour markers

The main application of tumour markers is in monitoring response to treatment. Pre- and post-treatment serial tumour marker results can provide evidence of treatment effectiveness and the identification of recurrence (NIH, 2015[2]; Aetna, 2016). A rise in tumour marker monitoring due to cancer progression, can cause physiological distress if alternative treatment is not available. As Duffy (2013) explained, it is up to the collaboration between clinician and oncologic patient to decide whether to monitor tumour markers or not. Cancer progression might be present, without a rise in tumour marker results, since due to differentiation, a tumour might not be able to produce a marker. Tumour regression is usually represented by a sustained decrease in tumour marker results.

Response to systemic therapy, whether hormonal or cytotoxic, may be reflected by decreasing levels of serum tumour markers. In this setting, the values of an individual tumour marker and whether it represents positive or negative values relative to an arbitrarily defined

[5] labtestsonline.org. [Internet]. Tumour Markers. USA: American Association for Clinical Chemistry (AACC), Inc.; c2001-16 [cited 2016 June 21]. Available from: https://labtestsonline.org/understanding/analytes/tumor-markers

cut-off is not as important as the trend analysis observed in serial monitoring. Interpretation of trends in tumour markers will depend on an understanding of the normal biologic variation of tumour markers as well as the analytic variation (Excellus Health Plan, 2015). Generally, the same tumour marker(s) used in surveillance following curative surgery for primary malignancy are then used for monitoring treatment in advanced malignancy. If tumour markers show serial progressive rise, this will suggest a treatment failure and hence treatment discontinuation and switching to an alternative therapy should take place. Otherwise, the patient can be involved in a trial to investigate new therapies. If tumour marker show progressive decrease, this will suggest regression of tumour and hence, treatment continuation should take place (Duffy, 2013).

Another clinical application of tumour markers is in determination of treatment efficacy and in detection of tumour recurrence. Patients who are no longer receiving therapy may be monitored for recurrence as evidenced by increasing tumour markers detected in serial monitoring, for example, serial monitoring of CA-125 in patients with ovarian cancer. The limitations of interpretation are similar to those described for monitoring therapy response (Excellus Health Plan, 2015).

Tumour markers can produce a different degree of reduction, but still indicate significant change. Relapse can be detected through post-treatment tumour marker results. Radiological or clinical relapse may follow biochemical relapse after several months to years. Since tumour markers have a role in post-treatment monitoring, they can help clinical management if requested and interpreted correctly (Sharma, 2009).

The Union for International Cancer Control (UICC) gave their recommendations on the use of tumour markers. They recommended that tumour markers should be used in monitoring

treatment of oncologic patients that cannot be evaluated using conventional criteria such as in the case of breast cancer patients with irradiated lesions (Cheung et al., 2000).

With regards to ovarian cancer, the Gynecological Cancer Intergroup (GCIG) recommended to use serial determination of CA 125. This is due to the fact that treatment response can be difficult following surgical debulking, since many patients have low-volume disease that may not be palpable or detectable by radiological procedures such as computed tomography scan or ultrasound (Rustin et al., 2011).

Monitoring tumour marker levels in advanced cancer can produce changes in serial marker which are not correlated to an increase or a decrease in tumour load (Duffy, 2007). Therapy-mediated tumour cell necrosis or apoptosis can result in transient increase or decrease in tumour marker levels in response to the initial treatment. Such an example is that after CT initiation, transient increases in CEA have been reported in patients with CRC. Transient changes have not yet been reported with biological therapies such as therapeutic antibodies such as cetuximab (Duffy, 2013; Vachani, 2016[6]).

In this research, the three solid tumours, cancer of the ovaries, pancreas and prostate were studied. These solid tumours were included on the basis of relevant tumour markers available which can be used to monitor treatment.

1.2.1. Tumour markers and ovarian cancer

CA 125, often referred to as the 'gold standard', is the most commonly used tumour marker in ovarian cancer. Monitoring progress response to treatment is assessed through CA 125 levels (Meyer and Rustin, 2000; Bast et al., 2005). Serial estimation of CA 125 has an

[6] Vachani C. Patient Guide to Tumour Markers [Internet]. The Abramson Cancer Center of the University of Pennsylvania; 2016 [cited 2016 Dec 2]. Available from: http://www.oncolink.org/treatment/article.cfm?id=296

important role in monitoring treatment response in oncologic patients suffering from epithelial serous ovarian cancer, since it has the potential in detecting disease recurrence whilst being less expensive than radiological procedures. A strong indicator of disease outcome is through the measuring of post-treatment CA 125 levels. Pre-treatment CA 125 level is usually carried out two weeks before initiation of treatment. Subsequent samples may be taken at intervals of 2-4 weeks during treatment, and 2-3 weeks during follow-up (Fritsche and Bast, 1998; Amayo and Kuria, 2009). A reduction of ≥50% from pre-treatment CA 125 level, sustained for at least 28 days is defined as a response (Fritsche and Bast, 1998; Cooper et al., 2002).

Post-treatment CA 125 is usually monitored every 3-4 months for a number of years (Crooke, 2010). Other authors including Fritsche and Bast (1998), Verheijen et al. (1999), Meyer and Rustin (2000) and Amayo and Kuria (2009) suggested that CA 125 should be monitored every 2-4 months for two years, in case the pre-treatment levels were high.

1.2.2. Tumour markers and pancreatic cancer

The main application of CA 19-9 in pancreatic adenocarcinoma is in monitoring known malignancy and not for population screening (Crooke, 2010). Serum CA 19-9 levels is used as an indicator for tumour resectability, effectiveness of CT and patient survival, whilst treatment response is also useful for stratification. It is documented that patients who were diagnosed with pancreatic cancer and the post-operative CA 19-9 level normalised will survive longer than those patients whose CA 19-9 did not normalise (Forsmark et al., 1994; Grem, 1997; Montgomery et al., 1997; Schlieman et al., 2003; Amayo and Kuria, 2009; Duffy et al., 2010).

Response to treatment especially in patients receiving palliative therapy can be assessed through serial CA 19-9 measurements, together with imaging studies. Adequate response to treatment is defined by a reduction of CA 19-9 greater than 20% of baseline value (Gogas et al., 1998; Amayo and Kuria, 2009). Such definitions as ≥20% or ≥50-75% decline in CA 19-9 serum levels within the first 6-8 weeks of treatment were reported by different authors (Ballehaninna and Chamberlain, 2011). Additional confirmative tests should be carried out before decisions to initiate or switch treatment (Wu et al., 2013). This is highlighted in the American Society of Clinical Oncology (ASCO) guidelines for the use of CA 19-9 as a marker for pancreatic cancer. CA 19-9 cannot be used solely for assessing treatment response but in conjunction to imaging for clinical findings and/or biopsy. During active treatment, CA 19-9 can be measured every 1-3 months. Disease progression is indicated through the rise in CA 19-9. Additional testing is required for confirmation (Locker et al., 2006; Wu et al., 2013).

1.2.3. Tumour markers and prostate cancer

Serial PSA measurements have an important role in the management of prostate cancer. This includes surveillance, selection of optimal treatment regimens, determination of prognosis and post-therapeutic monitoring (Amayo and Kuria, 2009). Similar to other tumour markers, an increase in PSA suggests cancer progression, whilst PSA level post-treatment should decrease due to cancer regression (Sikaris, 2011).

Semjon and Schmid (2002) stated that there is a relationship between pre-treatment PSA values and disease stage and prognosis. If PSA level is above 50ug/L, this will indicate the possibility of presence of extra glandular spread. An important predictor of metastatic disease is PSA doubling time. After a successful surgery, the PSA values should be

insignificant, while continuous elevation suggests presence of residual disease (Semjon and Schmid, 2002; Amayo and Kuria, 2009).

For post-operative period, untraceable level of PSA value is not always an indication of surgical cure (Pound et al., 1999; Amling et al., 2001; Semjon and Schmid, 2002). Three consecutive rises in PSA above the nadir defines biochemical recurrence. Even though PSA levels should be ideally undetectable post-radical prostatectomy, patient with 'biochemical recurrence' may still experience a slow increase in PSA. Nevertheless, the slowly rising of PSA does not mean that the residual tissue is an aggressive cancer (Tollefson et al., 2007). Patients that are not at high risk should not start treatment immediately. Patients at high risk such as with low free to total PSA ratios or fast doubling times, should have initiation of treatment (Vollmer, 2002).

1.3. Oncology demographic data

The demographic data is represented here with a focus on the three tumours considered in this research namely ovarian, pancreatic and prostate cancer. As per data from the Malta Demographic Review 2014[7], submitted by the National Statistics Office (NSO) in 2016, the total number of deaths including males (1,655) and females (1,615) accounted to 3,270. The total number of deaths due to neoplasms, contributed to 28% of the total number of deaths in 2014.

As per data from the Malta National Cancer Registry and the National Mortality Registry (2004-2014)[8], the incidence and mortality of all cancers (excluding non-melanoma skin

[7] nso.gov.mt [Internet]. Demographic Review 2014. Malta: National Statistics Office; c2014 [cited 2017 Jan 2]. Available from: https://nso.gov.mt/en/nso/Media/Salient-Points-of-Publications/Pages/Demographic-Indicators.aspx

[8] health.gov.mt [Internet]. Malta: National Cancer Register; c2016 [cited 2017 Jan 2]. Available from: http://health.gov.mt/en/dhir/Pages/Registries/cancers.aspx

cancers) and of cancer of the ovary, pancreas and prostate are highlighted in Table 1.1 and Table 1.2. The data on cancer site and morphology is coded using the International Classification of Diseases for Oncology, second edition (WHO, 1990)[8]. The incidence and mortality tables had been updated in October 2016. The tables include information on incidence and mortality by year, gender and age.

Table 1.1 Trends in incidence of cancers (2004-2014)

All cancers (ICD-10 C00-C80), excluding cutaneous basal cell and squamous cell carcinomas; and cancer of the ovary; pancreas; and prostate
Maltese Islands: trends in incidence 2004-2014
Number of new cases by year of cancer registration

Type of cancer	Gender		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
All cancers	Males All Ages	n	661	769	773	761	856	895	965	985	881	844	1045
	Females All Ages	n	676	760	772	765	797	896	916	1021	956	843	1005
Ovarian cancer	Females All ages	n	32	30	36	40	47	42	49	37	40	36	55
		%	4.7	3.9	4.7	5.2	5.9	4.7	5.3	3.6	4.2	4.3	5.5
Pancreatic cancer	Males All Ages	n	16	23	21	31	38	37	39	40	34	34	38
		%	2.4	3.0	2.7	4.1	4.4	4.1	4.0	4.1	3.9	4.0	3.6
	Females All Ages	n	19	14	31	21	27	30	35	31	44	31	42
		%	2.8	1.8	4.0	2.7	3.4	3.3	3.8	3.0	4.6	3.7	4.2
Prostate cancer	Males All Ages	n	140	162	138	131	158	183	209	210	163	227	189
		%	21.2	21.1	17.9	17.2	18.5	20.4	21.7	21.3	18.5	26.9	18.1

Source: Malta National Cancer Registry, Department of Health Information, Malta
Data extracted: July 2016

Table 1.1 highlights the incidence of all malignant cancers (excluding non-melanoma skin cancers) and of cancer of the ovary, pancreas and prostate. In general, there is an overall increase in the incidence of the cancers over years.

Table 1.2 Trends in mortality of cancers (2004-2014)

All deaths from cancer (ICD-10: all C codes), excluding cutaneous basal cell and squamous cell carcinomas; and cancer of the ovary; pancreas; and prostate
Residents of the Maltese Islands: trends in mortality 2004-2014
Number of deaths by year of death

Type of cancer	Gender		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
All cancers	Males All Ages	n	388	388	435	439	478	464	455	473	487	460	523
	Females All Ages	n	323	313	347	365	359	373	397	402	433	388	389
Ovarian cancer	Females All ages	n	28	23	23	27	32	35	37	37	29	29	29
		%	8.7	7.3	6.6	7.4	8.9	9.4	9.3	9.2	6.7	7.5	7.5
Pancreatic cancer	Males All Ages	n	25	17	24	36	41	33	41	32	37	34	47
		%	6.4	4.4	5.5	8.2	8.6	7.1	9.0	6.8	7.6	7.4	9.0
	Females All Ages	n	24	17	23	26	32	26	32	31	36	38	41
		%	7.4	5.4	6.6	7.1	8.9	7.0	8.1	7.7	8.3	9.8	10.5
Prostate cancer	Males All Ages	n	34	44	30	28	36	31	30	36	33	37	43
		%	9.0	11.3	6.9	6.4	7.5	6.7	6.6	7.6	6.8	8.0	8.2

Source: Malta National Cancer Registry, Department of Health Information, Malta
Data extracted: July 2016

Table 1.2 highlights the mortality of all malignant cancers (excluding non-melanoma skin cancers) and of cancer of the ovary, pancreas and prostate. In general, there is an overall increase in the mortality of the cancers over years.

In Malta, the National Cancer Platform[9] was established on the 3rd of February 2015. This website helps bridging together non-governmental organisations working in the cancer field to join forces and ensuring a holistic, coordinated service for oncologic patients and their families. Each organisation remains autonomous, keeping its identity and way of working, while providing comprehensive information and support to its members. Through the platform, members of organisations that offer support to people affected by cancer and their families, become familiar with the work being carried out by other organisations offering similar, or complementary services. The platform facilitates exchange of information to the benefit of the service users. This website, prepared by the National Cancer Platform provides various information such as a detailed list about different non-government organisations such as Malta Community Chest Fund, Puttinu Cares, Aurora Support Service and Hospice Malta. It also includes information about National Cancer Platform and organisations' events both upcoming and past events. A resource section is also available where information about cancer statistics in Malta amongst other information is provided. The national cancer register in Malta compiles data from different sources of information and reports received at their end.

1.4. Pharmaceutical care in oncology

The term "pharmaceutical care" was defined by Hepler and Strand in 1990. It is "the responsible provision of drug therapy" by the collaboration of a clinical pharmacist with the patient, as well as other members of the multidisciplinary team (MDT) in designing, implementing and monitoring a therapeutic plan that will produce specific outcomes (WHO, 1994; McGivney et al., 2007; Liekweg et al., 2012; Holle and Boehnke, 2014). According to

[9] nationalcancerplatform.org [Internet]. Malta: National Caner Platform; c2016 [cited 2017 Jan 12]. Available from: http://www.nationalcancerplatform.org.mt/about/

the American Pharmacists Association (2016)[10], the pharmacist requires to work in collaboration with the patient and the health care team (HCT). This is essential in health promotion and disease prevention. To assure that medication regimens are safe and effective, medication assessment, monitoring, initiation and modification are crucial. The aim of pharmaceutical care is to improve quality of life (QOL) and clinical outcomes of the patient. In a report published by WHO in 1994, it was stated that "the elements of pharmaceutical care for individual patients, taken together, describe comprehensive pharmaceutical care, the delivery of which requires an ongoing, covenantal relationship between the pharmacist and the patient."

As stated by Lin et al. (2015), a multidisciplinary approach to care has been applied in a variety of settings in clinical oncology. Multidisciplinary care integrates various disciplines and existing resources to optimise treatment plans and improve patients' quality of life. Multidisciplinary care models are likely to enhance patient safety (Norton and Baker, 2007). Since oncologic patients with solid tumours are mainly treated in outpatient setting highlights the essence for structured patient counselling on their individual oncology medications including medication reconciliation (MR) especially during transitional care (Weingart et al., 2007). In the National Comprehensive Cancer Network® (NCCN) task force report, it was stated that the inclusion of a clinical oncology pharmacist to the HCT will ensure optimisation of oncology medications (Schwartz et al., 2010).

As antineoplastic drug therapy follows established protocols, the pharmaceutical care models in oncology should reduce treatment-related toxicity whilst focusing more on maximising

[10] American Pharmacists Association. Principles of practice for pharmaceutical care [Internet]. Washington: APhA; c2016 [cited 2016 Nov 7]. Available from: http://www.pharmacist.com/principles-practice-pharmaceutical-care

supportive care strategies (Liekweg et al., 2004). The pharmaceutical care models described in literature include individualised patient information on adverse drug reactions (ADRs) (Skalla et al., 2004; Liekweg et al., 2012). The pharmacist must deal with different patients according to their specific individualised needs (Elf and Wikblad, 2001; Liekweg et al., 2012). Individually tailored information leads to patient satisfaction and aids to initiate self-care.

1.4.1. Individualised pharmaceutical care

The term ‘‘oncology pharmacy’’ has developed into a new pharmaceutical discipline with its own programme. In 1995, the International Society for Oncology Pharmacy Practitioners (ISOPP) was founded. The aim of the ISOPP is ‘‘to determine the optimal medical treatment for cancer patients, thereby improving their quality of life.’’ Presently, optimising individualised pharmaceutical therapy for oncologic patients is a further action in cancer care (Liekweg et al., 2004; Jaehde et al., 2008; Al-Quteimat, 2014).

Tumour markers clinically aid in personalised medicine management since monitoring serial measurements of the tumour marker together with clinical findings will influence clinical decisions for the best way forward to either continue the treatment or switch to an alternative treatment. Tumour markers help in a personalised approach to cancer treatment since personalised medicine approach has the potential to increase efficacy and decrease toxicity (Duffy and Crown, 2008; Liekweg et al., 2012).

Antineoplastic medications for oncologic patients are highly individualised. Different oncology medications have various targets and mechanisms of actions. Since oncology medications can produce severe ADRs, preventing treatment-related ADRs is of utmost importance. Both clinicians and the clinical pharmacists must keep up-to date with evidence-based clinical practice guidelines (Liekweg et al., 2012).

Treatment of cancer is shifting from the traditional "trial-and-error" approach to a personalised approach, i.e., "giving the right drug at the right dose to the right patient." Duffy and Crown (2008) reported that to achieve personalised approach, prognostic markers must be strong and independent. These can reliably separate oncologic patients with aggressive forms (who are treatment candidates) from those with indolent disease (who may not be treatment candidates). Markers should predict treatment response or resistance and lastly markers should help to identify candidates who are likely to develop severe ADRs from specific treatments. The role of clinical oncology pharmacist has been studied for many years for developing treatment plans with the objective to optimising oncology medications, improve patient outcomes, while simultaneously minimising the complications of treatment, and reduce costs. Clinical oncology pharmacists provide "value-added" to patient care (Pon, 1996; Lin et al., 2015). Clinical oncology pharmacists have the role to provide medication-related advice, and in collaboration with the MDT especially physicians, to develop personalised treatment plans (Lin et al., 2015).

Patient-centered care and working holistically within a MDT will result in providing the best cancer treatment outcome for the patients. Recommendations include the familiarisation with the latest evidence-based clinical guidelines in addition to more basic information about the use of tumour markers. The laboratory personnel have the role to set up systems with alerts for inappropriate tumour marker request (McGinley and Kilpatrick, 2003). In 2013, Cornetta and Brown defined personalised care as a holistic approach that considers an individual's physical, mental and spiritual well-being.

According to De Silva (2014)[11], there are four principles of the framework for person-centered care. The first principle is that patients are treated with dignity, compassion and respect. The second and third principles are that care is personalised and coordinated, offering support and treatment. The fourth principle deals about enabling people to live an independent life through supporting people in recognition and development of their abilities. Using a personalised approach involves looking at the patient from a holistic point of view. In understanding the patient holistically, individualised pharmaceutical care will focus not only on the patient's oncological conditions and symptoms but also on their whole wellbeing (De Silva, 2014).

Figure 1.1 The four principles of person-centered care
Adapted from: De Silva D. Person-centred care made simple. London: The Health Foundation Inspiring Improvement, 2014.

Health care professionals (HCPs) must have good communication with their patients. Evidence-based written information tailored to each patient's needs should be provided. The optimal management of personalised care is based on a trusting relationship between the

[11] De Silva D. Person-centred care made simple [Internet]. London: The Health Foundation Inspiring Improvement, 2014 [cited 2016 Apr 12]. Available from: http://www.health.org.uk/sites/default/files/PersonCentredCareMadeSimple.pdf

patient, the physician, and most importantly - the multidisciplinary HCT taking care of the patient (NICE, 2009)[12]. A holistic approach should take into consideration not only the biological characteristics of the tumour but also the patient's physiological and psychological status over their lifetime. Through the use of personalised medicine, the patient should be at an advantage. The patient would not only improve the probability of positive treatment response but also reduce treatment-associated ADRs. Understanding the patient holistically is the way forward in cancer care. Whilst providing additional benefits to the patients, it might also lead to monetary benefits (Gupta et al., 2004; Batchelder and Miller, 2006; Trusheim et al., 2007; Duffy and Crown, 2008).

1.5. The pharmacist contribution in clinical oncology

There are a number of publications which underpin the role of the clinical pharmacist in oncology and an insight is here being put forward capturing publications related to specific issues in this research. The role of clinical oncology pharmacist in identifying and resolving drug-related problems (DRPs) is widely documented in many countries worldwide. Based on the available evidence, clinical oncology pharmacists play an important role in all aspects of cancer screening and risk assessment, patient education, opioid pain control and monitoring ADRs. Clinical oncology pharmacists may contribute to both clinical and societal outcomes (Lin et al., 2015).

Although pharmacists' contributions to oncology have not been fully recognised, there is reason to be optimistic that clinical pharmacists will have an expanded role on oncology teams. Introducing individualised treatment plans, monitoring CT together with nursing staff,

[12] nice.org.uk [Internet]. NICE. Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence. National Institute of Health and Care Excellence (NICE); 2009 [cited 2016 Dec 1]. Available from: http://www.nice.org.uk/guidance/cg76/resources/medicines-adherence-involving-patients-in-decisions-about-prescribed-medicines-and-supporting-adherence-975631782085

and providing patient education about medications could serve as starting points for introducing clinical pharmacists to multidisciplinary oncology teams (Lin et al., 2015). A clinical pharmacist is also responsible for identifying, resolving and preventing DRPs such as untreated indications, ADRs and interactions (Ma, 2014).

Even though, DRPs are common and reduce life quality together with morbidity and mortality, the clinical pharmacist has shown that they can identify and resolve DRPs, leading to treatment optimisation. The clinical pharmacist liaises with the physician to provide interventions to DRPs, thus providing a proactive approach rather than a reactive approach (Viktil and Blix, 2008). A MDT approach should be used in cancer treatment. Pharmacists can assist physicians in the diagnosis and treatment of cancer on multiple levels, as shown by the literature that was reviewed. In oncology, various professional disciplines can maximise their respective contributions to improve diagnosis and individualise treatment for better patient care (Lin et al., 2015). In 2008, Viktil and Blix reported about the impact of clinical pharmacists on DRPs and clinical outcomes. DRPs are "frequent and may result in reduced quality of life, and even morbidity and mortality." The clinical pharmacist has the role to identify and prevent DRPs in a proactive approach rather than a reactive approach. This is defined by the pharmacist being integrated within the MDT discussions - at both the stages of ordering and at prescribing, where all types of ADRs are to be discussed.

The role of the clinical pharmacist has been explored in different settings. Various publications looked at the role of the outpatient clinical pharmacist interventions**.** Studies supported the expanded roles of pharmacists in practising within a MDT and in patient counselling and education. Beney et al. (2000) reported that all studies demonstrated that pharmacist intervention decreased hospital and emergency room admissions; the number of

speciality physician visits or the number and costs of drugs and improved the patient's condition.

Kaboli et al. (2006) published a review of 36 studies about the role of the inpatient clinical pharmacist. They found that clinical pharmacist service reduced ADRs or medication errors (MEs); improved care in inpatients, medication adherence, knowledge and appropriateness; and reduced the length of hospital stay. It was concluded that when the clinical pharmacist is integrated within a MDT, reconciling medication and counselling patients on discharge medication and follow-up, resulted in better outcomes.

The vast majority of clinical oncology work remained undocumented. A typical example is the direct patient care where the academia does not suffice in enough knowledge. This lack of information lead to the underestimation of the importance of their services (Shah et al., 2006; Bernard et al., 2010).

In the mid-1980s, there were two articles published by Eddlemon et al. (1984) and Caselnova et al. (1985), describing the role of the pharmacist in oncology patient care. In 1984, Eddlemon et al. described the implementation of an inpatient oncology satellite pharmacy, which allowed the pharmacy department to expand its services and decrease the potential risk to personnel. Apart from preparing all cytotoxic drug products, the pharmacist had the role in providing clinical services to oncologic patient such as in monitoring drug therapy and providing drug information to the MDT. Caselnova et al. (1985) analysed the role of the pharmacist in an outpatient clinic. The authors concluded that the pharmacists were well accepted by the members of HCT. The pharmacists who were trained in an established IV therapy certification course had various roles such as clinical and distributive services, including patient monitoring, medication storage, delivery, administration and disposal.

Thorn et al. (1989) assessed before and after implementation of preprinted CT order forms. The pharmacists also carried out educational intervention for house-staff physicians on writing CT orders highlighting the 9 components; patient's diagnosis, height, weight, body surface area (BSA), drug regimen, dose, dosage, frequency and route. The authors found out that after the implementation of the form, compliance exceeded 90% for 8 of the 9 components and 12 MEs were prevented by the form.

In 1992, Davies et al. reported about the development of a clinical pharmacy documentation system in an out-patient oncology center. After a 12-month period of pharmacist clinical interventions, which were divided into two categories; consultation/drug information and therapeutic interventions, 246 and 343 interventions respectively were recorded.

Cohen et al. (1996) evaluated how to prevent MEs in cancer CT. A detailed checklist covering prescribing, transcribing, dispensing, and administration should be used. Preprinted anticancer medication order forms containing checklist can help avoid errors. The checklist had shown signs of improvement to eliminate MEs.

In 1999, Wong and Gray reported about the implementation and evaluation of clinical pharmacy services (CPSs) in ambulatory haematology-oncology clinics. The authors stated that "a clinical pharmacist has a significant role in outpatient clinics and can potentially lead to an overall decrease in health care costs and to an improvement of the quality of patient care." To obtain a medication history; a chart review, patient interview and pharmacy patient profile review were performed. DRPs were identified, resulting in interventions (such as patient counselling, therapeutic recommendations, drug information, detection of ADRs and drug interactions, detection of patient non-compliance, enrolment of patient into indigent drug problems and detection of prescribing errors). Patient outcomes were analysed through

the use of primary research data. The mediums were both follow-up telephone calls and/or through face-to-face interviews on the following clinic visit. A total of 211 pharmacist interventions were documented over a 36-day period. Most of the interventions involved patient counselling. Therapeutic recommendations were accepted by physicians 94.5% of the time (Wong and Gray, 1999; Ruder et al., 2010).

Bremberg et al. (2006) evaluated the importance of the pharmacist contribution to an oncology ward in a Swedish hospital. DRPs were identified via drug chart reviews which are based on data from medical files, laboratory investigation, and patient and/or relative interviews. A questionnaire was handed to physician and nurses to evaluate the pharmacist's contribution to the ward. A total of 114 DRPs were identified, for which every DRP, the pharmacist gave proposals for solutions.

In 2006, Shah et al. evaluated CPSs in a haematology/oncology outpatient setting. The authors developed documentation templates to use Pendragan Forms 3.2 software with personal digital assistant documentation of pharmacist clinical activities. Clinical pharmacists activities were divided into three categories: supportive care issues (constipation/diarrhoea, nausea/vomiting, pain); drug-specific intervention (ADR prevention, drug addition, drug discontinuation, drug dose adjustment, laboratory monitoring, medication administration record (MAR) correction, pharmacokinetic monitoring) and writing prescriptions (new, refill, renew). After the 12-months study period including 228 oncologic patients; supportive care issues, drug-specific interventions and writing prescriptions amounted to 342, 308 and 445 respectively. This study highlighted the key role pharmacists play in direct patient care.

During a randomized controlled trial, Bakitas et al. (2009) concluded that a multicomponent, psychoeducational intervention (Project ENABLE II [Educate, Nurture, Advise, Before Life

Ends]), which was conducted by advanced practice nurses to oncologic patients after a new diagnosis of an advanced cancer, and consisted of 4 weekly education and problem-solving sessions (developed during ENABLE I) and monthly telephone follow-up sessions until death or study completion had higher scores in QOL and mood than oncologic patients that were provided usual oncology care. A certified palliative care physician and nurse practitioner invited the intervention participants and their caregiver to attend monthly group shared medical appointments (SMAs). The participants and caregivers could ask questions about medical problems or related issues (e.g., symptom management, insurance, social services) and could have more in-depth discussions than is practical during typical clinic visits.

In 2009, Delaney et al. found out that a clinical oncology pharmacist should become a "permanent member" of the outpatient NeuroOncology clinic. In this study, a pharmacist took a complete medication history and provided standardised counselling (CT administration, ADR management, dosing of supportive medications, drug interactions, communication with other pharmacists to ensure that prescriptions were provided and any other medication-related questions). The pharmacist phoned the patients at home the following day and then five days after starting treatment to review treatment protocols and address any medication-related questions. The pharmacist was to be available for questions outside of clinic hours and to answer medication questions from the staff. Pharmacist interventions were classified into 3 categories. The first category included direct patient care (collect medication history, answer drug information questions for patients, recommend non-drug treatment, counsel patient on CT treatments, counsel patients on non-chemotherapy treatments, counsel patients on blood work, counsel patients on operation clinic). Another category included direct contact with the HCT (identify DRPs, answer drug information questions for staff) and the last category included coordination of care (patient preparation,

provide information to dispensary, enter pertinent information into computer, monitor laboratory results and therapeutic drug levels, contact community pharmacy). Thirteen oncologic patients each having an average of 9 interactions were seen by the pharmacist. The study period took a duration of four months. Out of the 13 oncologic patients, 55% of interactions took place outside of scheduled visits. It was concluded that 90% of the sample responded that the pharmacist should remain with the Neuro-Oncology team.

Patient adherence to oncologic regimens are more relevant in oncology, since oral treatments are adopted for use in cancer care. Adherence and persistence rates ranged from 16% to 100% using different oncologic medications and different methods of measurement. Decreased drug efficacy and increased consumption of health care resources are examples of consequences of non-adherence (Ruddy et al., 2009).

In the report by Sessions et al. (2010), it was emphasized that oncology pharmacists can support with direct patient care and educational activities. The authors summarised four examples in North Carolina. In their study, they analysed the University of North Carolina, Moses H. Cone Health System, Duke University, and Charles George VA Medical Center.

The first example included the University of North Carolina Lineberger Comprehensive Cancer Center-North Carolina Cancer Hospital. In this hospital, clinical pharmacist practitioner (CPP) initiated a first-cycle CT counselling service. The main aim was to focus on the counselling of all new oncologic patients on their CT and potential ADRs, leading to the establishment of a cancer-associated thrombosis clinic. The aim of a cancer-associated thrombosis clinic was to provide patients receiving anticoagulants a care plan. Oncologists were now not required to follow these patients in their own clinics for routine monitoring of anticoagulation. Finally, the CPP developed more than 200 CT order templates. With the introduction of the CT order

template, oncologists spend less time writing CT orders whilst reducing the chance of prescription errors.

The second example focused on Moses H. Cone Oncology Clinic (Greensboro, NC), which is an outpatient hospital-based clinic. Although, the CPP had to manage the pharmacy and admixture requirements, the clinical role incorporated seeing and assessing of patients in a high-risk anticoagulation clinic whilst using prescriptive authority (including a Drug Enforcement Administration number and National Provider Identifier). The CPP consulted on supportive care measures, symptom management, toxicity management, and patient education for patients at the outpatient clinic and collaborated on consultations at the inpatient unit per request. The pharmacist contributed in the code situations of the infusion area. With prescriptive authority, the pharmacist could confirm whether there were any inconsistencies in CT and other regimens, order laboratory tests, and covered incidental situations when physicians were not in their office. The main aim was to confirm that there is a continuity of care for patients.

The third example referred to the adult outpatient haematology and oncology clinics of the Duke Comprehensive Cancer Center (Durham, NC), which are part of the Duke University Health System. In these clinics, the pharmacists did not have responsibilities in the investigational of oncology pharmacy. The pharmacist clinical role involved seeing and assessing patients in the ambulatory clinic setting, whilst CPP consultation emphasised on supportive care issues such as pain management, nausea, vomiting, myelosuppression, toxicity management, drug interactions and patient education. In this clinic, the CPP was also able to install a standard template and service for CT education for other pharmacists in the infusion area. The CPP was also responsible for creating standard CT order templates for both

standard of care regimens as well as investigational protocols in the outpatient setting. The pharmacist also led the initiative to create supportive care guidelines for the management of chemotherapy-induced nausea and vomiting (CINV), myelosuppression, infusion and hypersensitivity reactions, epidermal growth factor receptor-inhibitor skin toxicities and vascular endothelial growth factor-inhibitor hypertension. The pharmacist also served as an investigator on numerous clinical trials involving care of patients with cancer.

In the last example, the Charles George VA Medical Center (Asheville, NC) was analysed. In this setting, the pharmacist was able to actively assess the patients receiving therapy, order and reorder anticancer therapy (including chemotherapy) and supportive care medication, perform limited physical examinations and thorough reviews of systems, whilst order necessary laboratory and radiographic examinations. Similar to other providers, another role of the pharmacist was to maintain the clinic; compile progress notes for patients; documents interventions, plans, and complexities of patient encounters; and documents time spent with each patient. The pharmacist could meet with patients who were in the process to start new anticancer therapies. The pharmacist's role was to counsel them on the administration and toxicities, whilst completing thorough medication reconciliations, assesses potential drug interactions, and frequently obtained consent for prescribed therapies. The pharmacist could write and sign for CT, although the first cycle must be consent by an oncologist. In Charles George VA Medical Center, the pharmacist could also run an erythropoiesis-stimulating agent anaemia clinic. This service was given by the pharmacist twice per week and focused on patients with chronic kidney disease that were not receiving dialysis.

According to Sessions et al. (2010), "oncology CPPs bring a thorough understanding of drug therapies, toxicities, monitoring, and pharmacoeconomics to the multidisciplinary team

unique to our profession." Pharmacy professionals are trying to achieve provider status through legislative reforms. Nevertheless, it is hoped that following the wave of health care reform, pharmacist are able to gain provider status. The authors concluded that oncology CPPs are of utmost importance when providing direct patient care to oncology patients.

In 2010, Ruder et al. confirmed that there is benefit in having a clinical oncology pharmacist at a community oncology clinic. Drug-related interventions (e.g. medication reconciliation, drug orders (DO), dosing calculations (DC), drug duplication (DD) and ADR management and prevention), consultative interventions (e.g. patient education sessions, patient visits, drug information questions from HCT and patients) and cost savings by the clinical oncology pharmacist were evaluated. At the end of the study, a total of 583 interventions were documented among 199 patients. Drug-related and consultative interventions accounted for 35% and 65% respectively. The on-site clinical oncology pharmacist saved $210,000 by admixing CT and resulted in positive ratings from both the patient and HCT surveys.

Dohler et al. (2011) had demonstrated the benefit of a clinical pharmacist in outpatient CT units. A multi professional cancer medication management (MCMM) model compromising of 38 tasks including 11 on patient education and counselling was compiled and an online questionnaire was used to evaluate the acceptance of the MCMM model and explore the multi professional team perceptions. The MCMM was rated to be reasonable (79%) and feasible (68%), and highlighted that the pharmacist has a role in being integrated in this model and carry responsibilities especially in patient education and counselling and DRPs.

In the study by McKee et al. (2011), a 20-item tool was developed and used to assess the role of the patient-pharmacist relationship in an outpatient CT academic clinic. The authors found out that 86% of the interviewees agree that oncologic patients should discuss their treatment

with a pharmacist. It was found that 76% of the respondents requested pharmacists' follow-up through future visits. This study concluded that patients would like to have pharmacist follow-up regularly, whilst also may be willing to pay for pharmacy counselling services.

Yennurajalingam et al. (2011) and Mancini (2012) emphasized that the clinical pharmacist has a role in management of symptoms of ADR and in identification of interactions. Oncologic patients may also receive regimens comprising multiple antineoplastic agents, as well as multiple lines of CT. This highlighted not only the need for management of symptoms and ADRs but also identification of potential drug interactions. In 2011, Yennurajalingam et al. analysed the effect of a palliative care consultation team in advanced oncologic patients receiving supportive care on an outpatient basis. Mean scores at baseline and follow-up visits of some cancer-related symptoms include fatigue 6.8 and 5.3, pain 5.3 and 4.1, depression 3.2 and 2.5, anxiety 3.7 and 2.8 and dyspnoea 2.7 and 2.5. Pharmacological interventions by PC during the initial consultation identified the most frequent medication changes such as initiation or discontinuation or change of dose or medication class type. This study concluded that oncologic patients receiving antineoplastic medications achieved significant improvement through the impact of a PC team. Mancini (2012) study described the role of the clinical oncology pharmacist as being incorporated within the MDT including of a nurse, dietician and social worker. The pharmacist responsibility involved medication reconciliation, consisting of implementation of a standardized pharmacist assessment which identified drug interactions (44%), ADRs (74.7%), duplicate therapies (46.7%), untreated conditions (73.3%) and lack of efficacy (94.7%). Mancini highlighted that pharmacists are "uniquely trained in medication therapy management." In a study by Valgus et al. (2010), pharmacist-led interdisciplinary model produced an improvement in symptom scores (assessed on a 5-point

Likert-type scale) for nausea and constipation with a reduction from an average of 4.0 to 1.0 and 3.3 to 2.0 respectively.

In 2012, Liekweg et al. reported about pharmaceutical care for patients diagnosed with breast and ovarian cancer recruited from six-academic and community-based outpatient clinics as well as two primary care oncologists. Oncologic patients were initially enrolled in a control group receiving standard care, but after implementation of pharmaceutical care were recruited into an intervention group. The intervention group received additional patient counselling on the management of treatment-associated ADRs and optimisation of supportive medication. The authors found out that oncologic patients suffering from ovarian or breast cancer benefited from pharmaceutical care, as highlighted by improved patient-reported outcomes such as emetic episodes, quality of life and patient satisfaction (with the educational information they received) after implementation.

Tuffaha et al. (2012) reported about the development, implementation and reported interventions of CPSs in the outpatient paediatric haematology-oncology clinics. The authors found out that these services are vital to confirm continuity of care and in optimisation of treatment. The interventions collected were categorized into four major classes: safety, education, clarification and therapeutic and their frequency of interventions were 500 (53%), 247 (26%), 113 (12%) and 79 (9%), respectively. The most frequent interventions were patient counselling 247 (26%) and CT evaluation 229 (24%). Less frequent interventions identified were drug interactions and ADRs with 10 (1%) each.

In 2014, Edwards et al. reported that a seamless care pharmacist (SCP) could ensure that oncologist patients are receiving the highest standards of care via identifying and resolving DRPs. The SCP conducted standardised comprehensive medication history review and

medication reconciliation, counselled the patients on their treatment, and identified and resolved any DRPs. The SCP identified an average of 3.7 DRPs per intervention oncologic patient, mostly common identified being that patient do not receive/take the drug therapy for which there is an indication (40%), followed by the patient not taking/receiving the prescribed drug appropriately (15.2%) and patient taking/receiving too little drug (10.4%). The intervention group sought additional health care interventions amongst which were visits to family physician (41.8%), followed by visits to emergency room and hospital admissions (15.3%).

Ma (2014) review paper, reported about the role of pharmacists in optimising the use of antineoplastic drugs in the clinical setting. The author identified studies that dealt with the seven critical steps that constitute safe and complete medication management, which include selection, procurement, prescribing/dosing/transcribing, storage, preparing/dispensing (includes delivery), administration and monitoring/evaluation/education. The Joint Commission defined selection as "appropriate choice of a medication for a specific indication." The oncology pharmacist has a role in drug selection and in providing drug information skills about pharmacology, dosing, ADRs, keep up-to date with most recent published and ongoing clinical trials and evidence-based clinical guidelines (Wong and Ignoffo, 1996; Ma, 2014). In recent years, pharmacogenomics area is being studied much more. Genetic marker identification will result in tailoring for optimal drug selection, dose and duration of treatment (Moen et al., 2012; O'Donnell and Ratain, 2012). Prescribing, dosing and transcribing is a key role for the clinical oncology pharmacist. The Joint Commission defined prescribing or ordering as "the specific items in a prescription and the logistics of placing the medication order." MEs are due to mistakes in the prescribing process.

CT regimens can be complex since dosing calculation are usually based on BSA. Other orders might require specifics for infusion times, route, diluents or container type.

Pastel et al. (1993) found out that the implementation of a newly developed CT order form resulted in a significant improvement in completeness of necessary prescription information compared to a standard treatment order form. The developed CT order form consisted of 13 standardized prescription components: diagnosis, height, weight, BSA, start date and time, dosage (mg/m^2), dose (mg), solution diluent and volume, infusion rate (drips only), route (i.e., IV push or IV drip), frequency of administration and total number of scheduled doses.

Serrano-Fabia et al. (2010) analysed MEs in multidisciplinary system with a computerised pharmacotherapy process in oncologic patients receiving antineoplastic CT. The authors found out that the detected ME distribution according to pharmacotherapeutic stage was: prescription 75.7%, preparation 21.0%, dispensing 1.8%, administration 1.1%, and follow-up 0.4%. This longitudinal, prospective 2-year cohort study, detected 20.9 MEs per 1000 patient-days and intercepted 98.8% of all MEs. According to the authors, "clinical pharmacists are key players in creating standardized electronic order sets that are linked to clinical laboratory tests and program for medication alerts for interactions and doses that exceed maximum allowable limits."

The implementation of a computerized provider order entry (CPOE) guided by multidisciplinary failure modes and effects analysis (FMEA) is being implemented in severe hospitals, in order to reduce improper dosing, incorrect DC, assure cumulative dose calculations and implement checklists for incomplete orders. Kim et al. (2006) found out that CPOE guided FMEA reduced ordering errors in paediatric CT.

Oncology pharmacist practice for supportive care includes various areas such as CT administration follow-up, gastro-intestinal side effect support, pain management and chronic disease medication management. Oncology pharmacist drug-specific interventions are various and include roles such as; MR and allergies, addition/discontinuation of drugs; dose adjustment due to organ impairment, weight, age; medication adherence; ADRs prevention and monitoring; support medication administration, premedication; therapeutic drug/PK/laboratory monitoring; switch treatment from intravenous to by-mouth formulations, writing prescriptions and refills (Wong and Ignoffo, 1996; Hutten et al., 2000; Council on Credentialing in Pharmacy, 2010; Hutchison and Castleberry, 2011).

In 2014, Miller and Hoare studied the difference between pre- and post- the introduction of a new pharmaceutical service. In the initial audit, 4.5% of prescriptions verified by an oncology pharmacist had clinically significant pharmacist interventions, compared to 17% in the repeat audit. Amongst the interventions to be observed such as identifying drug interactions, incorrect dosage, failure to prescribe supportive medicines; patient education and MR accounted to 61%. Both staff and patient feedback were positive.

In Chew et al. (2015) study, clinical pharmacists studied the reason for intervening and its related drug(s). Each intervention was evaluated by an expert panel MDT consisting of two oncologists and a pharmacist using a five-point scale. It was found out that half of the interventions were evaluated as clinically 'significant' or 'very significant'. This study resulted in a total of 331 interventions, where 147 cases were due to missing CT orders, while 184 cases had potential DRPs (such as inappropriate dose (overdose or underdose), omission of drug, ADR, symptoms management, inappropriate dosing regimen).

In 2015, Delpeuch et al. evaluated the role of CPSs in a haematology/oncology inpatient setting. The clinical pharmacist identified 552 DRPs, which included mostly inappropriate treatment of around 20%, untreated indications of more than 14%, inappropriate administrations and drug-drug interactions (DDIs) were both circa 14%, underdosing approximately 12%, whilst lack of monitoring, overdosing, administration omissions and ADRs were all less than 10%, ranging from 2.5% to 9.6%.

Randolph et al. (2016) prospective pilot study in an ambulatory cancer center found out that a full-time clinical pharmacist provided both financial benefit and is positively perceived by oncology patients and healthcare staff. After evaluation of 962 clinical pharmacist interventions, it resulted in a net benefit of US$138.441. The most common interventions were for CT regimen review amounted to 69% and 97%, and were carried out by the pharmacy resident and the centralized oncology pharmacist respectively. Patient counselling interventions amounted to 24% were carried out by the resident pharmacist. Other interventions that were carried out included; ADR follow up, ADR reported, ADR management or prevention, dose adjustment, drug allergy management or prevention, drug information, drug interaction, drug not indicated, incompatibilities/stabilities, medication history, monitoring recommendation, order clarification, supportive care/untreated diagnosis, therapy duplication, and therapeutic/disease state recommendation. The anonymous patient and staff satisfaction survey nabbed on a 5-point Likert scale revealed a positive perception of the clinical oncology pharmacist both by the oncologic patient and the healthcare staff.

In 2016, Farias et al. evaluated the implementation of a CPS in haematology. The intervention consisted of an anticancer prescription validation (analysis of patients' characteristics,

laboratory tests, compliance with the therapeutic protocol and with pharmacotechnical parameters). After implementation of this service, DRPs were increased by 106.5%, amongst which included dose adjustment (35% vs 25%) and drug withdrawal (33% vs 40%) at period A and period B respectively. The pharmacy service contributed to increase the detection and resolution of DRPs, and it was an effective method to promote the safe and rational use of anticancer medications.

The main contribution of a pharmacist in the oncology refer to development of individualised pharmaceutical care plan, managing medications through medication reconciliation, monitoring ADRs and patient compliance.

1.5.1. Pharmaceutical care plan

The pharmacist's roles have shifted from product-oriented and medication dispensing service to more patient-centered services such as pharmaceutical care provision, which includes pharmaceutical care issues (PCIs) identification, prevention and resolution. The clinical pharmacist optimizes the benefits of drug therapy (Krska et al., 2000; Bremberg et al., 2006; Hudson et al., 2007; Chua et al., 2012; Tuffaha et al., 2012).

Pharmaceutical care plan (PCP) is defined as "one or more pharmaceutical care issues for an individual patient, together with the desired output(s) and the action(s) planned to achieve the output(s)" (Krska et al., 2000; Waight, 2011). Pharmaceutical care planning is widely documented. The keys to pharmaceutical care planning are highlighted in this quote by Professor Steve Hudson (2003) which states that; "successful pharmaceutical care planning depends on the pharmacist being integrated within the MDT and using a documented system of monitoring drug therapy in patient care." This quote has value in our local scenario since Professor Steve Hudson used to work within the clinical team in Malta. According to Global

Clinical Pharmacy Academy (2013)[13], a PCP is a "patient-centered systematic approach." The clinical pharmacist designs a written format, ensuring proper drug use and achieving definite outcome. Patient care is improved through assuring that the drug is safe, effective and cost-effective.

In a report entitled 'The role of the pharmacist in the health care system' submitted by WHO[14], it is highlighted that the team approach is vital to achieve the optimum use of the resources. Pharmaceutical care is provided in collaboration with HCPs such as physicians, nurses and others. According to WHO report, to be proactive in the adoption and promotion of pharmaceutical care provision, the pharmacist should:

a. Introduce the concept into association mission statements
b. Establish appropriate practice guidelines and standards
c. Develop relevant audit procedures
d. Encourage individual pharmacists to embrace this concept in their professional practice
e. Promote pharmacist representation on all relevant healthcare policy groups
f. Systematically interact with other HCPs to develop pharmaceutical care
g. Establish centres to promote and facilitate practice research and studies
h. Facilitate the dissemination of information on pharmaceutical care through international pharmaceutical associations such as Commonwealth Pharmaceutical Association (CPA) and the International Pharmaceutical Federation (FIP).

[13] clinicalphar.com [Internet]. Pharmaceutical care plan. Global Clinical Pharmacy Academy; c2013. [cited 2017 Oct 7]. Available from: http://clinicalphar.com/pharmaceuticalcareplan.html
[14] WHO. The Role of the pharmacist in the health care system [Internet]. Geneva: World Health Organization, 1994 [cited 2016 Sept 6]. Available from: http://apps.who.int/medicinedocs/en/d/Jh2995e/

Drug therapy problems are the "heart and soul" of the practice of pharmaceutical care. Drug-related problems (DRPs) are defined as "problems in the pharmacotherapy of the individual patient that actually or potentially interfere with desired health outcomes" (van Mil, 2005; Pharmaceutical Care Network Europe (PCNE) Foundation, 2016). Amongst the most common PCIs are: ADRs, drug choice problem, dosing problem, drug-use problem and interactions (Beijnen, 2004; Riechelmann et al., 2005; Scripture and Figg, 2006; Jaehde et al., 2008; Riechelmann and Del Giglio, 2009; Chung et al., 2011; Tavakoli-Ardakani et al., 2013; Stoll and Kopittke, 2015; PCNE, 2016). Other terminology such as PCIs has also been used. PCIs were described by the Scottish practice guidelines as "an element of a pharmaceutical need which is addressed by the pharmacist" (Krska et al., 2002). This patient-centered approach based on pharmaceutical care incorporating tumour markers will result in an improved more efficient quality of service given to patients within a MDT (Song et al., 2010). Blood tumour markers measurement is a valuable tool in the monitoring of therapeutic response in oncologic patients.

1.5.2. Medication reconciliation

Medication reconciliation (MR) "exclusively involves interventions in which pharmacists play a key role." As defined by Agency for Healthcare Research and Quality (AHRQ)[15], MR refers "to the process of avoiding such inadvertent inconsistencies across transitions in care by reviewing the patient's complete medication regimen at the time of admission, transfer, and discharge and comparing it with the regimen being considered for the new setting of care."

[15] AHRQ. Medication reconciliation [Internet]. US: AHRQ; 2015 [cited 2016 Oct 5]. Available from: https://psnet.ahrq.gov/primers/primer/1/medication-reconciliation

This is discussed in detail in a report published by AHRQ in 2013. In this report, 18 studies of MR were assessed in relation to clinically significant unintended discrepancies. It was found out that in three interventional studies, pharmacists played a key role, which does not reflect routine practice. Additional enhancements beyond MR itself, included the creation of one database of electronic medical record (EMR) with the inclusion of preadmission medication history data. A HCP-consumer partnership model was designed to empower patients understanding and management of their medications (Nilsen et al., 2006; Lingaratnam et al., 2012). The authors remarked on how to reduce MEs at transition points. This is envisaged through patient empowerment and having sufficient information about their medications, hence facilitating the MR process.

In 2011, Chung et al. found out that the development and implementation of an interdisciplinary oncology program, involving both nursing, pharmacy team members and medical oncologists, in a community hospital, resulted in a reduction in medication-error rates, expansion in pharmacy services and cost savings. The development of a new practice patient-centered model included; creation of standardized CT monitoring form (including patient details, treatment protocol, pertinent labs, CT medication, cycle and frequency) and CT order forms (patient info, regimen, iv fluid, pre-medication, CT, labs). Various pharmacy collaborative agreements, development of protocols (such as those for CINV and chemotherapy-induced anaemia), improved pharmacy processes and established standards (such as in monitoring) were also included. Data was collected for CT orders pre- and post-program implementation. The authors concluded that the reduction in total errors, which amounted to 45%, were related to CT drugs. They also stated that missing information was the main cause for errors.

Lingaratnam et al. (2012) reported that the interventions of the use of a patient brochure (which is both a learning tool for patient to document their current medications, and also a document which aids HCP staff undertaking MR on admission) and form (medicines list encased in an A4 plastic pocket foldable into wallet size to ensure portability and durability was given to each patient after receiving counselling from the clinical pharmacist) facilitated self-reporting of drug information, MR efforts by the clinical pharmacist and also assisted with minimising MEs. This study found out that both the brochure/form were patient-friendly and facilitated MR on admission. Both the clinical pharmacist and the nurses play a significant role in ensuring drug safety.

Jaehde et al. (2008) reviewed the consequence of DRPs and identified how the pharmacist can contribute to minimise treatment-associated risks in systemic cancer therapy. ADRs, DDIs, MEs and non-adherence are the most frequently reported DRPs. DRPs could originate from several steps of the treatment path such as prescription, ordering, compounding, storage, administration and monitoring. Together with the MDT, pharmacists have a responsibility in assuring safety and quality in systemic oncology medications.

It is being highlighted that the role of the oncology clinical pharmacist interventions has a positive impact in patient care. A systematic review carried out by Tam et al. (2005), studied the frequency, type and clinical importance of medication history errors at hospital admission. They found out that medication history errors (omission, commission, incorrect frequency, incorrect dose) occurred in up to 67% of cases. These studies found that 27%-54% of patients had at least one medication history error. In a study by Cornish et al. (2005), 45.7%-61.6% had at least one unintended discrepancy (drug omission, discrepant dose, discrepant frequency, incorrect drug), where drug omission was the most common error

identified, amounting to 46.4%. A closer teamwork approach between patient and the HCT is a way of reducing error frequency.

In 2015, Tenti et al. reported about MR in oncology and monitoring of preventable drug interactions. At the end of the study, 100 adult patients recruited who were undergoing infusion therapy had been distributed a MR form, to analyse all the possible drug interactions between cancer and non-cancer drugs and all drugs and non-conventional medicine. In this observational prospective study, the pharmacist identified 77 drug interactions that required a dose adjustment or close monitoring detected and some contraindicated potentially ADRs.

1.5.3. Adverse drug reactions

In a report published by WHO in 2002[16], ADR is defined as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."

The most feared consequences associated with oncology medications are ADRs (Feyer et al., 2008). CINV is considered substantially distressing for the patients and should be addressed by oncology care services. Clinical pharmacists have extensive knowledge of drug therapy and their participation in a multidisciplinary oncology team can prevent or mitigate CT side effects. The role of clinical pharmacists in providing supportive care on a MDT includes monitoring prescriptions, assessing nausea and constipation and recommending treatments to physicians to control these symptoms (Lin et al., 2015).

[16] WHO. The importance of pharmacovigilance safety monitoring of medicinal products [Internet]. Geneva: World Health Organisation, 2002. [cited 2016 Sept 6]. Available from: http://apps.who.int/medicinedocs/en/d/Js4893e/

Patients' perception of the ADRs of cancer CT have been studied from the 80s. In 1983, Coates et al. found out that nausea, vomiting and alopecia were the major physical ADRs, while fatigue and "affects my family or partner" were ranked 8th and 10th respectively. Coates at al. (1983) study contrasted with a study carried out in 2002 by Carelle et al., where it was highlighted that psychosocial QOL complaints "affects my family or partner" ranked as the most severe ADRs, followed by alopecia and fatigue, being ranked 2nd and 3rd respectively.

According to Walsh et al. (2000), significant symptom distress is experienced in patients with advanced malignancy. The frequency of the most common symptoms included fatigue, nausea (90%); confusion, pain, weight loss, lack of appetite (80%); shortness of breath (50%) and anxiety (25%). Lau et al. (2004) identified the most common ADRs in oncology patients receiving chemotherapeutic agents and assessed the incidence, predictability, preventability and severity. It was noted that constipation was ranked first but this ADR was due to opioid use. Nausea ± vomiting, fatigue, alopecia, drowsiness, myelosuppression, skin reactions, anorexia, mucositis, and diarrhoea ranked 2nd to 10th respectively. The authors found out that 88% of ADRs were predictable, of which 46.1% were probably preventable, because of omission or inadequate/appropriate use of preventative measures. Sharma et al. (2005) reported that although management of ADRs have become the main focus for clinical research and new drugs, CINV, oral mucositis and diarrhoea are still reported and thus clinical researchers must continue improving personalised medicine to further control symptom management.

In 2005, Sun et al. reported about the rankings and symptom assessments of ADRs from CT in patients with ovarian cancer. "Most favourable health states included perfect health, clinical remission and complete control of CINV. Least favourable health states included more severe

CINV health states and death. Patients on first-line CT had less symptom distress, and rated sexual dysfunction, fatigue and memory loss more favourably than patients on second- or third-line CT ($p < 0.05$)." According to Jaehde et al. (2008), chemotherapeutic agents are cytotoxic and damage normal cells to varying degrees while simultaneously acting on malignant cells. The most common side effects of CT include nausea, vomiting, fatigue and myelosuppression, with approximately 50% of these side effects being preventable. Hong et al. (2016) reported that more oncologic patients experienced moderate to severe symptom distress after treatment initiation for 8 to 13 symptoms. The patients completed the Symptom Distress Scale-15 before treatment (T1) and during cancer treatment (T2), and reported up to two most bothersome issues among symptoms rated with moderate-to severe distress. It was reported that impact on sexual activity/interest, pain, fatigue and insomnia were the most prevalent symptoms with moderate-to-severe distress.

The first and most important step to improve management of ADRs is the implementation of evidence-based clinical practice guidelines into practice within a MDT. Dranitsaris et al. (2001) evaluated a six-step pharmacist-driven multifaceted intervention program (dissemination of the guideline, the use of opinion leaders, interactive educational workshops, therapeutic reminders in the form of preprinted orders, pharmacists clinical interventions for the event of inappropriate antiemetic orders, and physician audit and feedback) and concluded that guideline implementation program for high cost agents as 5-hydroxytryptamine receptor antagonists (5-HT_3RAs) antiemetics will result in both positive clinical and economical outcomes.

Rough and Carro (1998) study found out that algorithms for CINV (incorporated the concepts: matching antiemetic therapy with the emetogenic potential of the antineoplastic regimen,

reducing ondansetron dosages, increasing the ratio of oral to intravenous therapy, and treating delayed-onset nausea and vomiting without using serotonin-receptor antagonists) integrated with a preprinted physician order form was cost-reducing. Engstrom et al. (1999) also found out that developing of antiemetic guidelines lead to cost-reduction. A standard antiemetic form was developed incorporating the emetogenic classification of medications and their corresponding antiemetic regimen. Patient satisfaction with the regimen-measured outcomes was assessed through the use of patient diary and visual analogue scale (VAS). These studies envisaged a positive effect of guidelines for antiemetic prophylaxis and therapy on both clinical and economic outcomes (Berard and Mahoney, 1995; Rough and Carro, 1998; Engstrom et al., 1999; Jaehde et al., 2008).

Bero et al. (1998) research was an overview of systematic review of interventions to promote the implementation of research findings. To close the gap between research and practice, the authors highlighted that consistently effective interventions to promote behavioural change among HCPs include; educational outreach visits, reminders (manual or computerised), computerised decision support systems, multifaceted interventions and interactive educational meetings. The pharmacist has a role in supporting and promoting adherence to guidelines to contribute towards the optimal use of treatment, while also controlling unnecessary hospital costs (Dranitsaris et al., 1995; Jaehde et al., 2008; Lin et al., 2015). Physicians prescribed $Can 757 and $Can 1814 worth of ondansetron in the intervention group and in the control group respectively, despite no significant difference.

Lin et al. (2012) studied the impact of step therapy policies requiring the use of an older 5-HT_3RA before palonosetron on risk of CINV associated with hospital or emergency department (ED) admissions. It was concluded that oncologic patients suffering from breast

or lung cancer started and maintained on palonosetron were at significantly lower risk of potentially costly CINV versus those on older 5-HT_3RAs. Implementation of standardised CT order forms containing also supportive care medications is another step forward to a better management of ADRs. Such forms should be published following a multidisciplinary approach. Order forms will help in prescribing a more appropriate antiemetics based on the level of emetogenicity of the antineoplastic administered. This had resulted in a reduction in drug expenditure achieved (Sano et al., 2005).

1.5.4. Compliance

World Health Organization has defined adherence (compliance) in a report entitled Adherence to long-term therapies - evidence for action[17], "as the extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider." Adherence is a multidimensional phenomenon and the five dimensions are shown in Table 1.3 (WHO, 2003).

Table 1.3 The five dimensions of adherence

Social/economic factors	Health care team/ system-related factors	Condition-related factors	Therapy-related factors	Patient-related factors
- Economic status - Cultural beliefs - Illiteracy - Age - Distance from treatment center	- Patient-provider relationship - Education of providers - Capacity of system - Duration of consultations - Medication distribution system	- Severity of symptoms - Level of disability - Rate of progression - Co-morbidities - Availability of effective treatments	- Complexity of regimen - Treatment duration - Changes in treatment - Side effects - Previous treatment failure	- Anxiety about side effects - Patients' motivation - Patients' expectations - Forgetfulness - Patients' knowledge about illness

Adapted from: WHO. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization, 2003

[17] WHO. Adherence to long-term therapies: evidence for action [Internet]. Geneva: World Health Organization, 2003 [cited 2016 Sept 6]. Available from: http://www.who.int/chp/knowledge/publications/adherence_report/en/

Few published studies have focused on adherence to oral anticancer medications, because the majority of CT is delivered intravenously. Adherence to oral anticancer medications is very important in oncology. Oral anticancer medications have become more widely used as an alternative to intravenous therapy. It is crucial that oncologic patients adhere to the prescribed treatment. Several studies evaluated adherence to anticancer medications and found that that adherence is difficult to predict and can vary from 16% and 100% (Partridge et al., 2002; Ruddy et al., 2009; Chandrashekar et al., 2013; Lafeuille et al., 2014; Felton et al., 2016).

In the past 15 years, oral anticancer medications have become more widely available for the treatment of a broad number of cancers and have increasingly been used as an alternative to intravenous therapy (Partridge et al., 2002; Ruddy et al., 2009; Gebbia et al., 2012). Poor compliance to oral anticancer medications will influence negatively clinical outcomes, and lead to increase in costs and number of hospitalisations (Gebbia et al., 2012). Due to the fact that CT has mainly been given intravenously in hospitals, most research focus on adherence to palliative care and supportive medication (Partridge et al., 2002; Jaehde et al., 2008). The rise in availability of oral anticancer medications resulted in patients being more intuitive to optimize medication outcome. With the introduction of oral anticancer medications, patients need to be more motivated and responsible to be compliant to their treatment. This has been the case, but some oncologic patients are not highly motivated leading to endangerment of their therapeutic goals.

In 2013, Verbrugghe et al. review analysed the determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs and found out that they are multifactorial and interrelated. The most predominant factors were older, younger

age and the influence of therapy related side effects. The majority of studies reviewed were about oncologic patients suffering from breast cancer (20), followed by 3 studies about patients with chronic myeloid leukaemia (CML) and another 2 studies include cancer patients in general.

Only few studies have been published investigating the level of adherence of cancer patients. There are various ways to assess adherence. Some authors assessed adherence via different assessment methods. Some studies have shown that the use of assessment methods as the sole basis for the adherence measurement is inadequate. To obtain an optimal measurement of patient adherence, a combination of several methods is suggested (Jaehde et al., 2008). In 2002, Partridge et al. published a review about adherence to therapy with oral antineoplastic agents. Amongst the studies evaluated, one study population was about ovarian cancer. Eleven subjects were receiving altretamine oral therapy, and the adherence measure was medication event monitoring system, MEMS^{TM}. The Overall Compliance (OC), which the authors define "as the number of bottle openings in a monitoring period as a percentage of that number expected on the assumption of perfect compliance", was found to be 97.4% (SD ± 6.9%). Waterhouse et al. (1993) assessed adherence to tamoxifen via the use of patient self-report (SR), pill counts (PCs) and microelectronic adherence monitoring (MEMS^{TM}). It was found out that SR adherence to oral tamoxifen was significantly higher than that suggested by either PC data or by MEMS adherence monitoring. To prove actual intake of the anticancer medication, plasma concentration monitoring is necessary.

In a retrospective study, Nilsson et al. (2006) studied about refill adherence to repeat prescriptions of cancer drugs to ambulatory patients. There was no statistically significant difference between the number of patients underusing for cancer medications (<80% use of

prescribed cancer medications) and that of patients underusing all other medications. It was found out that oncologic patients on oral long-term medications have a non-adherence rate similar to that of patients receiving medications for chronic conditions (Nilsson et al., 2006; Lin et al., 2015). This study highlighted the important role of the clinical pharmacist in educating and counselling oncologic patients and in clarifying misunderstandings or fears that might contribute to drug non-adherence.

Lafeuille et al. (2014) evaluated adherence patterns for abiraterone acetate (AA) and concomitant prednisolone use in patients with prostate cancer. Adherence was measured using the medication possession ratio (MPR), which was calculated as the sum of days of supply divided by the days on therapy in patients with at least 2 AA prescriptions. The mean daily dose was within 1% of the recommended dose and adherence was high with a mean MPR above 90%. Walter et al. (2014) assessed adherence to oral CT capecitabine using different measurement methods. Adherence to capecitabine was evaluated using three assessment methods: self-report, pill count, and use of a microelectronic monitoring system (MEMS) and the overall adherence rates were 99, 100, and 61%, respectively. Adherence to capecitabine was defined as >80% of adherence according to the three methods of measurement. These methods can be used to evaluate adherence to other oral anticancer medications.

There are varieties of interventions that can be used to improve adherence in different disease areas (Osterberg and Blaschke, 2005; Jaehde et al., 2008). Osterberg and Blaschke (2005) review classified these interventions into four general categories; patient education; improved dosing schedules; increased hours when the clinics are open and improved communication between physicians and patients.

Levine et al. (1987) investigated compliance with oral self-administered allopurinol (daily medication) and prednisolone (intermittent medication) assessed through (measured based on) plasma concentrations as well as compliance with monthly scheduled clinic appointments with newly diagnosed haematological malignancy. Control patients were adherent to allopurinol and prednisolone only 16.8% and 26.8% respectively. Patients in the intervention group (combinations of education, home psychological support and restructuring, and training in medication taking) had increased adherence rate of 44-48% for those who received any one of the intervention programs. Control patients were compliant with monthly clinic appointments, an average of 66.4% of the time, whereas intervention patients attended clinic between 84% and 93% of the time. Control patients and intervention patients were compliant with monthly clinic appointments with an average of 66.4% and between 84% and 93% of the time respectively. Cancer patients seem to benefit especially from interventions towards an optimised adherence, resulting in improved outcomes. Health outcome effects for cancer patients were especially noteworthy and reflected improvements in survival and relapse outcomes. Cancer patients also showed improved drug compliance through direct assessment (urine tracers), in self-reported improvements of compliance and in enhanced appointment keeping. The predominant focus of cancer interventions was educational and affective.

The Cochrane Review on intervention for enhancing medication adherence published in 2014, concludes that “There is no evidence that low adherence can be ’cured’. Thus, effective methods to improve adherence must be maintained for as long as the treatment is needed, requiring interventions that can be integrated into the care system in a cost-effective manner.” The most frequently targeted conditions in randomized controlled trial (RCT) were various such as HIV/AIDS, hypertension (HT) and diabetes (Nieuwlaat et al., 2014). Only one

study targeting cancer was included in this review, which was the study by Kato et al. (2008). The authors assessed the effectiveness of a video-game intervention for improving adherence and other behavioural outcomes for adolescents and young adults with malignancies including acute leukaemia, lymphoma, and soft-tissue sarcoma. The video-game intervention significantly improved treatment adherence to both trimethoprim and 6-mercaptopurine, which was assessed through electronic pill-monitoring device and serum metabolite assays respectively, and indicators of cancer-related self-efficacy and knowledge.

Spoelstra et al. (2015) assessed the flexibility of a text messaging intervention to promote self-management for patients prescribed oral anticancer agents. Patients were assigned randomly to the control or intervention group. The intervention group received a daily text message for adherence and a weekly AVR (automated voice response) for symptoms. They were given a toolkit at baseline consisting of a notebook of evidence-based information that disuse common ADRs, management of treatment-associated ADRs and compliance to OA. The control group used weekly AVR assessment tool and the toolkit was given at exit. Both adherence and symptoms improved after the intervention. As expected, the intervention group experienced less symptoms than the control group.

1.6. Drug-related problems classification systems

Basger et al. (2015) reported that more than 20 different types of classification systems for DRPs and their causes are available. Table 1.4 summarizes some of the classification systems for DRPs (van Mil et al., 2004; Adusumilli and Adepu, 2014; Basger et al., 2014; Basger et al., 2015).

In 2015, Basger et al. developed an “aggregated system” for classifying causes of DRPs. A selection of 6 were purposively chosen to represent both well-established (Cipolle et al.,

1998; PCNE version 6.2; Westerlund version 5) and more recently developed systems (DOCUMENT; Norwegian; iMAP). Systems that had been used frequently include Cipolle et al. (1998), PCNE version 5.01, Westerlund and DOCUMENT. The authors added the latest published version of the most commonly used unmodified classification system i.e. Cipolle et al. (2012). There are 3 versions for Cipolle et al. classification; 1998, 2004 and 2012. To date no studies had been identified that implemented the 2012 version. PCNE version 6.2, 7.0 and 8.0 were later published.

Table 1.4 Different types of drug-related problems classification systems

Name of classification system	Source
The ABC of DRPs	Meyboom et al., 2000
ASHP Classification	ASHP, 1996
Cipolle/Morley/Strand Classification	Cipolle et al., 1998, 2004, 2012
DOCUMENT system	Williams et al., 2011
Granada consensus	Grupo de Investigacíon en Aténcion Farmacéutica, 2002
Hanlon Approach	Hanlon et al., 1992, 1997
Hepler/Strand Classification	Hepler and Strand, 1990
Krska et al System	Krska et al., 2002
Individualised medication assessment and planning (iMAP)	Crisp et al., 2011
Mackie Classification	Mackie, 2002
NCC-MERP Taxonomy of medication errors	NCC-MERP, 2017[18]
Norwegian system	Ruths et al., 2007
PAS Coding System	van Mil and Tromp, 1997
PCNE System	PCNE v 1, 2, 3, 4, 5.01, 6.2, 7.0, 8.0
PI-DOC	Schaefer, 1995, 2002
SHB-SEP Classification	SHB-SEP, 2003
Westerlund System	Westerlund, 2002

[18] National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) [Internet]. About medication errors. c1996 [cited 2016 Apr 20]. Available from: www.nccmerp.org/aboutmederrors.htm

Table 1.5 Characteristics of the two drug-related problems classification systems chosen to construct an aggregated system

Name of System and Country of Develop-ment	Method of Development; Other Systems Used in Development	Intended Health Care Setting(s)	Number of Categories Identified as Cause of DRPs	Number of Categories Identified as DRPs	Provision of Clinical Examples; Instructions to Facilitate Application	Type and Result	Interrater Indices Applied by Systems		
							Number of Categories in System Rated	Number of Patients Rated	Number and Type of Raters, and Training in Application of the System
Cipolle et al., 2004, USA	A research group in the United States, as described by Hepler and Strand in 1990[5]	Multiple	33 Categories	7 Categories	Limited examples; instructions in chapter	Interrater agreement of 72.3%	7 Categories	300 Patient records	4 Panelists; training unstated
Cipolle et al., 2012, USA	A research group in the United States, as described by Hepler and Strand in 1990[5]	Multiple	37 Categories	7 Categories (per 2004 version)	Limited example; instructions in chapter	—	—	—	—
PCNE version 6.2 system, Europe	Constructed during working conferences beginning in 1999, resulting in the current (6th) version	Multiple	8 Categories, 35 sub-categories	4 Categories, 11 sub-categories		—	—	—	—

Adapted from: Basger B, Moles R, Chen T. Development of an aggregated system for classifying causes of drug-related problems. Ann Pharmacother. 2015;49(4):405-18.

A comparison of Cipolle et al., 2004 and 2012 and PCNE v6.2 DRP classification systems

Basger et al. (2015) defined an unmodified classification system as "one cited and used by others in its originally developed form i.e. not developed for use by a particular study." Unmodified as well as modified classification systems had been reported in various health care settings (Table 1.6).

Table 1.6 Studies applying one of the two chosen classification systems in unmodified or modified form

Classification System	Unmodified	Modified
System of Cipolle et al., 1998 and 2004, USA. Both versions were identical	- ***Community pharmacy patients*** (Wermeille et al., 2004; Ross and Bloodworth, 2012) - ***Hospital inpatients*** (Gillespie et al., 2009; Mekonnen et al., 2013), - ***Home medicines review patients*** (Strand et al., 2004), - ***Medicine or outpatient clinics*** (Isetts et al., 2003; Westberg and Sorensen, 2005; Nicholas et al., 2007; Isetts et al., 2008; Harris et al., 2009; Ramalho de Oliveira et al., 2010; de Sa Borges et al., 2010; Hall and Pater, 2011; Harrison et al., 2012; Stratton et al., 2012; Milos et al., 2013), - ***Hospital inpatients and medicine clinic patients*** (Isetts et al., 2012)	- ***Aged care facilities*** (Ruths et al., 2003; Finkers et al., 2007; Stuijt et al., 2008; Nishtala et al., 2011), - ***Community pharmacy patients*** (Barnett et al., 2009; Young et al., 2012; Leendertse et al., 2013), - ***Discharge from hospital*** (Naunton and Peterson, 2003), - ***Hospital inpatients*** (Samoy et al., 2006; Christensen et al., 2011; Bondesson et al., 2012; Bondesson et al., 2013; Zaal et al., 2013), - ***Home medicines review patients*** (Gilbert et al., 2002; Triller et al., 2003; Roughead et al., 2004; Gisev et al., 2010; Castelino et al., 2011), - ***Medicine or outpatient clinics*** (Villa et al., 2009; Smith et al., 2011), - ***Multiple health care settings*** (Rao et al., 2007)
System of Cipolle et al., 2012, USA	No studies identified	No studies identified
PCNE version 6.2 system, Europe	- ***Community pharmacy*** (Leikola et al., 2012), - ***Emergency departments*** (Nickel et al., 2013; Rashed et al., 2013), - ***Hospital inpatients*** (Mannheimer et al., 2006; Lampert et al., 2008; Taegtmeyer et al., 2011; Rashed et al., 2012; Taegtmeyer et al., 2012), - ***Community and medicine clinics*** (Touchette et al., 2012)	- ***Community research program*** (van Roozendaal and Krass, 2009), - ***Community pharmacy*** (Hatah et al., 2014), - ***Discharge from hospital*** (Bladh et al., 2011; Ahmad et al., 2012), - ***Hospital inpatients*** (Zaman Huri and Fun Wee, 2013), - ***Medicine or outpatient clinics*** (Hooper et al., 2009; Chan et al., 2012; Chan et al., 2014), - ***Mixed health care settings*** (Eichenberger et al., 2010; Granas et al., 2010)

Studies applying one of the two chosen systems in unmodified or modified form in various health care setting(s)

A universally accepted system to classify DRPs has not yet been adopted, despite significant developmental work, as well as frequent use of some systems. For this research study, the researcher chose to modify and aggregate two classification systems; one from the USA, 2004 version of Cipolle et al. and the classification system from Europe - PCNE version 6.2. Both these classifications are intended for multiple health care settings.

In Cipolle et al. classification, commonly referred to as the Strand classification, since Strand et al. published done version in 1999; the term "drug-therapy problem" has replaced the term "drug-related problem." Drug-therapy problem refers to a system approach and also reflects patient's perspective and includes issues in the whole drug therapy chain. Community pharmacies in the US tend to use more this classification rather than others, in their day to day pharmaceutical care plan. This classification do not include potential DRPs and thus, it can only be implemented once the event had taken place (van Mil et al., 2004; Adusumilli and Adepu, 2014). According to Cipolle et al. classification, a DRP is "any undesirable event experienced by the patient that involves or is suspected to involve drug therapy and that actually or potentially interferes with a desired patient outcome." In this classification, the DRPs were classified as follows:

i. Need for additional therapy
ii. Unnecessary therapy
iii. Wrong drug
iv. Dosage is too low
v. Adverse drug reaction
vi. Dose is too high
vii. Compliance

The PCNE DRP classification is hierarchically structured and comprises of separate codes for "problems, causes and interventions" (PCNE, 2010). This classification originated from a working conference of the PCNE, with the aim to develop a standardised classification system which could be used internationally. The first version was validated and used in a Portuguese study amongst others. This version was later replaced with version 2 (van Mil et al., 2004). By 2002, version 3 was available on the Internet. In this version, the problem categories were brought in line with PI-Doc and the first Granada Consensus. A year later, in 2003, version 4 was published, which was also available online. Version 4 was implemented in countries such as Portugal, Northern Ireland and Malta. Version 5.01 followed in 2006, where an extra cause, "C4.10 Patient takes food that interacts with drugs" and an extra Outcome "O0.0 Outcome not known" were added. Version 6.2 was published in 2010 and available online. The latest version of the classification is version 7.0 and published in 2016 (PCNE, 2016). Lastly, PCNE version 8.0 was published in April 2017.

According to PCNE classification, a DRP is "a drug related problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes." In this classification, the DRPs were classified as follows:

i. Drug selection
ii. Drug form
iii. Dose selection
iv. Treatment duration
v. Drug use/administration process
vi. Logistics
vii. Patient
viii. Other

1.7. Aim

The aim of this research was to develop a pharmaceutical personalised approach through the design and implementation of a pharmaceutical care plan (PCP) incorporating tumour markers for patients suffering from ovarian, pancreatic and prostate cancer.

Chapter 2

Methodology

2.1. Literature search

An extensive literature search using different databases such as PubMed and Medline was conducted to locate literature detailing the current status on documenting oncology pharmaceutical care. The main search terms used were tumour markers, oncology medications, solid tumours, pharmaceutical care issues, DRPs, drug-therapy problems, medicine-related problems, pharmaceutical care, pharmaceutical care plan, pharmacists, oncology pharmacists, clinical pharmacists, clinical oncology pharmacist, clinical pharmacy, interventions and MDT.

To date, no current studies have been carried out locally about PCIs in the oncology area. There have been studies in other areas such as the one carried out by Dr Louise Grech (2015) in the rheumatology area.

A number of guidelines on the appropriate use of serum tumour markers in the management of oncology patients are published. Recently published guidelines relating to the use of tumour markers in various cancers from various organizations, such as the Association for Clinical Biochemistry and Laboratory Medicine (ACB)[19,20], the Association of Clinical Biochemists in Ireland (ACBI), ASCO[21], European Group on Tumour Markers (EGTM), European Society for Medical Oncology® Oncology Clinical Practice Guidelines (ESMO Guidelines®), NACB, NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), the

[19] abc.org [Internet]. The Association for Clinical Biochemistry and Laboratory Medicine; c2017 [cited 2016 Nov 2]. Available from: http://www.acb.org.uk/.
[20] abc.org [Internet]. The Association for Clinical Biochemistry and Laboratory Medicine. Recommendations as a result of the ACB national audit on tumour marker service provision; 2013 [cited 2016 May 7]. Available from: http://www.acb.org.uk/docs/default-source/guidelines/tumour-marker-guidelines.pdf?sfvrsn=4
[21] asco.org [Internet]. American Society of Clinical Oncology. ASCO Practice Guidelines; c2017 [cited 2016 Nov 7]. Available from: https://www.asco.org/practice-guidelines/quality-guidelines/guidelines.

National Institute for Health and Care Excellence (NICE), Pan Birmingham Cancer Network (PBCN)[22] and the Scottish Intercollegiate Guidelines (SIGN)[23] were reviewed.

Similar guidelines and protocols from NHS Trusts such as Royal Surrey Country Hospital[24] were also reviewed. Guidelines are key tools to promote best practice with local ownership. Guidelines, recommendations and standards of care for the management of ovarian, pancreatic and prostate cancer were reviewed. Appropriate requesting of tests is likely to be improved if communication between clinical and laboratory staff is more effective.

2.2. Study design

This study was conducted to identify PCIs encountered by oncologic patients suffering from ovarian, pancreatic or prostate cancer, whilst monitoring serial tumour marker results. Patients considered for this study were oncologic patients receiving any anticancer medications. The inclusion and exclusion criteria are reported in section 2.3.

The researcher designed, developed and implemented a PCP. Face-to face interviews and MR were conducted. The patient's medical files were reviewed for medical and drug history (DH), family history and previous cancer treatments. Blood results, including tumour marker results were noted from the start of the study to the end of their treatment. Information collected was recorded on the PCP. The researcher counselled the patients on their treatment, identified and resolved PCIs. Follow-up consultations were conducted with the patients throughout their course of treatment or until the end of the study i.e. December 2016 if their

[22] PBCN. Gynaecological cancer, upper gastro-intestinal cancer, urological cancer [Internet]. Birmingham: Pan Birmingham Cancer Network clinical guidelines; 2017 [cited 2016 Jan 12]. Available from: https://www.uhb.nhs.uk/pan-birmingham-cancer-network-clinical-guidelines.htm

[23] SIGN. Management of epithelial ovarian cancer [Internet]. Edinburgh: Scottish Intercollegiate Guidelines Network; 2013 [cited 2016 Jan 12]. Available from: http://www.sign.ac.uk/guidelines/fulltext/135/index.html

[24] stlukescanceralliance.co.uk [Internet]. St Luke's Cancer Alliance. Chemotherapy Policies and Protocols. [cited 2016 Jan 12]. Available from: http://stlukescanceralliance.co.uk/

treatment had not yet been completed. Throughout the study, the patient could have either finished the treatment and did not require starting new treatment since the condition was stable, had a change in treatment since the condition had progressed, discontinued treatment since she/he was not fit for continuation of treatment or the patient may had deceased. For the purpose of this study, pre- and post-treatment tumour marker results analysis were studied by dividing the oncologic patients into three categories; finished treatment, switched treatment or not finished.

The researcher noted that patients might either have had postponement in the appointment either due to bone marrow suppression, such as febrile neutropenia, leukopenia, or thrombocytopenia or due to other reasons and cycle interval varies between different treatments. In view of this, tumour marker results were referred to as tumour marker test 1 denoting the pre-treatment tumour marker test, and the others listed course collectively. Pre-treatment tumour marker test was defined as the tumour marker taken nearest to the start of the treatment. Post-treatment tumour marker result was defined as the tumour marker post-finishing treatment. If treatment was not yet finished, post-treatment tumour marker was defined as the one taken in December since the study had finished in December 2016. If treatment was switched to an alternative treatment, post-treatment tumour marker result was defined as the one after finishing the treatment i.e. before starting the new treatment. Monitoring tumour marker trends was conducted for all treatments.

2.3. Study population

To obtain a homogenous study population, inclusion and exclusion criteria were defined (Table 2.1). Eligible patients suffering from at least one of the following primary solid tumour cancers; ovarian, pancreatic or prostate cancer, were invited to participate in the research. A

main criterion of inclusion was that the patients were currently managed on at least one oncology medication. No selected systemic therapies were included. For the study, patients had to be at least 18 years of age, able to understand Maltese or English language, and to be mentally healthy. The patients were assured that anonymity would be maintained and that a refusal to participate would not in any way affect the quality of their care.

Table 2.1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criterion
- Suffering from at least one of the following solid tumour cancers; ovarian, pancreatic or prostate cancer - Managed on at least one oncology medication - Age at least 18 years of age - Ability to understand and speak either Maltese or English language - Mentally healthy - Written informed consent	- Did not provide written consent

Rationale for the inclusion criteria

- **Selection of solid tumour cancers**

There are various types of solid tumours (Gavhane et al., 2011). Ovarian, pancreatic and prostate cancer were selected for this research study, since their respective humoral tumour markers are available locally and there is a good number of patients. As per international guidelines, the tumour markers CA 125, CA 19-9 and PSA are the tumour markers recommended in the monitoring of patients undertaking oncology medications for ovarian, pancreatic and prostate cancer respectively. Serial measurement is a useful marker to assess the response to oncology medications.

- **Selection of oncology medications**

This study recruited oncologic patients receiving at least one antineoplastic therapy. No predefined cancer medications were included in the study. Since the number of patients suffering from the above solid tumours is already small within the study time frame, receiving at least one antineoplastic medication would help to recruit the maximum number of oncologic patients possible.

- **Language selection**

Malta is a bilingual island and has two official languages: Maltese and English. Maltese is also the national language. Both the study information sheet and consent form were compiled in both Maltese and English language. It was an essence that the patients could understand Maltese or English language.

- **Research subjects**

As per Guidelines for the University of Malta Research Ethics Committee (UREC), the patient selection eliminated the following categories:

- **Under the age of 18:** In Malta, the age of 18 is the legal age for consent to treatments in the research study. Thus, in this study, patients who have not attained the legal age were eliminated from the selection criteria.
- **Mentally disabled persons:** In this study, mentally disabled patients could not be included in patient selection.

Patients who fulfilled the inclusion criteria were given a study information sheet in either Maltese or English according to preference (Appendix A). The study information preceding the interview informed the patients about the content of the study. Patients agreeing to participate were asked to sign a consent form (Appendix B).

Approval from the participating clinicians, the Clinical Chairperson of the Department of Haemato-Oncology at Sir Anthony Mamo Oncology Centre, the Data Protection Officer at Mater Dei Hospital/ Sir Anthony Mamo Oncology Centre and the Chief Executive Officer at Mater Dei Hospital/ Sir Anthony Mamo were sought. Ethics approval from the UREC was obtained (Appendix C).

This study population should represent the whole population within the study period. SAMOC day care ward days schedule are usually planned for specific treatments. Such an example is that on Thursdays usually the patients receiving gemcitabine treatment are being admitted irrespective of the indication. Gemcitabine treatment duration is long and is usually approximately six months. During the short study period, few new cases or old cases that had a relapse were identified. Many patients would have an appointment from week to week depending on their treatment schedule depending on the protocol followed.

2.4. Pharmaceutical care for patients with ovarian, pancreatic and prostate cancer

The researcher designed a PCP by incorporating the data fields and PCIs. The PCP was validated by a focus group consisting of one oncology consultant, one clinical pharmacist, three pharmacists and two doctors. The PCP is a data collection tool incorporating the trends in the tumour markers carried out at specific intervals as per recommended interval by the clinician and evidence-based guidelines.

The developed 4-page PCP (Appendix D), was designed to include the modified classification system for PCIs. It consisted mainly of two main sections; Section A (2 pages) and Section B (2 pages). Section A included patient's details, social history, family history (FH), diagnosis, past medical history (PMH), current medications, including non-oncologic medications, and

relevant laboratory investigations, including tumour marker results. Section B included individualised PCIs identified for each patient categorised as per classification developed.

Patient's details

These include the patient's surname, name, patient reference number (i.e. identity card number), contact number, date of birth, age (age at study completion), consultant, ward, gender, ethnic origin, marital status, current living situation, family history of cancer. Smoking status was divided into 4 categories; past history, none, 0-1 pack/day and >1 pack/day. In Malta, cigarette packets contain a minimum of 20 cigarettes. Caffeine consumption was divided into 4 categories; past history, none, 1-2 beverages per day and >2 beverages per day. Caffeine containing products include coffee, tea and soft drinks such as coke amongst others. Alcohol consumption was also divided into 4 categories; past history, none, <2 units per week, between 2 to 6 units per week and more than 6 units per week.

Level of education was divided into 7 categories; pre-primary, primary, special schools, secondary, post-secondary general, post-secondary vocational, tertiary and other. For the purpose of this research study, special schools were eliminated since patients who are not mentally fit were not eligible for inclusion into the study. Post-secondary general refers to the post-compulsory academic stream of education and covers Junior College, Sir M.A. Refalo Higher Secondary, Giovanni Curmi Higher Secondary and church and independent post-secondary general schools. Post-secondary vocational education refers to state-led institutions, namely the Institute of Tourism Studies (ITS) and the Malta College of Arts, Science and Technology (MCAST). Tertiary education in Malta is provided by the University of Malta. Occupation was divided into 8 categories including housewife, worker, employee,

self-employed, public servant, pensioner, craftsman, and other. Other category also included students.

Diagnosis

Includes cancer type/location/histologic subtype; diagnosis date, tumour size, lymph nodes, metastatic, stage (I – IV) and other information about the cancer if applicable. Ovarian cancer staging was based on the tumour-node-metastasis (TNM) and International Federation of Gynaecology and Obstetrics (FIGO) classification (Helm et al., 2016). Pancreatic and prostate cancer staging were based on the TNM classification and the anatomic stages/prognostic groups (Dragovich et al., 2015; Ghavamian et al., 2015).

Relevant Medical History

This section includes a table compiling the approximate date and problem description. Problem descriptions include hypertension, diabetes, hypercholesterolaemia, asthma, chronic obstructive pulmonary disease (COPD), thyroid problems, cardiovascular problems such as ischaemic heart disease (IHD), stroke and congestive heart failure (CHF), bowel problems, renal problems, epilepsy, psychiatric problems, issues with mobility, deep vein thrombosis (DVT) and dementia. Known drug sensitivities are included in this section.

Current medications

This table compiles a list of current medications including the dose (usually in mg), the dosage form, frequency of administration, route, the start date and stop date if applicable. It consists of a row entitled 'ADRs from medications and any medications that the patient takes without prescription i.e. over the counter (OTC) medications such as herbals and vitamins.

Previous treatment(s) for cancer

This includes both systemic therapy (such as CT, hormonal therapy and other) and radiotherapy. The name of the treatment, the date when treatment was prescribed, the number of cycles and the patient's response was documented. Other treatments (such as surgery) were also included in this section.

Antineoplastic medications

There are various antineoplastic regimens that are indicated for ovarian, pancreatic and prostate cancer.

In ovarian cancer, locally frequently prescribed treatments include;

- carboplatin-based chemotherapy - carboplatin and paclitaxel, carboplatin and pegylated liposomal doxorubicin, carboplatin as monotherapy
- non-platinum-based chemotherapy - pegylated liposomal doxorubicin, gemcitabine, topotecan, or
- a combination of chemotherapy and monoclonal antibody such as carboplatin and paclitaxel and bevacizumab

In pancreatic cancer, locally frequently prescribed treatments include;

- Folfirinox i.e. calcium folinate (folinic acid), fluorouracil (5-FU), irinotecan, oxaliplatin
- Gemcitabine
- Combination treatment - GemCap regimen i.e. gemcitabine and capecitabine; GTX regimen i.e. gemcitabine, docetaxel and capecitabine; 5FU/FA i.e. 5-fluorouracil and folinic acid

In prostate cancer, locally frequently prescribed treatments include;

- Docetaxel

- Vinorelbine
- Oral treatment - cyclophosphamide, abiraterone acetate, enzalutamide
- Goserelin acetate 10.8mg injection (Zoladex® LA)

For CT regimens, it is important to keep a precise record of cycle number especially in cases of complex CT regimens and the dates of cycles. Height (in cm) and weight (in kg) are taken prior to each CT cycle to calculate the BSA which is required to determine the dose. In some cases, dose reduction is also required especially in cases of renal or liver impairment or due to presence of ADRs, including both haematological and non-haematological toxicities.

Monitoring

In Malta, blood tests are analysed at the Pathology Department at Mater Dei Hospital Laboratories[25]. The Pathology Department offers the full range of services that are generally required by the clinician. The Department's test list consists of about 600 different tests as well as a large number of specialized tests that are subcontracted to the overseas supplier. The complete test menu consists of about 1700 tests. Most tests take only a few days to be carried out but some require a longer time to process. Testing of an urgent nature is carried out 24x7.

Key laboratory investigations included in the PCP were;-

- Full Blood Count (FBC) - the most important parameters are the following; white blood cell count (WBC), neutrophils (Neut), haemoglobin (Hb) and platelets (PLT).

[25] heath.gov.mt [Internet]. Government of Malta: Pathology Department; c2016 [cited 2017 Feb 7]. Available from: https://health.gov.mt/en/MDH/Pages/MDH-Pathology-Department.aspx

- Liver Function Tests (LFT's) - consists of serum parameters mainly of alkaline phosphatase (AlkP), alanine aminotransferase (ALT), gamma gutamyl transferase (GGT) and bilirubin.
- Urea and Electrolytes (U&E's) - consists of chloride (Cl), creatinine (Creat), potassium (K), sodium (Na), urea and estimated glomerular filtration rate (eGFR).
- Tumour markers - this section of the lab investigations is of utmost important. Figure 2.1 is an extract taken from page 2 showing a section of the monitoring parameters. Tumour marker tests analysed locally are the following; AFP, CA 125, CA 19-9, CEA, HCG, LDH and PSA. For research purpose, CA 125, CA 19-9 and PSA have been studied. Tumour marker tests are monitored serially as per advised by evidence-based clinical guidelines and protocols. Reference ranges are updated from time to time and the clinical pharmacist carries the responsibility to keep up to date.

MONITORING											
Test			Range	Dates							
Tumour markers (serum)	AFP	alphafetoprotein	0-6.64 IU/mL								
	CA 125	cancer antigen 125	0-30.2 U/mL								
	CA 19-9	cancer antigen 19-9	0-33 U/mL								
	CEA	carcinoembryonic antigen	0-2.5 ng/mL								
	HCG	human chorionic gonadotrophin	0-2.7 mIU/mL								
	LDH	lactate dehydrogenase	135-220 U/l								
	PSA	prostate specific antigen	0-4 ng/mL								

Figure 2.1 Monitoring parameters

Others

This section can include other laboratory investigations such as thyroid function tests (TFTs) including thyroid stimulating hormone (TSH) and free thyroxine (T_4); blood glucose such as glucose-fasting (plasma); calcium (serum), magnesium (serum) and phosphate (serum).

Clinical monitoring abnormality

Any abnormal values of the relevant laboratory investigations and the dates they were taken were recorded. This will allow trends to be observed through treatment changes.

The PCP template categorises individualised PCIs identified for each patient subsequently screened. These classifications were amended and adapted to accommodate local service requirements. These care issues are further classified according to the newly developed classification of the drug therapy problems designed specifically by the researcher. Tumour marker results were included within the newly designed PCP template for cancer patients. This study examined classification of PCIs by modifying and aggregating Cipolle et al. (2004) and PCNE v.6.2. The first seven PCIs represent those articulated by Cipolle et al. (2004) and PCNE v.6.2. The last three PCIs were created specifically for this study to include a wider range of PCIs encountered in this study. These include counselling needs, monitoring needs and seamless care needs. In this research, the term PCIs was used instead of DRPs. The reason being is that PCIs cover a wider spectrum of care issues. Another reason is that pharmaceutical care was provided directly to the patient by a pharmacist.

PCIs have been classified into 11 categories as followed:

1. Additional medication needs
2. Unnecessary medication use
3. Dose is too high
4. Dose is too low
5. Inappropriate compliance and failure to receive medicines appropriately
6. Adverse drug reactions (ADR's)
7. Interactions
8. Counselling needs
9. Monitoring needs
10. Seamless care needs

11. Other

The PCIs were identified from the routine monitoring in the patients individualised care plan. The date was recorded in the "Date" column. The number corresponding to the identified PCI was recorded in the "Pharmaceutical Care Issue (PCI)" column. The action taken by the pharmacist was documented in the "Action" column, while the output was noted in the column "Output."

Figure 2.2 is an extract taken from page 4 showing the section where individualised care issues and the pharmacist's actions are documented.

INDIVIDUALISED CARE ISSUES			
Date	Pharmaceutical Care Issue (PCI)	Action	Output

Figure 2.2 Individualised care issues

2.5. Study setting

In Malta, only one oncology centre within the public health system Sir Anthony Mamo Oncology Centre (SAMOC) exists. SAMOC building commenced in 2012. The migration of patients and services from Sir Paul Boffa Hospital in Floriana, which was the first oncology hospital in Malta to SAMOC was completed by September 2015. Beds at the new hospital were increased from the 78 at Sir Paul Boffa Hospital to 113, the outpatient clinics from two to twelve and palliative care beds were increased from the 10 at Sir Paul Boffa Hospital to 16 at SAMOC[26]. SAMOC is a three-levelled centre. Level 1 consists of oncology outpatients, adult

[26] timesofmalta.com [Internet]. Oncology Hospital welcomes first patients. Malta: Times of Malta; c2017 [cited 2017 Jan 2]. Available from: http://www.timesofmalta.com/articles/view/20141222/local/updated-oncology-hospital-welcomes-first-patients.549300

oncology ward 1 and 2, radioisotope unit, administration and cafeteria. Level 0 consists of day care unit, haematology unit, palliative care unit, phlembotomy, pharmacy, chapel and main reception. Level -1 consists of radiotherapy department, paediatric/adolescent ward, theatre and clinical support unit (occupational therapy, physiotherapy, social work service, psychological services)[27]. Patients were recruited from the oncology day care unit, adult oncology ward 1 which provides care to female patients and ward 2 which provides care to male patients (inpatients) in SAMOC. The developed PCP was implemented at SAMOC and the study period took a duration of five months.

2.6. Data analysis

All data collected was analysed using the IBM Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA version 24). Descriptive statistics were obtained for all data. Sample means and standard deviations (SDs) were presented for continuous variables, while frequencies and percentages were calculated for categorical variables. Statistical significance was determined using chi-square (χ^2) tests for categorical variables. The one-way ANOVA test was used to compare the mean number of current medications, previous treatments and current oncology treatments with the three cancer types. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the normality assumption of the tumour marker scores, followed by Wilcoxon signed-rank test or one-tailed paired sample t-test depending on the p-value generated. Graphical representation of tumour marker results monitoring were performed using Microsoft Excel 2013.

[27] health.gov.mt [Internet]. Sir Anthony Mamo Oncology Centre. Malta: Government of Malta; c2016 [cited 2017 Jan 2]. Available from: https://health.gov.mt/en/SAMOC/Pages/default.aspx

Chapter 3

Results

3.1. Patient characteristics

A total of 67 patients (35 male, 32 female) were enrolled in this study. The mean age was 65 ± 10.4 years (range: 26-83 years). Oncologic patients suffering from ovarian, pancreatic and prostate cancer were 19, 27 and 21 respectively.

Categorical variables such as gender, age, marital status, ethnic origin, current living situation, family history of cancer, smoking status, caffeine consumption, alcohol consumption, level of education and occupation were correlated with cancer type.

Table 3.1 gives a detailed background to epidemiological data and lifestyle characteristics for the patients included in this study.

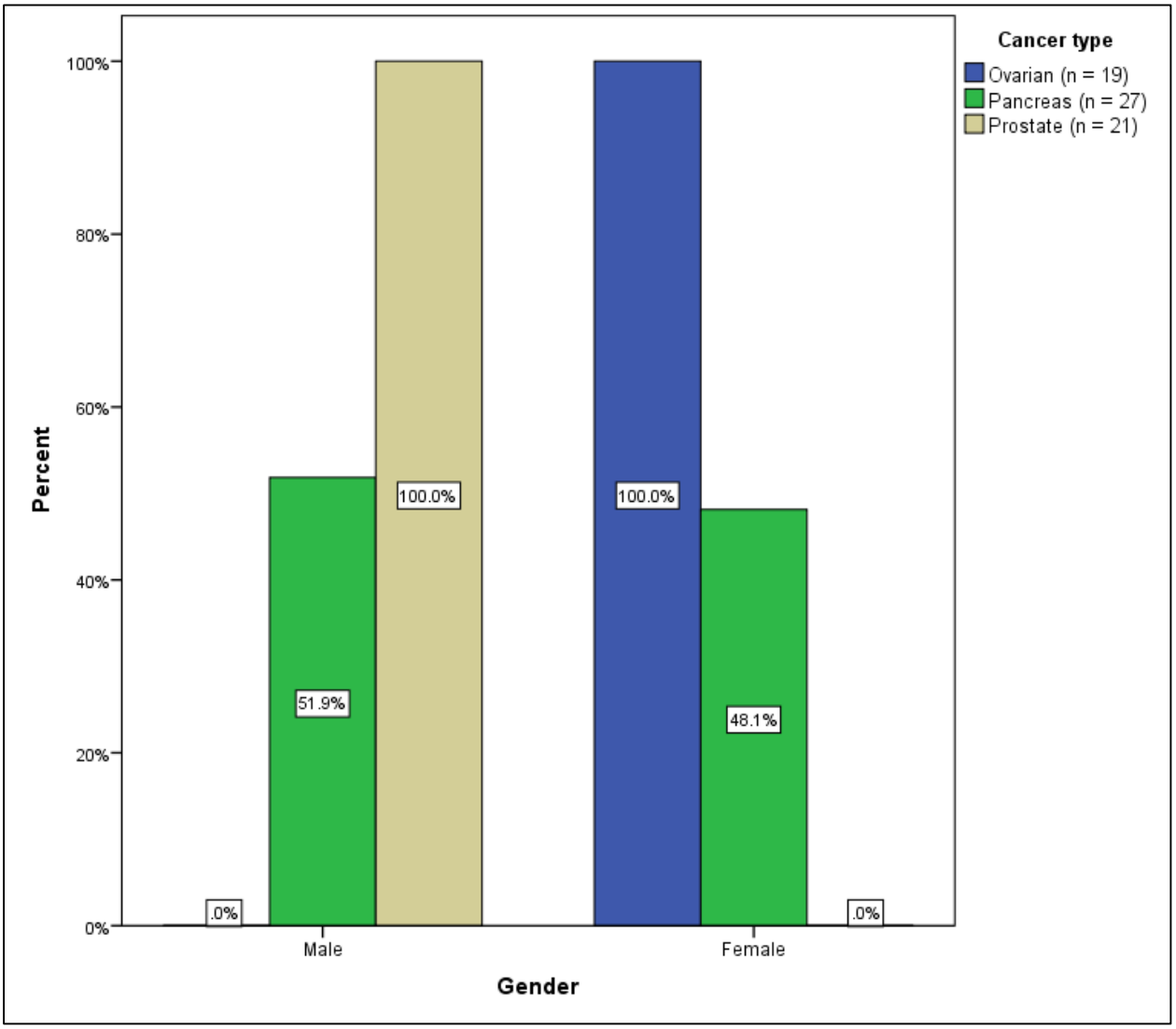
Table 3.1 Patient characteristics (N = 67)

Characteristic	Ovarian n = 19 n (%)	Pancreas n = 27 n (%)	Prostate n = 21 n (%)	Total N = 67	X^2	P value
Gender						
Male	NA*	14 (51.9)	21(100)	35 (52.2)	39.983	**< 0.001**
Female	19 (100)	13 (48.1)	NA*	32 (47.8)		
Age (years)						
< 46	2 (10.5)	0 (0)	0 (0)	2 (3.0)	23.324	**0.003**
46-55	6 (31.6)	6 (22.2)	1 (4.8)	13 (19.4)		
56-65	3 (15.8)	8 (29.6)	1 (4.8)	12 (17.9)		
66-75	8 (42.1)	10 (37.0)	11 (52.4)	29 (43.3)		
76-85	0 (0)	3 (11.1)	8 (38.1)	11 (16.4)		
Mean age ± SD (range) (years)		65 ± 10.4 (26-83)				
Marital status						
Single	2 (10.5)	4 (14.8)	1 (4.8)	7 (10.4)	8.035	0.236
Widow	2 (10.5)	1 (3.7)	3 (14.3)	6 (9.0)		
Married/partner	13 (68.4)	22 (81.5)	17 (81.0)	52 (77.6)		
Separated/divorced	2 (10.5)	0 (0)	0 (0)	2 (3.0)		
Ethnic origin						
Maltese	19 (100)	27 (100)	20 (95.2)	66 (98.5)	2.224	0.329
Other	0 (0)	0 (0)	1 (4.8)	1 (1.5)		
Current living situation						
Living with family/partner	14 (73.7)	24 (88.9)	17 (81.0)	55 (82.1)	4.164	0.384
Living alone	5 (26.3)	3 (11.1)	3 (14.3)	11 (16.4)		
Other	0 (0)	0 (0)	1 (4.8)	1 (1.5)		
Family history						
Yes	11 (57.9)	19 (70.4)	15 (71.4)	45 (67.2)	1.039	0.595
No	8 (42.1)	8 (29.6)	6 (28.6)	22 (32.8)		
Smoking status						
Past history	4 (21.1)	8 (29.6)	11 (52.4)	23 (34.3)	6.562	0.161
None	14 (73.7)	15 (55.6)	9 (42.9)	38 (56.7)		
0-1 pack/day	1 (5.3)	4 (14.8)	1 (4.8)	6 (9.0)		
>1 pack/day	0 (0)	0 (0)	0 (0)	0 (0)		
Caffeine consumption						
Past history	1 (5.3)	2 (7.4)	0 (0)	3 (4.5)	10.969	0.089
None	3 (15.8)	3 (11.1)	0 (0)	6 (9.0)		
1-2 beverages/day	11 (57.9)	13 (48.1)	19 (90.5)	43 (64.2)		
>2 beverages/day	4 (21.1)	9 (33.3)	2 (9.5)	15 (22.4)		
Alcohol consumption						
Past history	1 (5.3)	9 (33.3)	2 (9.5)	12 (17.9)	8.261	0.082
None	14 (73.7	16 (59.3)	16 (76.2)	46 (68.7)		
<2 U/week	4 (21.1)	2 (7.4)	3 (14.3)	9 (13.4)		
2-6 U/week	0 (0)	0 (0)	0 (0)	0 (0)		
>6 U/week	0 (0)	0 (0)	0 (0)	0 (0)		
Level of education						
Pre-Primary	0 (0)	1(3.7)	5 (23.8)	6 (9.0)	17.302	0.068
Primary	5 (26.3)	6 (22.2)	8 (38.1)	19 (28.4)		
Secondary	12 (63.2)	18 (66.7)	6 (28.6)	36 (53.7)		
Post-secondary	0 (0)	0 (0)	1 (4.8)	1 (1.5)		
Vocational	1 (5.3)	0 (0)	0 (0)	1 (1.5)		
Tertiary	1 (5.3)	2 (7.4)	1 (4.8)	4 (6.0)		
Other	0 (0)	0 (0)	0 (0)	0 (0)		
Occupation						
Housewife	5 (26.3)	3 (11.1)	0 (0)	8 (11.9)	13.493	0.096
Worker	0 (0)	0 (0)	0 (0)	0 (0)		
Employee	4 (21.1)	4 (14.8)	1 (4.8)	9 (13.4)		
Self-employed	0 (0)	0 (0)	0 (0)	0 (0)		
Public servant	0 (0)	1 (3.7)	0 (0)	1 (1.5)		
Pensioner	10 (52.6)	18 (66.7)	20 (95.2)	48 (71.6)		
Craftsman	0 (0)	0 (0)	0 (0)	0 (0)		
Other	0 (0)	1 (3.7)	0 (0)	1 (1.5)		

*Not applicable

3.1.1. Gender

The patients enrolled in the study consisted of 35 (52.2%) male and 32 (47.8%) female, amongst which, 19 had ovarian cancer, 14 male and 13 female had pancreatic cancer, while 21 had prostatic cancer. A significant association between gender and cancer type was observed ($p < 0.001$).

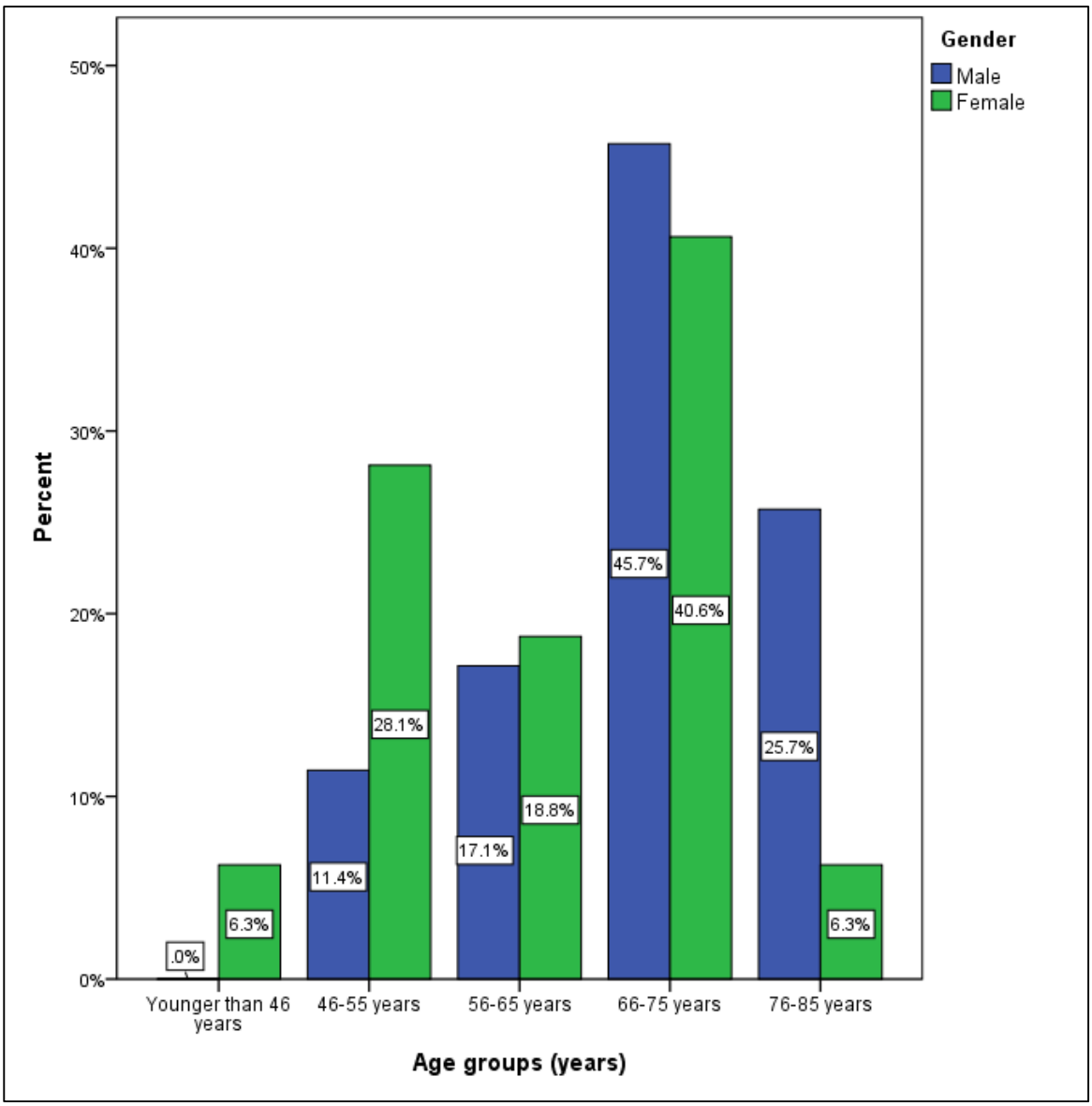


$X^2(2) = 39.983$, **$p < 0.001$**

Figure 3.1 Percentage of patients grouped by gender and cancer type (N = 67)

3.1.2. Age

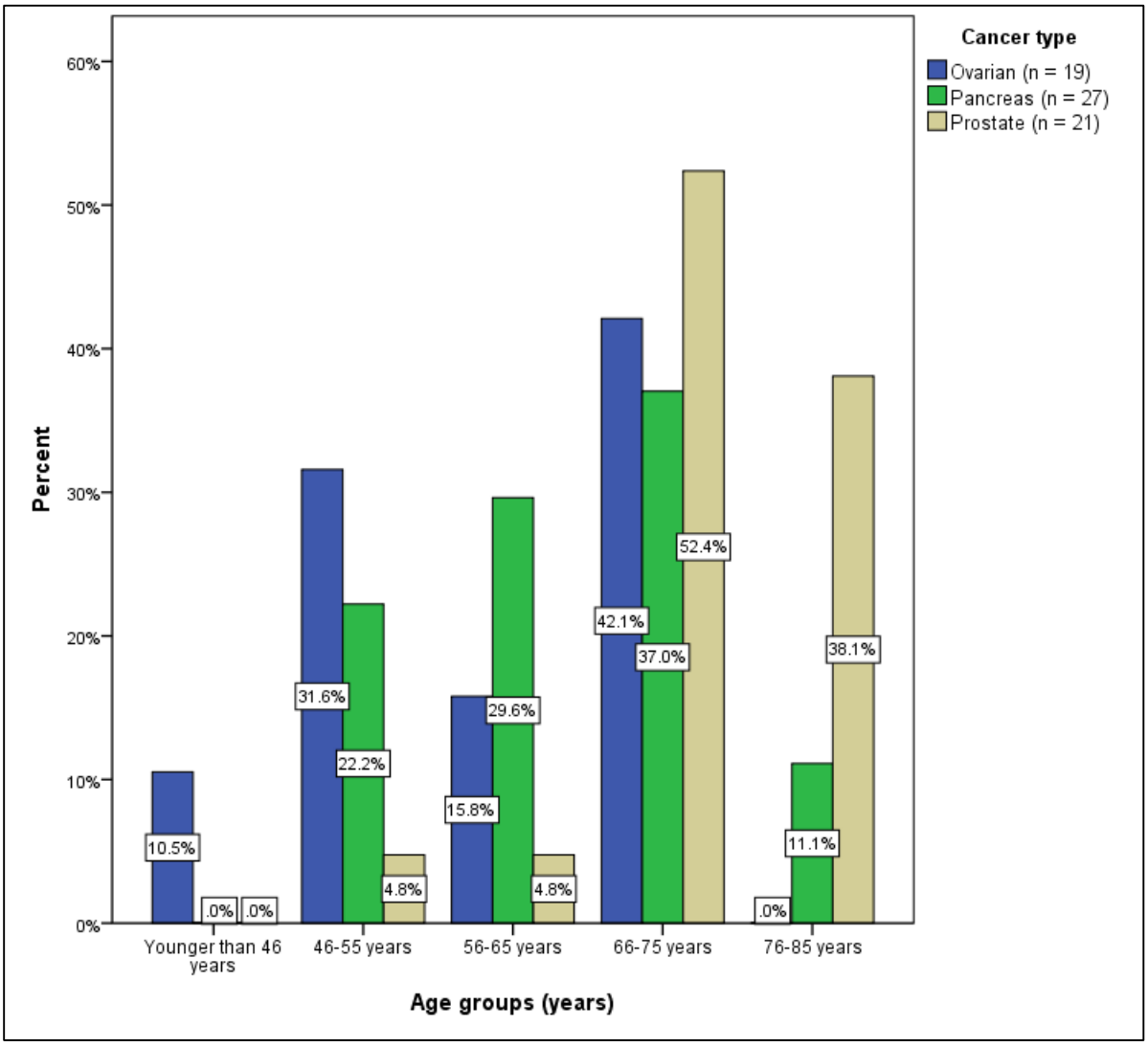
The mean age of the patient population was 65 ± 10.4 years, ranging from 26 to 83 years, representing a patient suffering from ovarian cancer and prostate cancer respectively. There is a larger percentage of males aged 66 years or more compared to females. Conversely, there is a larger percentage of females aged 65 years or less compared to males.



$X^2(4) = 8.571$, $p = 0.073$

Figure 3.2 Percentage of patients grouped by age groups and gender (N = 67)

There is a significant association between age and cancer type (p = 0.003). The age groups most commonly correlated to cancer were as follows in decreasing order; 66-75 years (43.3%), 46-55 years (19.4%), 56-65 years (17.9%), 76-85 years (16.4%) and <46 years (3.0%). Ovarian patients tend to be younger in age. Patients aged 55 years or less had a higher probability to suffer from ovarian cancer. Patients aged 56-65 years had a higher probability to suffer from pancreas, while patients aged 66 years or over had a higher probability to suffer from prostate cancer.

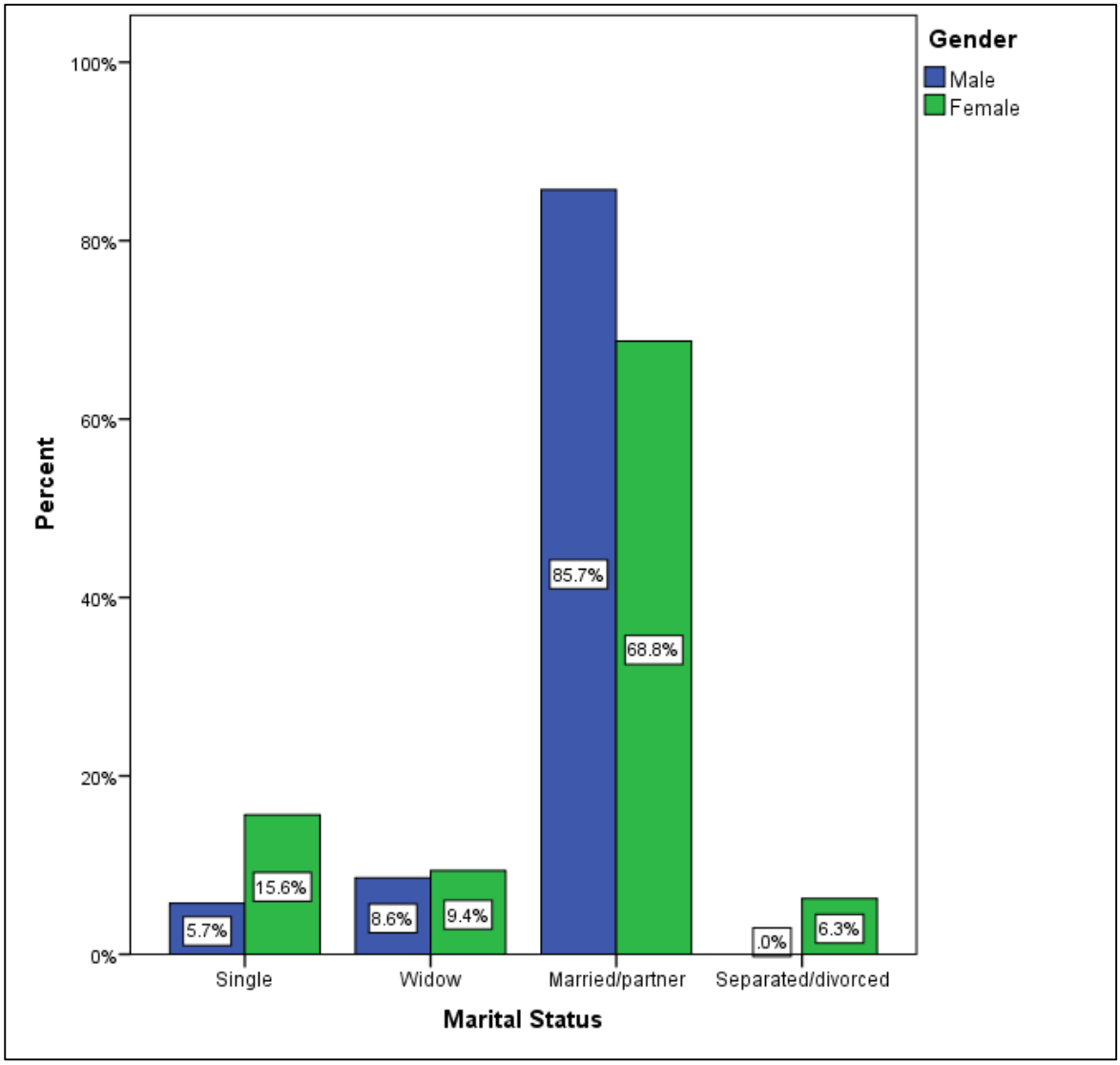


$X^2(8) = 23.324$, **p = 0.003**

Figure 3.3 Percentage of patients grouped by age groups and cancer type (N = 67)

3.1.3. Marital status

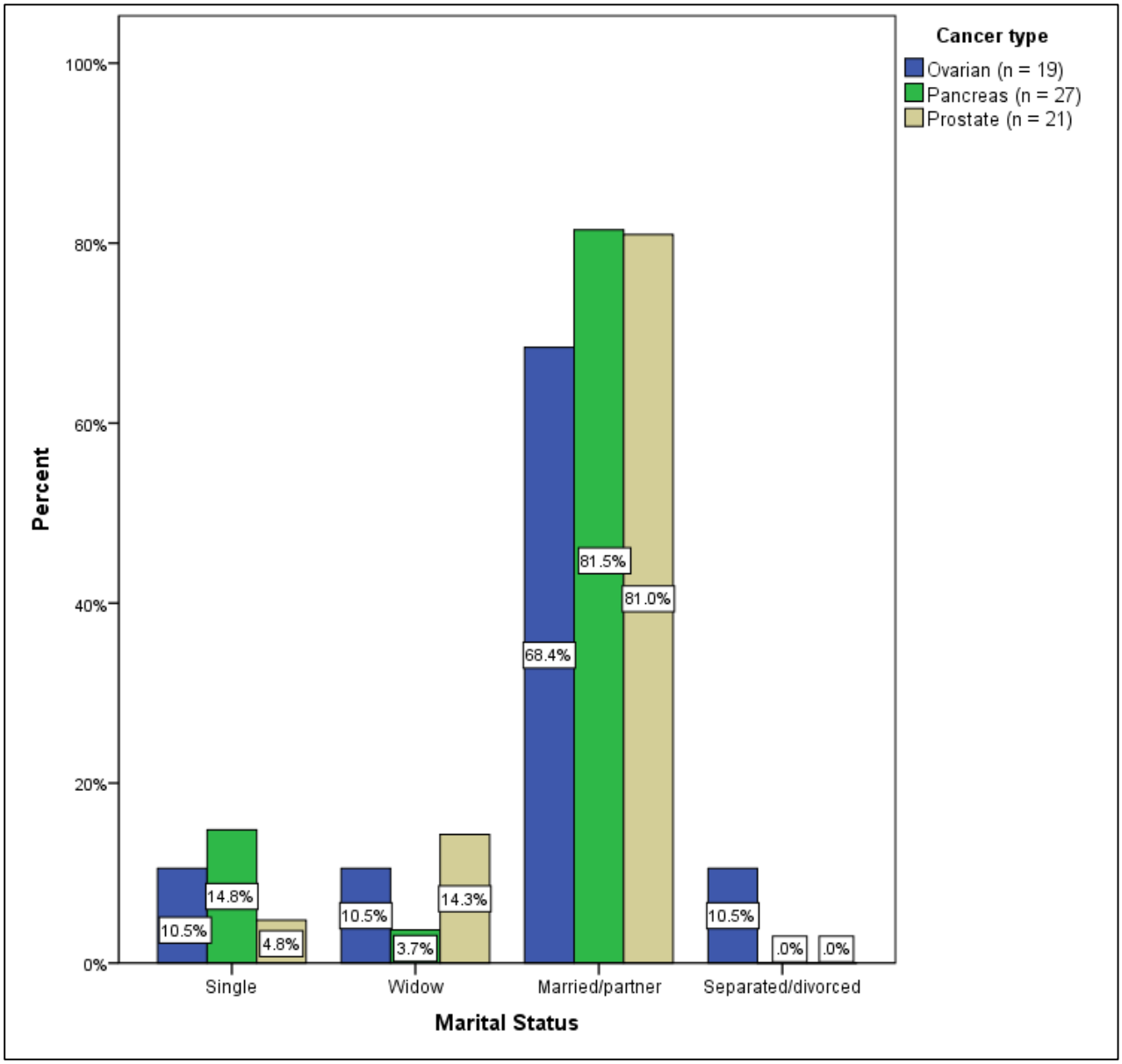
Both the majority of male (85.7%) and female (68.8%) patients had a marital status of married/partner. More than three-quarters (77.6%), of the patients were either married or had a partner, while separated/divorced corresponded to 3%.



$X^2(3) = 4.391$, $p = 0.222$

Figure 3.4 Percentage of patients grouped by marital status and gender (N = 67)

In all the three cancer types studied, married/partner (77.6%) was the most common marital status, followed by single (10.4%), widow (9.0%) and separated/divorced (3.0%). Patients who were married or had a partner, suffered mostly from cancer of the pancreas (81.5%), prostate (81%) and ovary (68.4%) respectively.

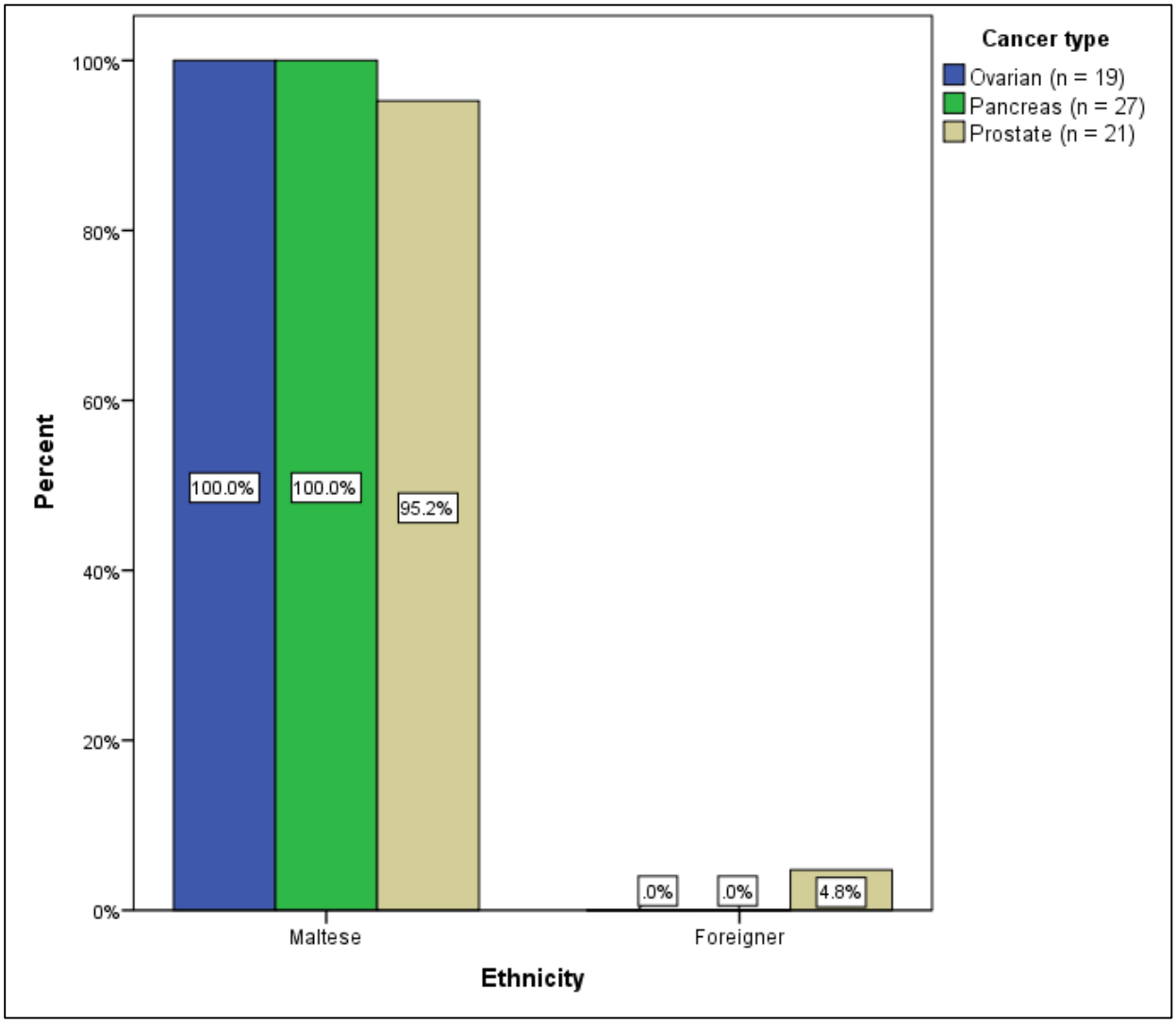


$X^2(6) = 8.035$, $p = 0.236$

Figure 3.5 Percentage of patients grouped by marital status and cancer type (N = 67)

3.1.4. Ethnic origin

The majority of the patients were Maltese (98.5%), while only one patient (1.5%) was a foreigner.

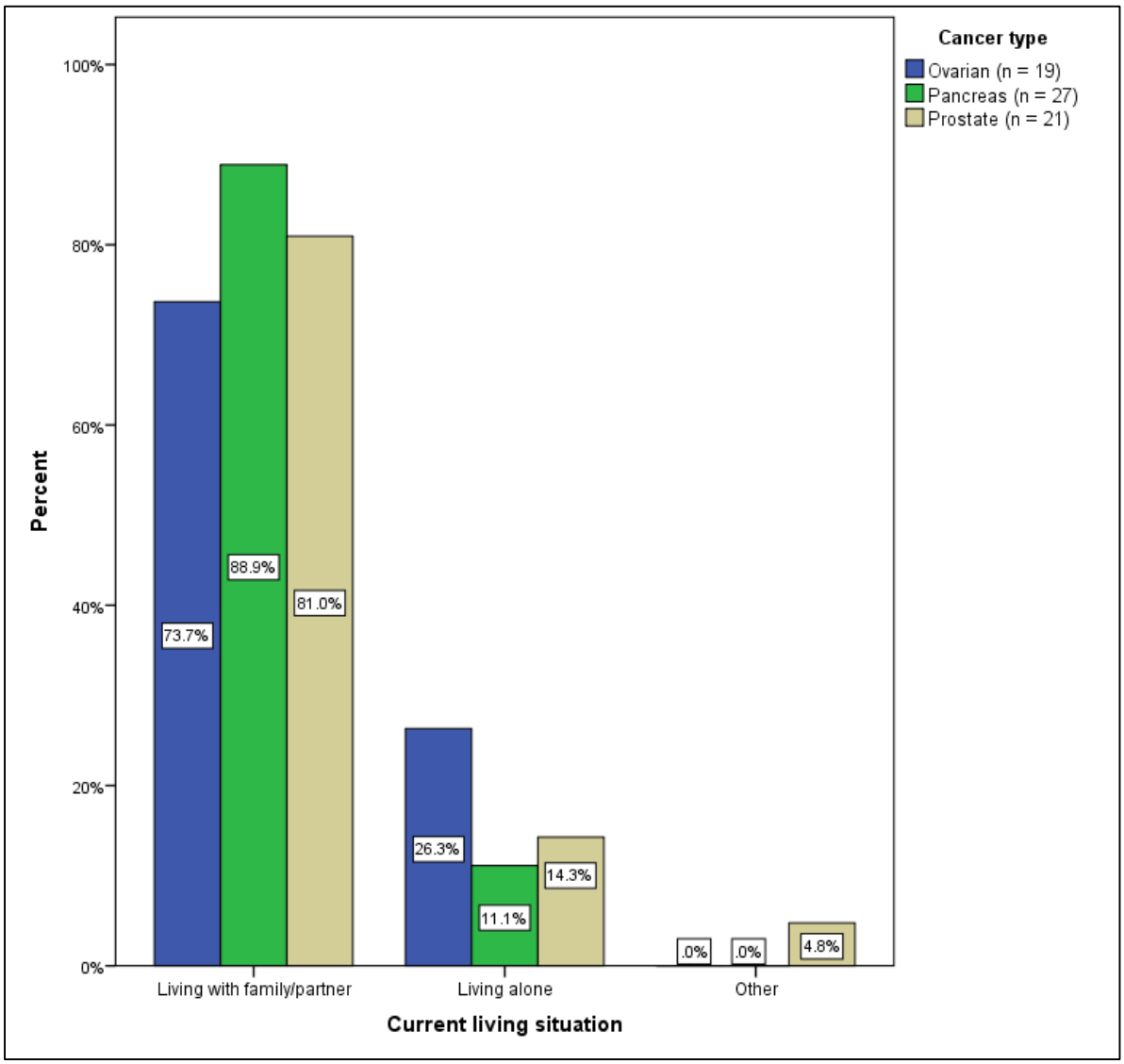


$X^2(2) = 2.224$, $p = 0.329$

Figure 3.6 Percentage of patients grouped by ethnicity and cancer type (N = 67)

3.1.5. Current living situation

More than three quarters of the patients, 82.1% were living with family or partner, followed by living alone (16.4%) and other (1.5%). Living with family or partner were found most frequently in patients suffering from pancreatic cancer (88.9%), while living alone and other were found most frequently in patients suffering from ovarian (26.3%) and prostate cancer (4.8%) respectively.

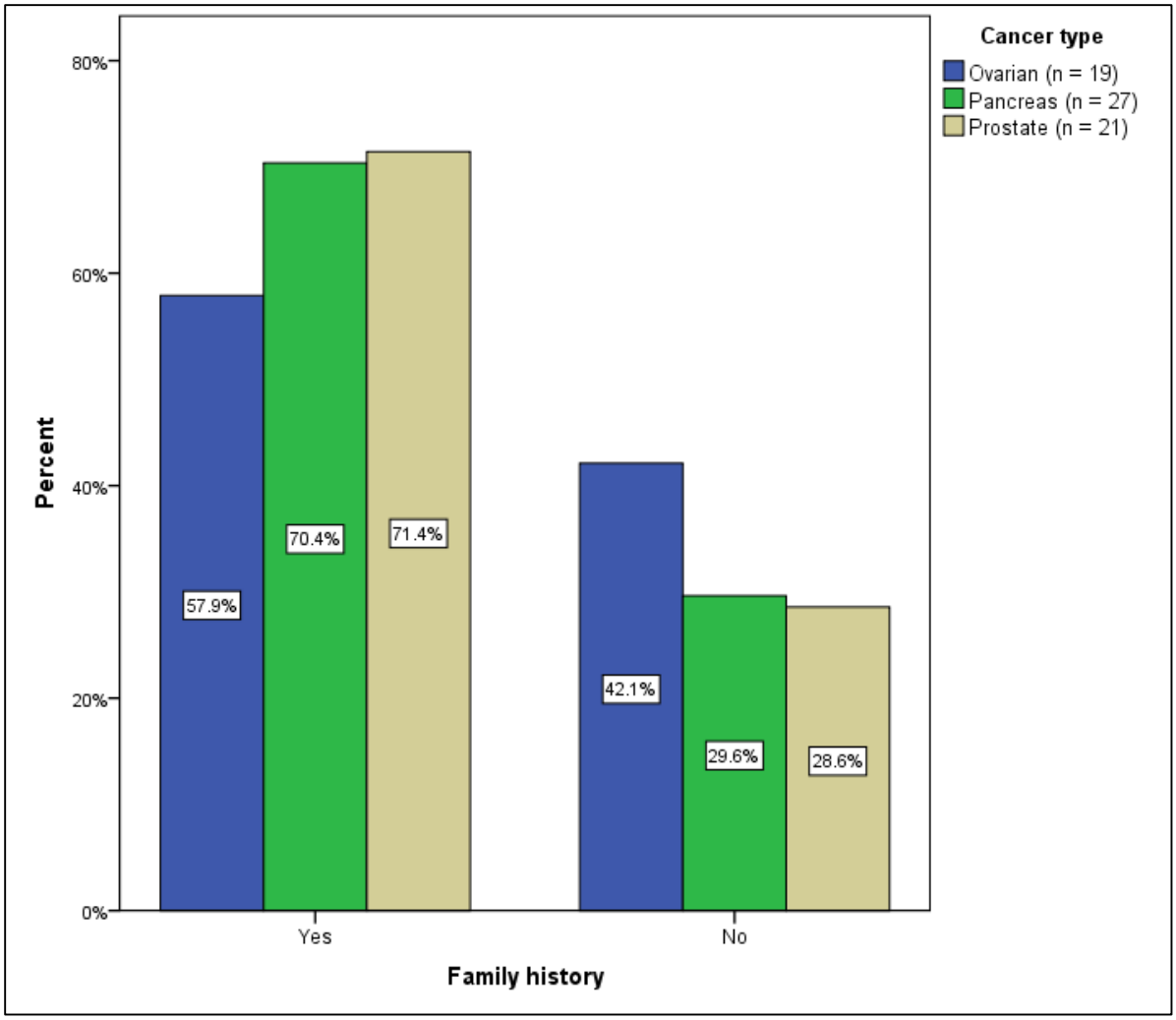


$X^2(4) = 4.164$, p = 0.384

Figure 3.7 Percentage of patients grouped by current living situation and cancer type (N = 67)

3.1.6. Family history of cancer

Approximately two-thirds (67.2%) of the population had a family history of carcinoma, mostly highlighted in the pancreas and prostate population, while 32.8% did not have a family history.

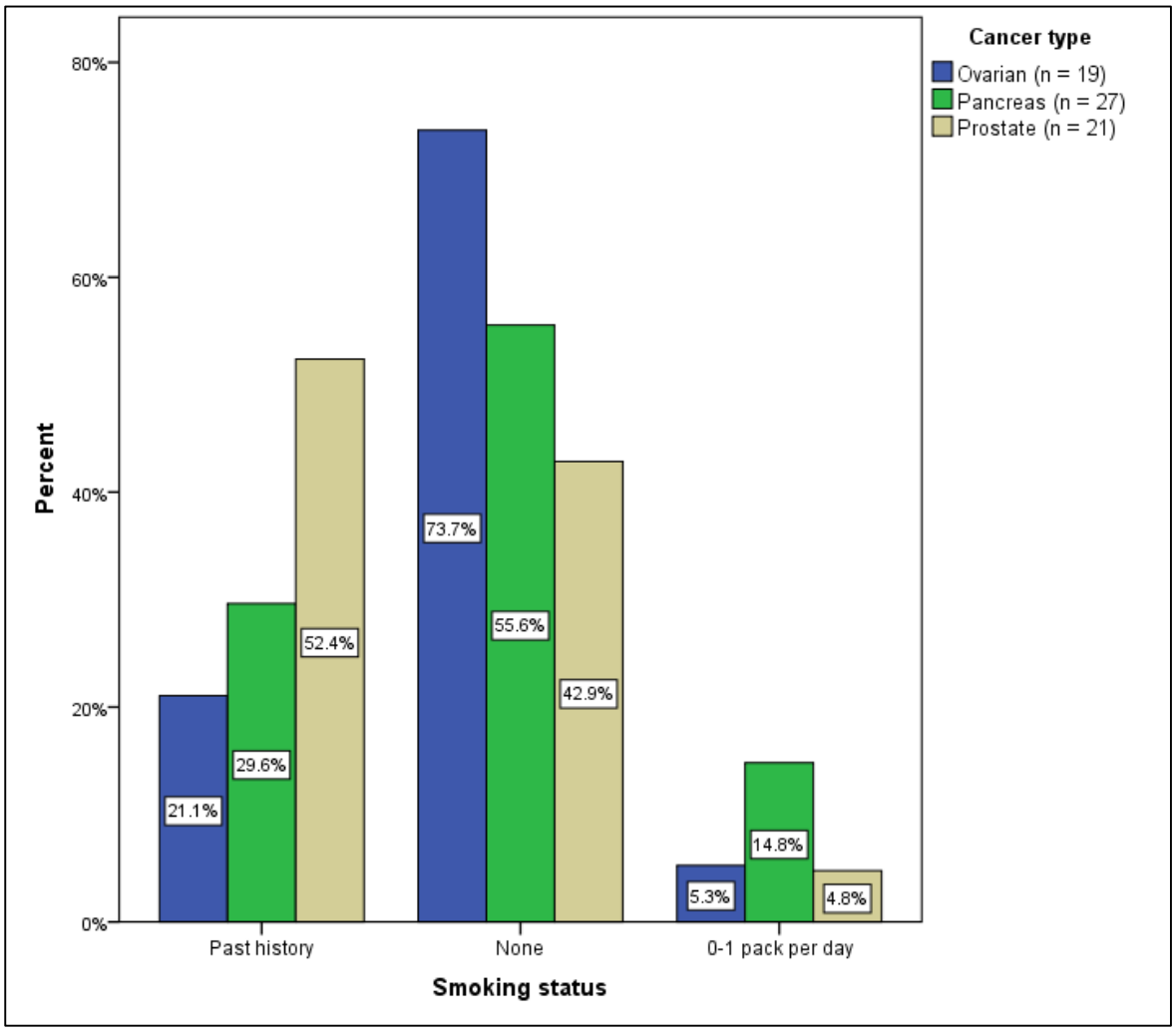


$X^2(2) = 1.039$, $p = 0.595$

Figure 3.8 Percentage of patients grouped by family history and cancer type (N = 67)

3.1.7. Smoking status

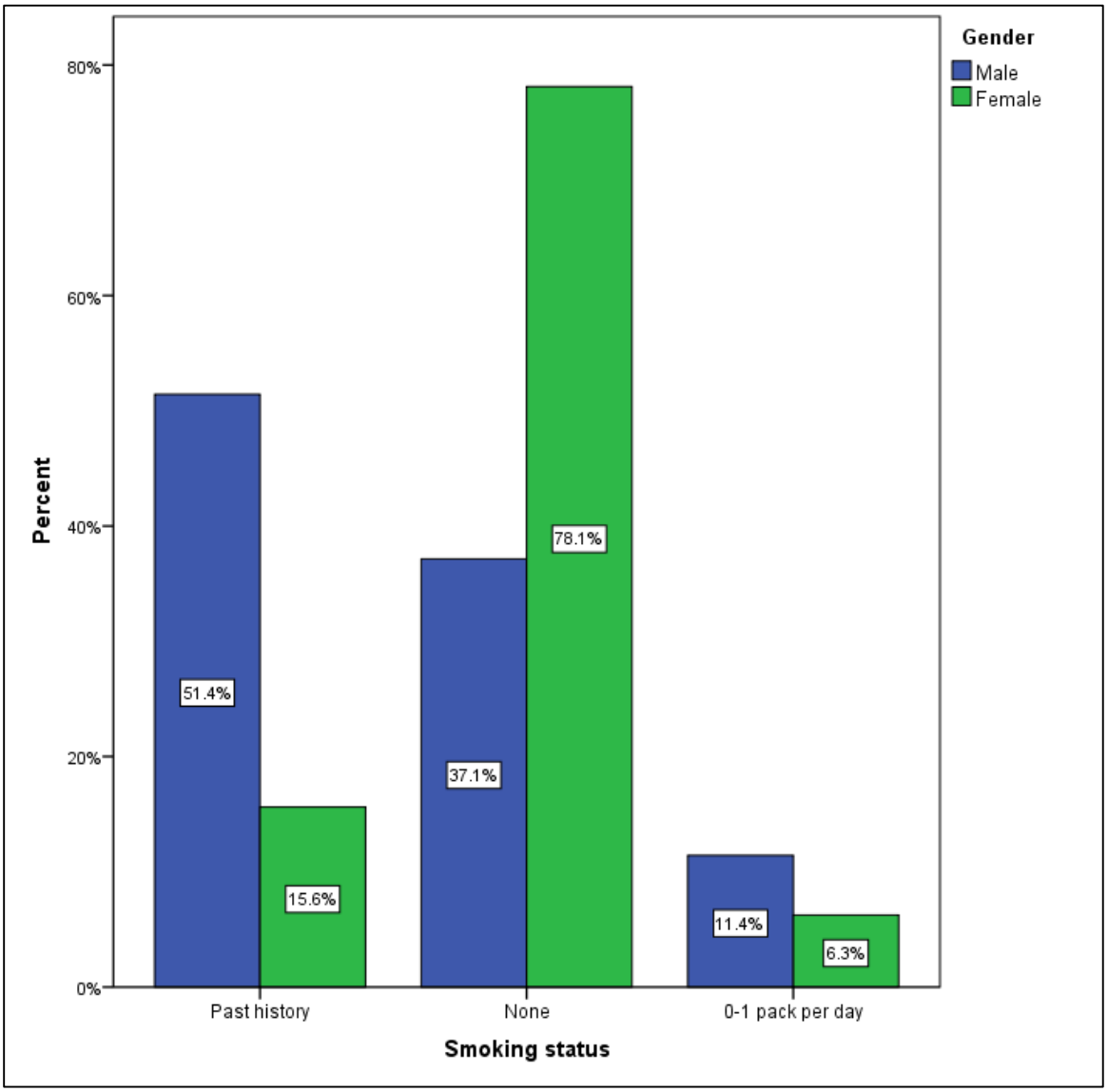
More than half of the population (56.7%) never smoked, followed by past history (34.3%) and the rest (9.0%) smoked between 0 to 1 pack per day. There is a larger percentage of patients suffering from prostate cancer (52.4%), who were past smokers, compared to the other cancer types (29.6%, 21.1%). There is a larger percentage of patients suffering from ovarian cancer (73.7%), who were non-smokers, compared to the other cancer types (55.6%, 42.9%). There is a larger percentage of patients suffering from pancreatic cancer (14.8%) who smoke at most 1 pack daily compared to the other cancer types (5.3%, 4.8%). Although there seems to be an association between smoking status and cancer type, this association is not significant (p = 0.161).



$X^2(4) = 6.562$, p = 0.161

Figure 3.9 Percentage of patients grouped by smoking status and cancer type (N = 67)

There is a larger percentage of females (78.1%), compared to males (37.1%) who never smoked. Conversely, there is a larger percentage of males (51.4%, 11.4%) compared to females (15.6%, 6.3%), who either are past smokers or smoke at most 1 pack per day. Since the p value (0.003) is less than the 0.05 level of significance, this implies that it can be generalised that there is a higher prevalence of male present smokers and past smokers than females.

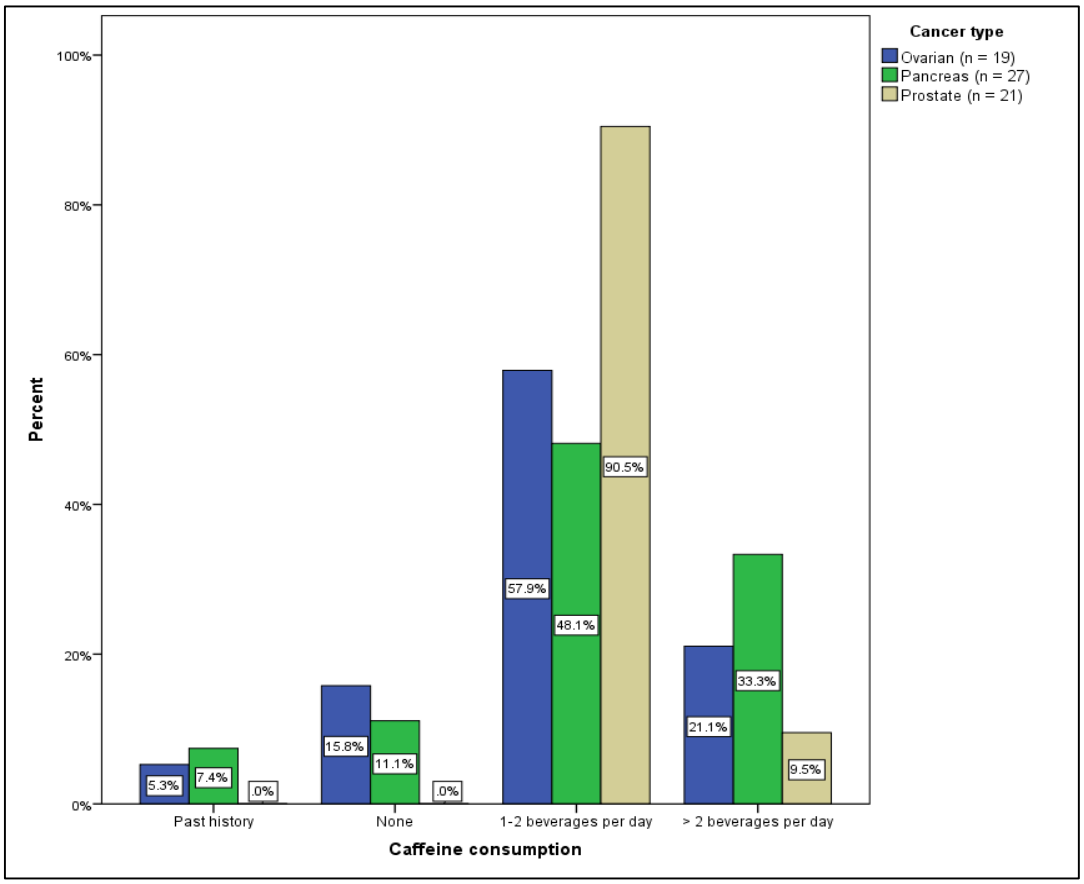


$X^2(2) = 11.693$, **p = 0.003**

Figure 3.10 Percentage of patients grouped by smoking status and gender (N = 67)

3.1.8. Caffeine consumption

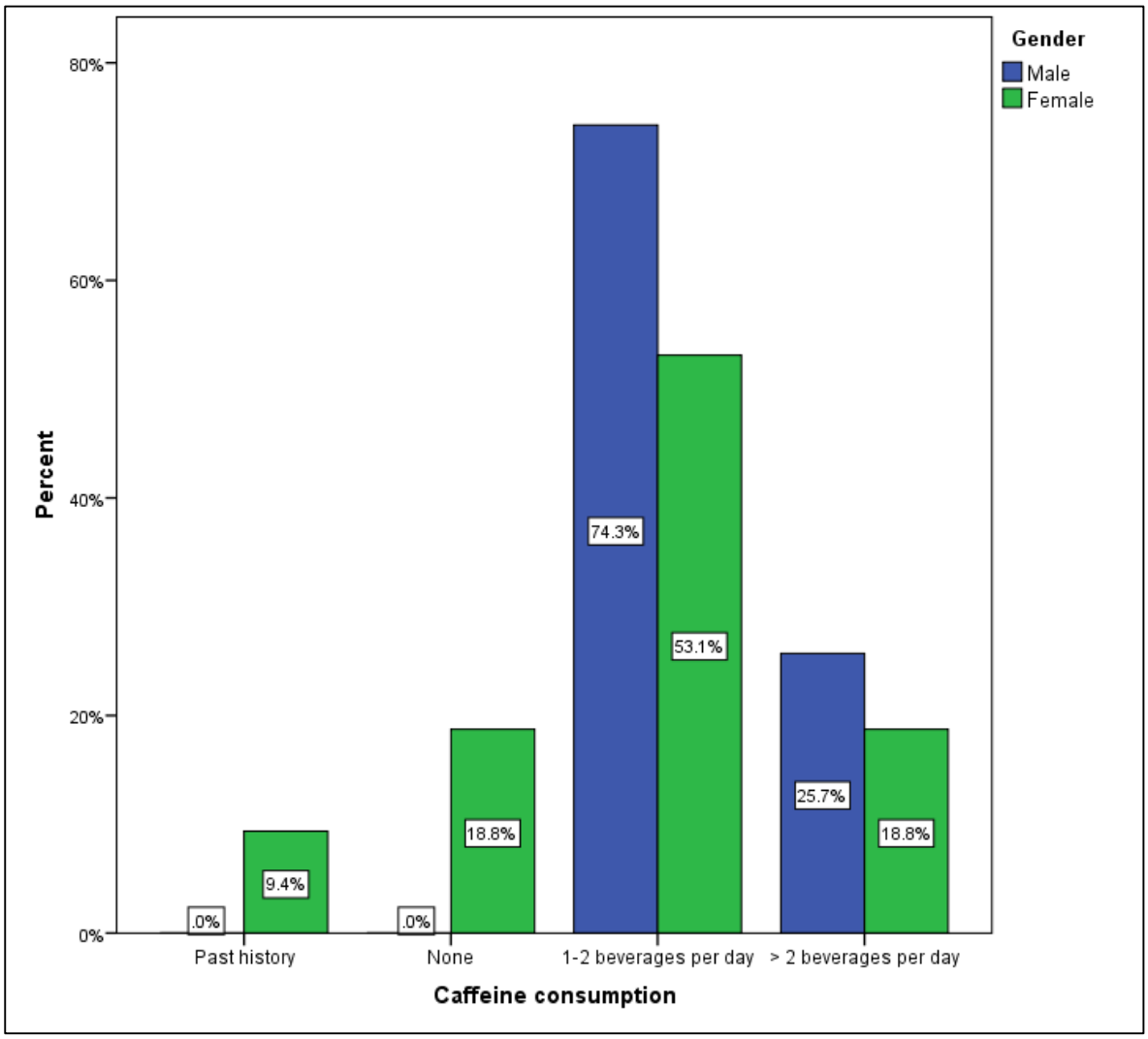
64.2%, 22.4%, 9.0% and 4.5% consumed 1-2, >2, nil or had a past history of beverages containing caffeine per day respectively. There is a larger percentage of patients suffering from pancreatic cancer (7.4%), who had past history of consumption of beverages containing caffeine, compared to the other cancer types (5.3%, 0%). There is a larger percentage of patients suffering from ovarian cancer (15.8%), who claimed that they never consumed beverages containing caffeine, compared to the other cancer types (11.1%, 0%). There is a larger percentage of patients suffering from prostate cancer (90.5%) who consumed 1 to 2 beverages containing caffeine per day compared to the other cancer types (57.9%, 48.1%). Lastly, there is a larger percentage of patients suffering from pancreatic cancer (33.3%) who consumed more than 2 beverages containing caffeine per day compared to the other cancer types (21.1%, 9.5%).



$X^2(6) = 10.969$, $p = 0.089$

Figure 3.11 Percentage of patients grouped by caffeine consumption and cancer type (N = 67)

There is a larger percentage of females (18.8%, 9.4%), compared to males (both 0%) who never consumed or had past history of consumption of beverages containing caffeine respectively. Conversely, there is a larger percentage of males (74.3%, 25.7%) compared to females (53.1%, 18.8%), who consumed either 1 to 2 or more than 2 beverages containing caffeine per day. Since the p value (0.010) is less than the 0.05 level of significance, this implies that it can be generalised that there is a higher prevalence of males who consume 1 to 2 or more than 2 beverages containing caffeine per day.

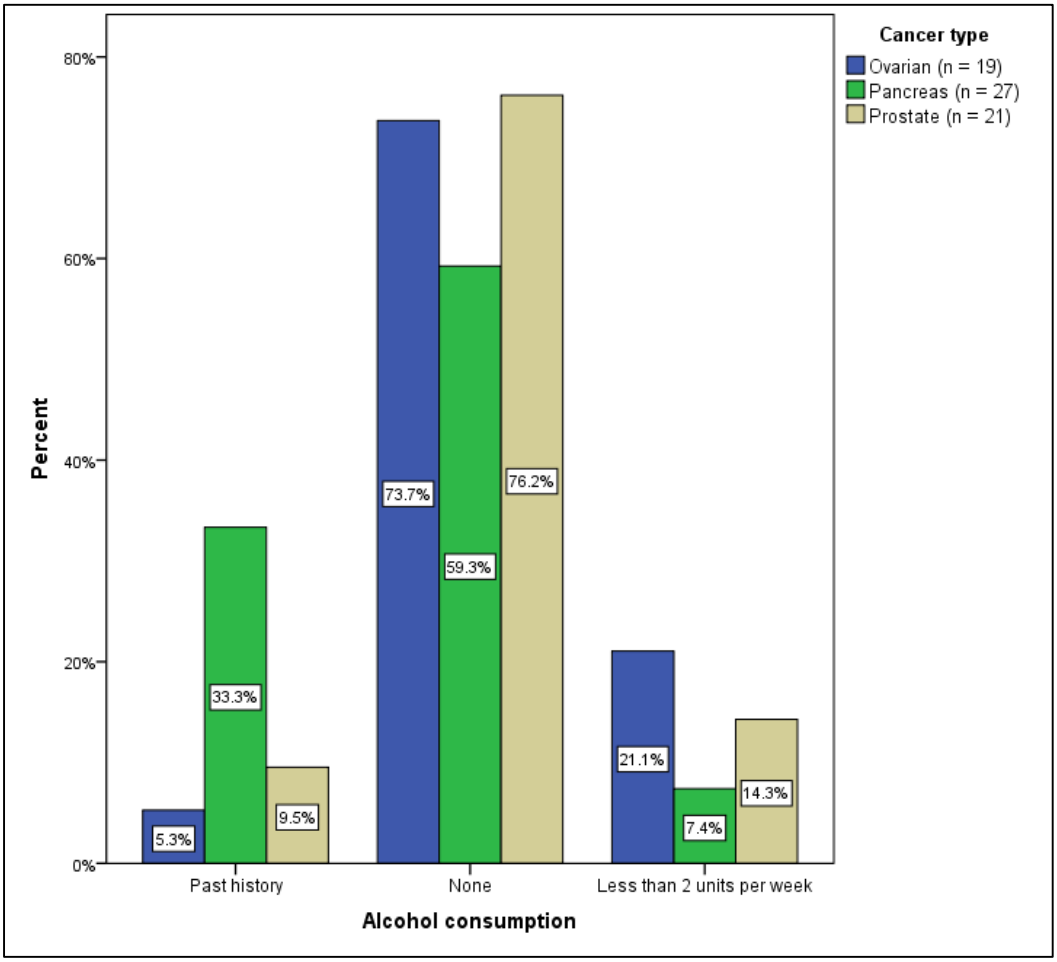


$X^2(3) = 11.372$, **p = 0.010**

Figure 3.12 Percentage of patients grouped by caffeine consumption and gender (N = 67)

3.1.9. Alcohol consumption

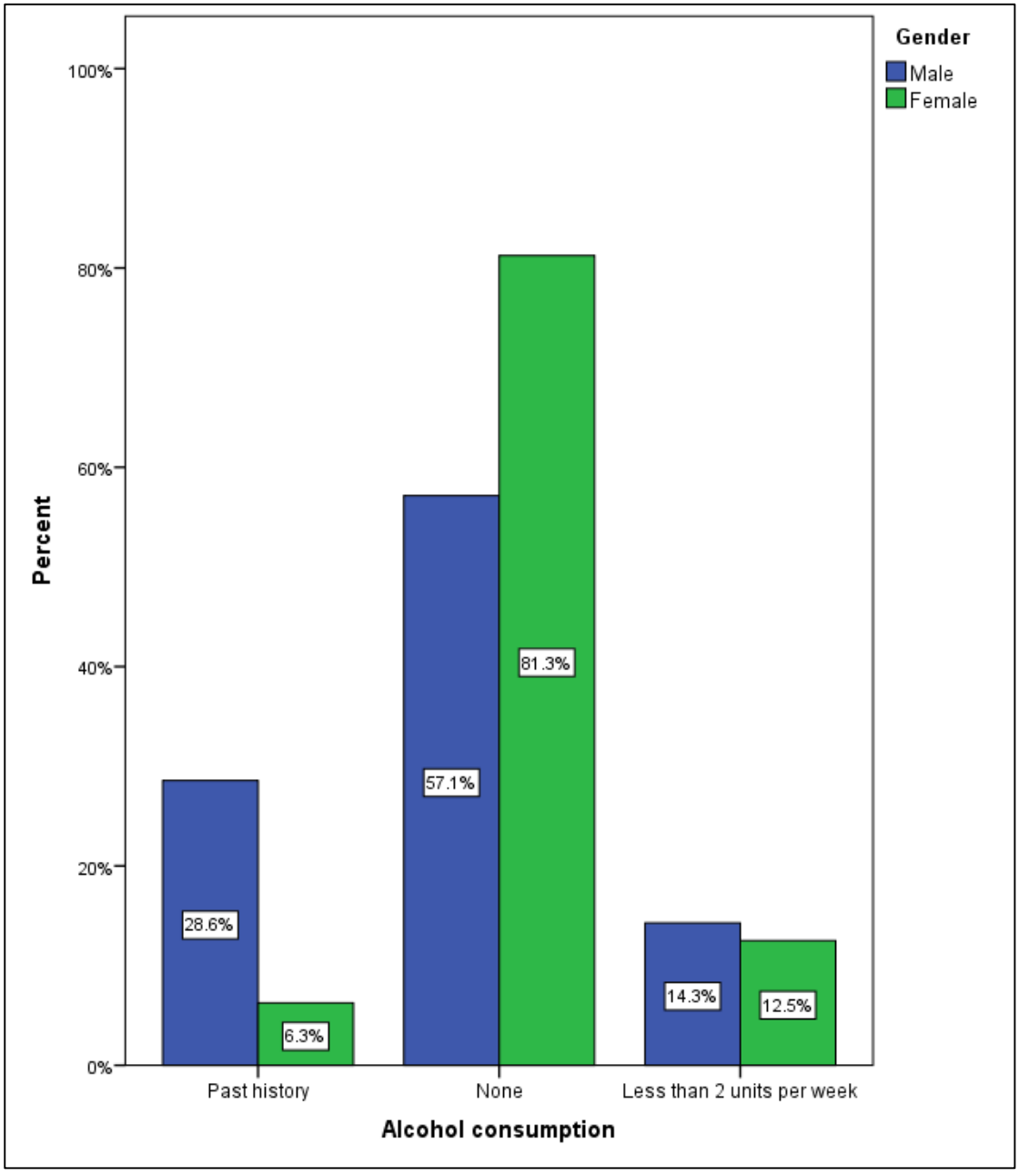
68.7% of the population stated that they did not consume alcohol, followed by past history (17.9%) and less than 2 units per week (13.4%). There is a larger percentage of patients suffering from pancreatic cancer (33.3%), who had past history of alcohol consumption compared to the other cancer types (9.5%, 5.3%). There is a larger percentage of patients suffering from prostate cancer (76.2%), who claimed that they never consumed alcohol compared to the other cancer types (73.7%, 59.3%). Lastly, there is a larger percentage of patients suffering from ovarian cancer (21.1%), who consumed less than 2 units per week compared to the other cancer types (14.3%, 7.4%).



$X^2(4) = 8.261$, $p = 0.0827$

Figure 3.13 Percentage of patients grouped by alcohol consumption and cancer type (N = 67)

There is a larger percentage of females (81.3%), compared to males (57.1%) who never consumed alcohol. Conversely, there is a larger percentage of males (28.6%, 14.3%) compared to females (6.3%, 12.5%), who either had past history of alcohol consumption or consumed less than 2 units per week. Since the p value (0.047) is less than the 0.05 level of significance, this implies that it can be generalised that there is a higher prevalence of males with past or current alcohol use.

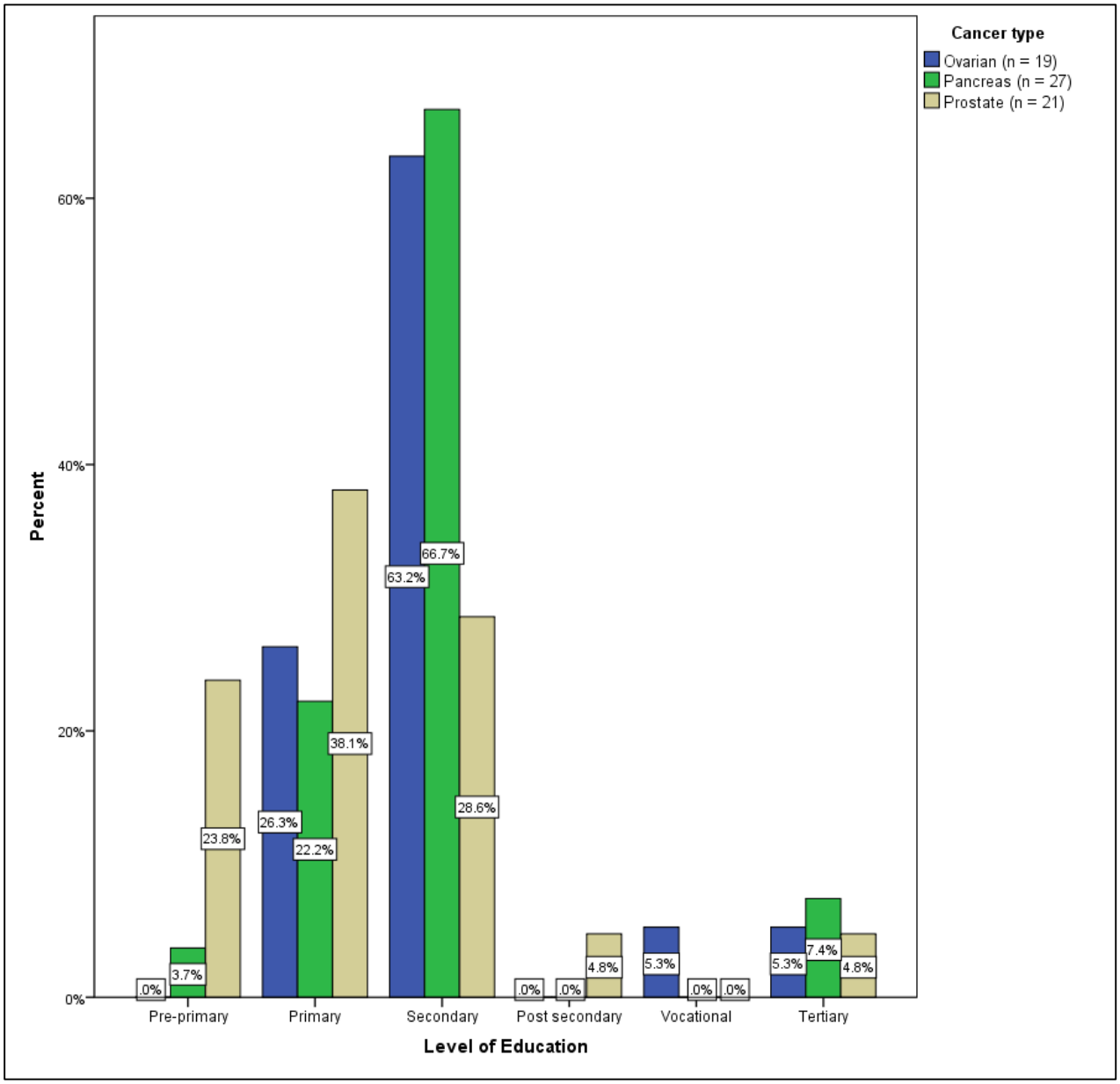


$X^2(2) = 6.105$, **p = 0.047**

Figure 3.14 Percentage of patients grouped by alcohol consumption and gender (N = 67)

3.1.10. Level of education

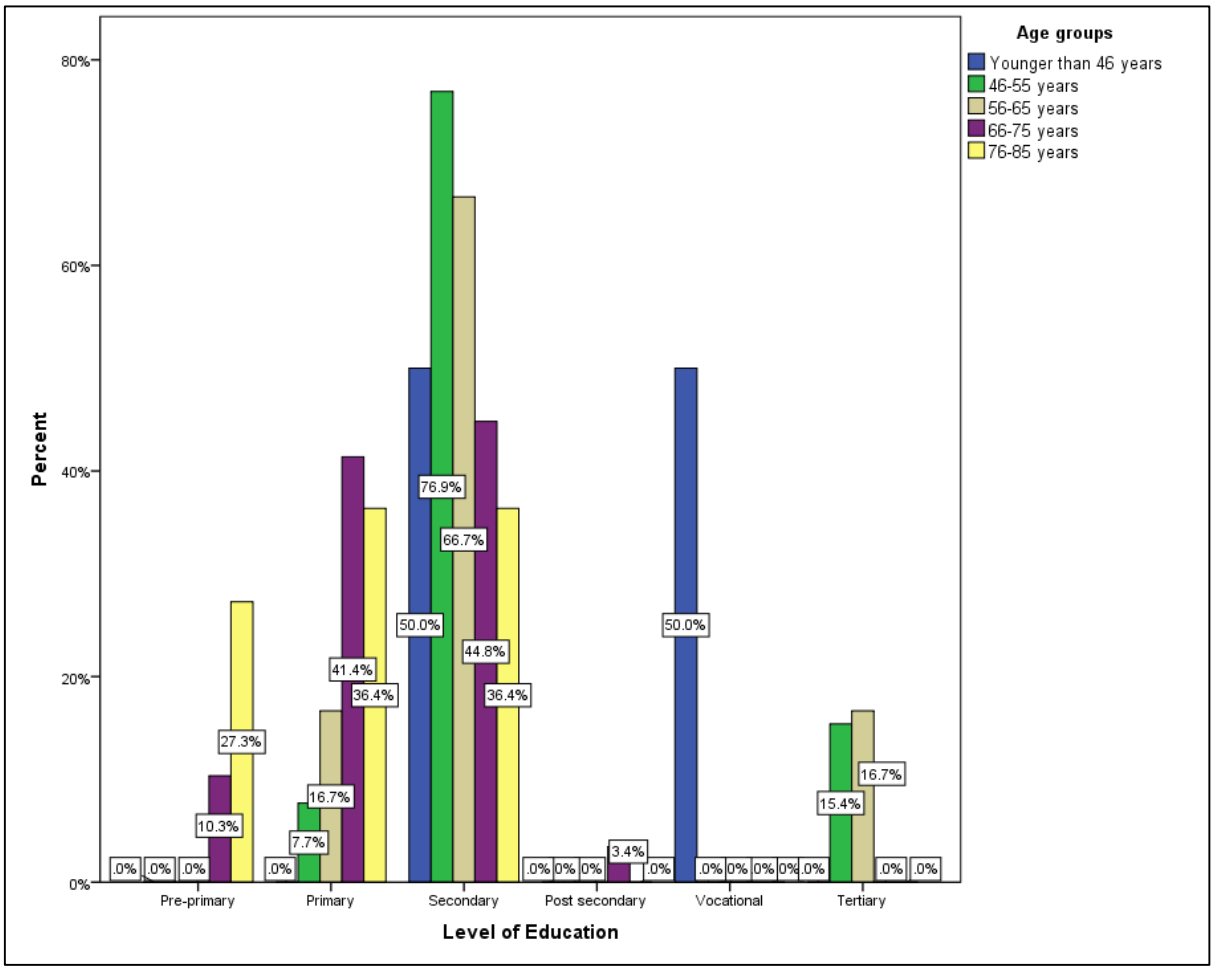
More than 50% (53.7%) of the population had secondary level of education, followed by primary level of education (28.4%). Although the p value is 0.068 ($p > 0.05$), there may be a signal that the lower the level of education, the higher the chance of having cancer.



$X^2(10) = 17.302$, $p = 0.068$

Figure 3.15 Percentage of patients grouped by level of education and cancer type (N = 67)

There is a significant association between level of education and age groups ($p < 0.001$). The majority of patients having secondary level of education (53.7%) were aged between 46-55 years (76.9%). Only one patient had a post-secondary vocational level of education since she was only 26 years.

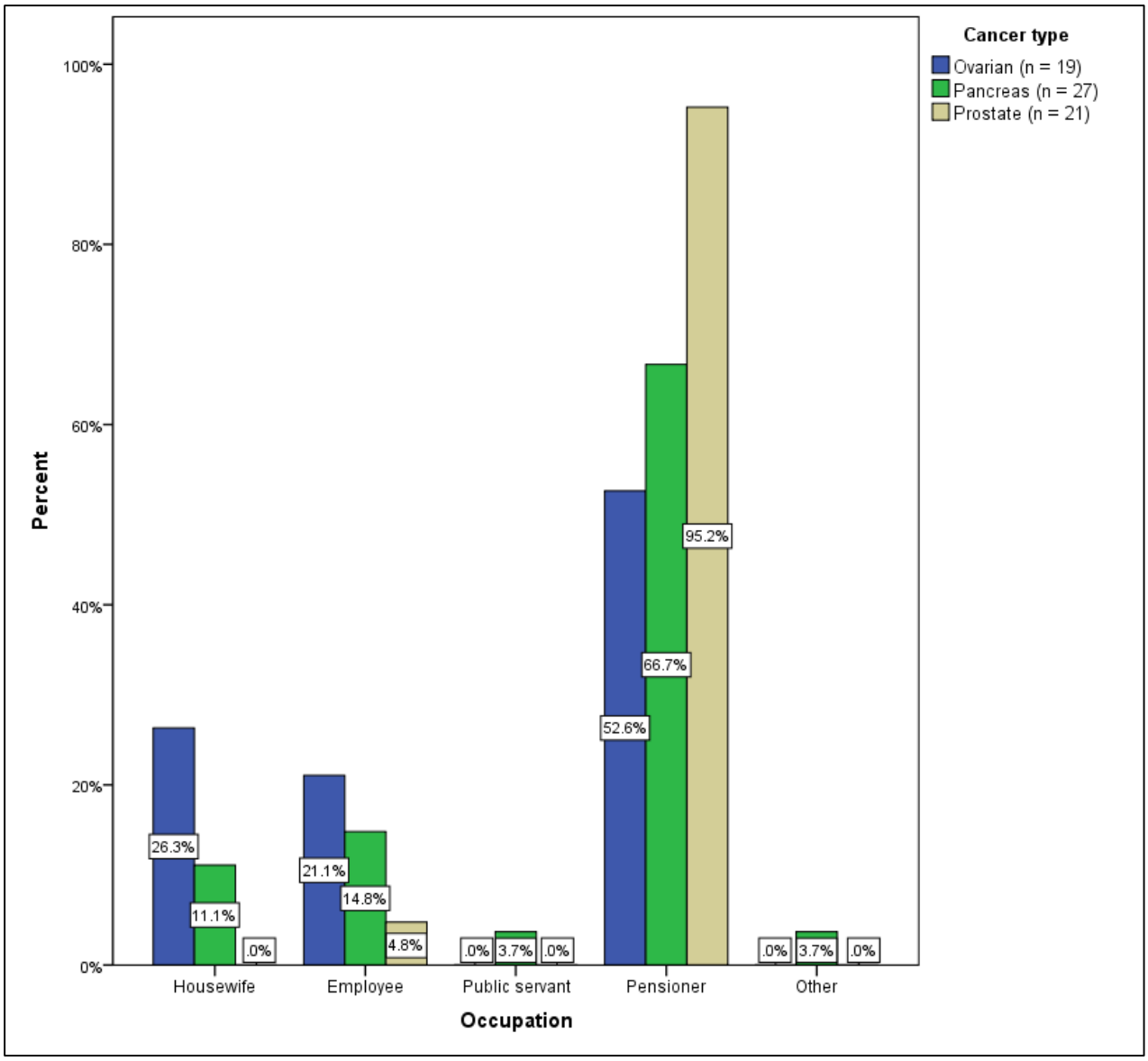


$X^2(20) = 54.961$, **$p < 0.001$**

Figure 3.16 Percentage of patients grouped by level of education and age groups (N = 67)

3.1.11. Occupation

Almost three-quarters (71.6%) of the patients were pensioners, followed by employees (13.4%), housewives (11.9%), public servants and others (1.5% each). There is a larger percentage of patients suffering from ovarian cancer, who were either housewives (26.3%) or employees (21.1%). There is a larger percentage of patients suffering from prostate cancer (95.2%), who were pensioners.



$X^2(8) = 13.493$, $p = 0.096$

Figure 3.17 Percentage of patients grouped by occupation and cancer type (N = 67)

3.2. Medical history

Medical history conditions were classified into fourteen categories. The rest of the medical history were listed with 'Others'. Other included amongst others; arrhythmias.

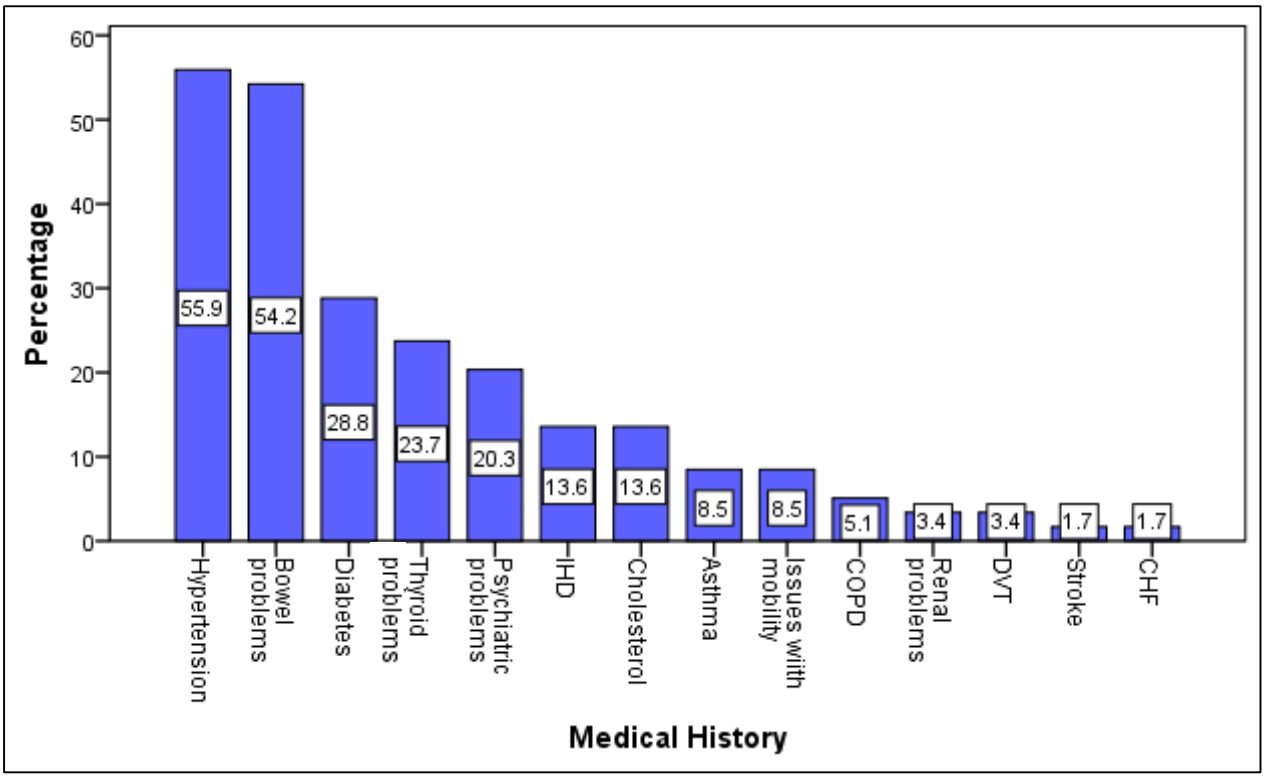


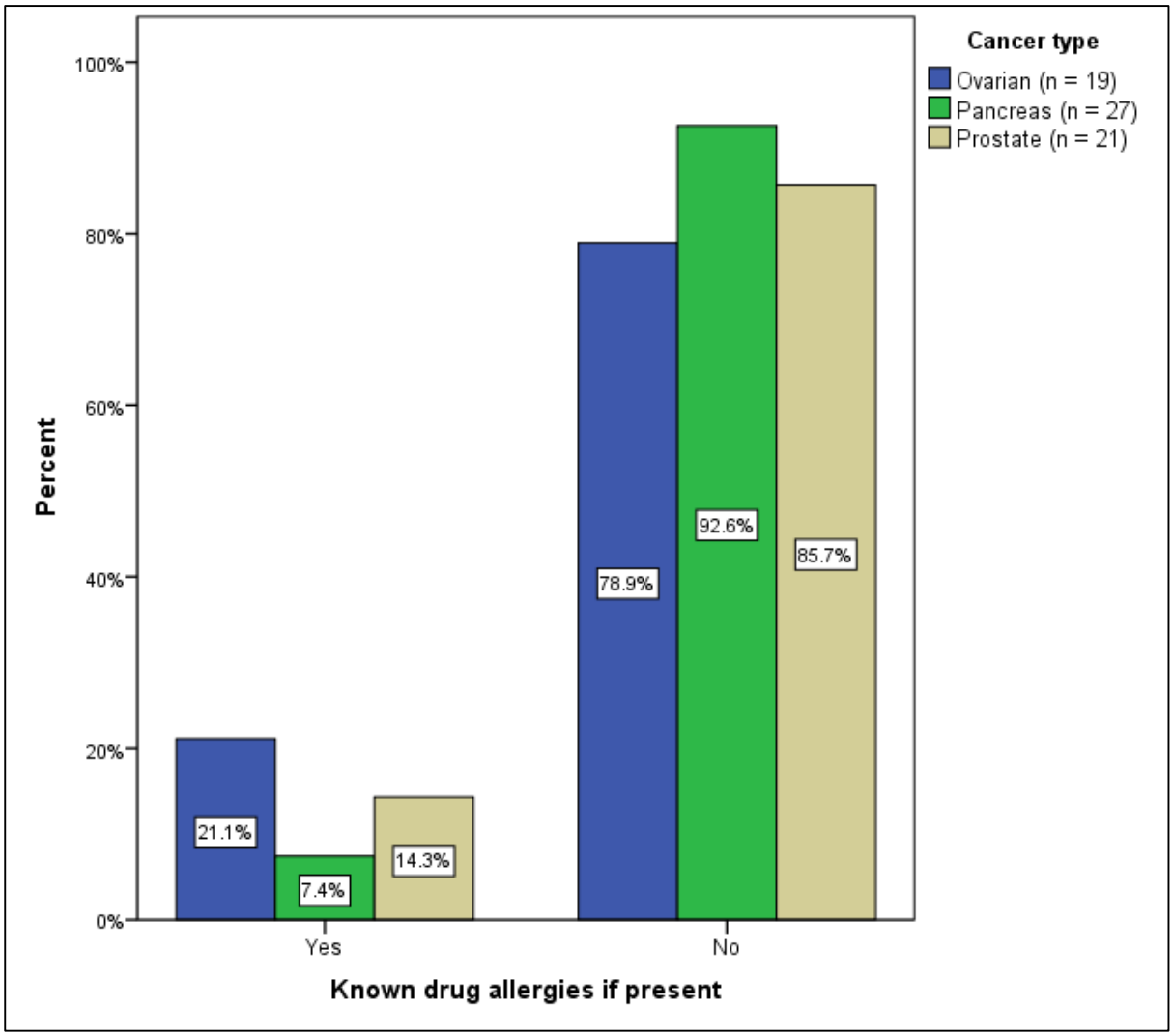
Figure 3.18 Medical history (N = 67)

Table 3.2 Medical history showing frequency and percentage (N = 67)

Medical history	Frequency	Percentage (%)
Hypertension	33	55.9
Bowel problems	32	54.2
Diabetes	17	28.8
Thyroid problems	14	23.7
Psychiatric problems	12	20.3
IHD	8	13.6
Cholesterol	8	13.6
Asthma	5	8.5
Issues with mobility	5	8.5
COPD	3	5.1
Renal problems	2	3.4
DVT	2	3.4
Stroke	1	1.7
CHF	1	1.7

3.3. Known drug sensitivities

Out of the total study population (N = 67), 86.6% of patients had no known drug sensitivities, while 13.4% had, amongst which included non-steroidal anti-inflammatory drugs (NSAIDs), codeine-containing medications, enalapril, ciprofloxacin and penicillin. There is a larger percentage of patients suffering from ovarian cancer (21.1%), who had a known drug allergy. There is a larger percentage of patients suffering from pancreatic cancer (92.6%), who did not have.



$X^2(2) = 1.805$, p = 0.406

Figure 3.19 Percentage of patients grouped by known drug sensitivities and cancer type (N = 67)

3.4. Current medications

Patients suffering from prostate, pancreatic and ovarian cancer took on average 3.43, 3.33 and 2.47 medications daily respectively. The difference in the number of current medications taken daily did not vary significantly between the three groups since p value (0.467) exceeded the 0.05 criterion.

Table 3.3 Mean number of current medications (N = 67)

Type of cancer	Sample Size	Mean	Std. Deviation	P-value
Ovarian	19	2.47	2.44	0.467
Pancreas	27	3.33	2.22	
Prostate	21	3.43	3.38	

3.5. Previous oncology systemic therapy

Patients suffering from prostate, ovarian and pancreatic cancer received on average 1.24, 1.05 and 0.41 previous oncology systemic therapy respectively before the start of this study. The mean number of previous oncology systemic treatments for patients suffering from pancreatic cancer is significantly lower than the mean number of previous oncology systemic treatments of the other cancer types. The difference in the number of previous oncology systemic therapy varied significantly between the three groups since the p value (0.008) did not exceed the 0.05 criterion.

Table 3.4 Mean number of previous oncology treatments (N = 67)

Type of cancer	Sample Size	Mean	Std. Deviation	P-value
Ovarian	19	1.05	1.03	0.008
Pancreas	27	0.41	0.64	
Prostate	21	1.24	1.18	

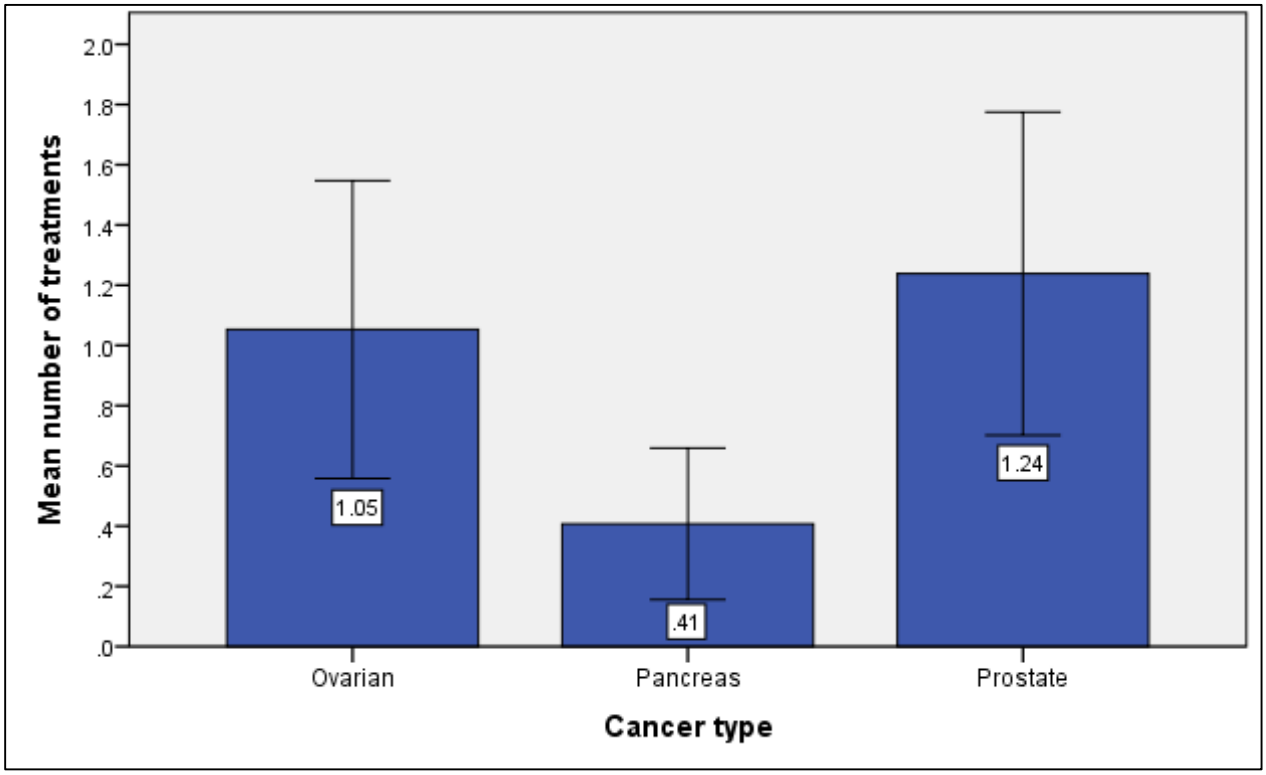


Figure 3.20 Mean number of previous oncology treatments grouped by cancer type (N = 67)

3.6. Oncology medications

At the start of the study, patients were receiving between 1 and 4 medications. The majority of the patients (27) were receiving one oncology medication such as topotecan, gemcitabine or docetaxel. Fifteen patients were receiving two oncology medications such as carboplatin and paclitaxel, gemcitabine and capecitabine. Fourteen patients were receiving three medications such carboplatin, paclitaxel and bevacizumab or GTX regimen i.e. gemcitabine, docetaxel and capecitabine. Eleven patients were receiving four oncology medications such as Folfirinox regimen (oxaliplatin, irinotecan, folinic acid and 5-fluorouracil). Oncology medications that patients received for ovarian, pancreatic and prostate cancer are highlighted in Table 3.7, Table 3.8 and Table 3.9 respectively.

Table 3.5 Number of oncology medications (N = 67*)*

Number of oncology medications	Number of patients (%)
One	27 (40.3)
Two	15 (22.4)
Three	14 (20.9)
Four	11 (16.4)

Patients suffering from pancreatic, prostate and ovarian cancer received on average 2.44, 2.10 and 1.74 oncology medications respectively. The mean number of current oncology medications for pancreatic cancer is marginally larger than the number of current oncology medications for the other cancer types. The difference in the number of current oncology medications did not vary significantly between the three groups since the p value (0.108) exceeded the 0.05 criterion.

Table 3.6 Mean number of current oncology medications (N = 67)

Type of cancer	Sample Size	Mean	Std. Deviation	P-value
Ovarian	19	1.74	0.73	0.108
Pancreas	27	2.44	1.42	
Prostate	21	2.10	0.89	

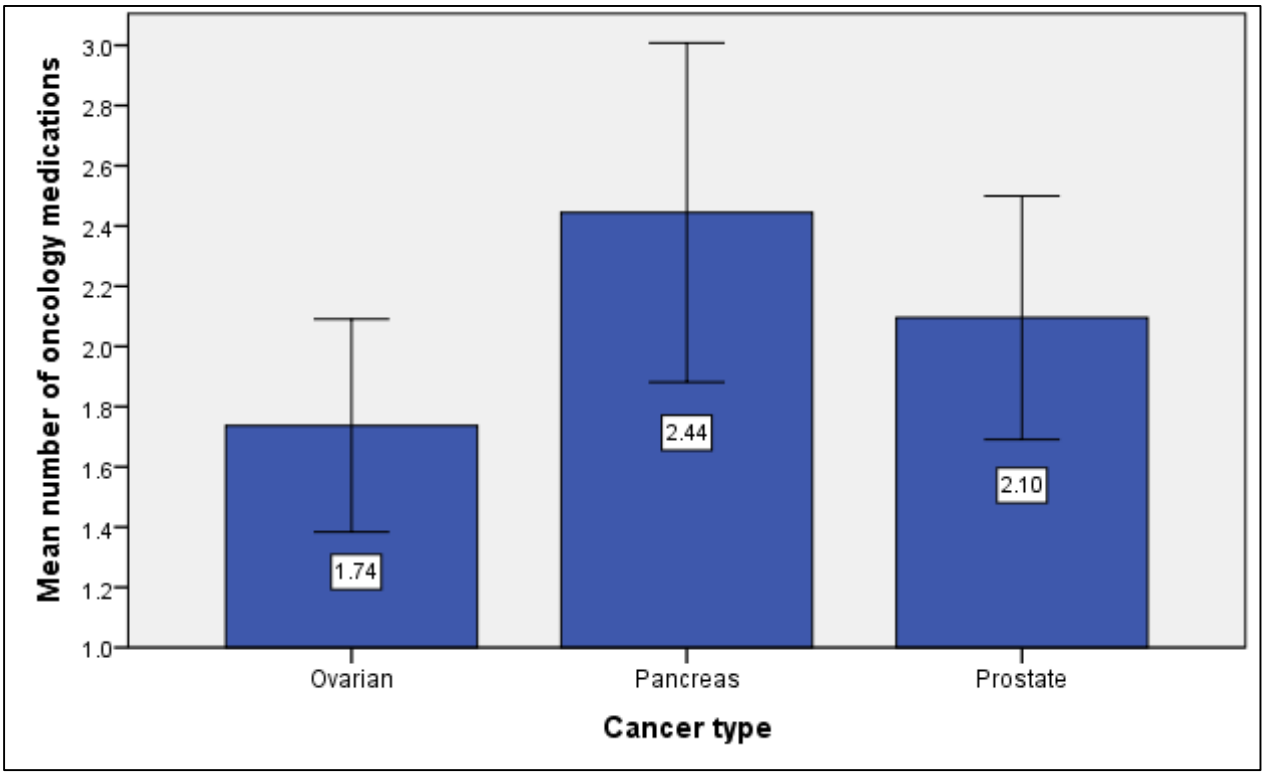


Figure 3.21 Mean number of current oncology medications grouped by cancer type (N = 67)

Table 3.7 Oncology medications for ovarian cancer (n = 19)

Oncology medications at start of study for ovarian cancer (n = 19)	**n (%)**
Carboplatin and paclitaxel	5 (26.3)
Carboplatin and olaparib	1 (5.3)*
Carboplatin alone	1 (5.3)
Carboplatin and pegylated liposomal doxorubicin	2 (10.5)
Pegylated liposomal doxorubicin alone	2 (10.5)*
Gemcitabine alone	3 (15.8)
Carboplatin, paclitaxel and bevacizumab	3 (15.8)*
Topotecan alone	2 (10.5)

*Three patients including one who was receiving carboplatin and olaparib, one on pegylated liposomal doxorubicin, and another on a combination of carboplatin, paclitaxel and bevacizumab required treatment switching to gemcitabine, gemcitabine, and pegylated liposomal doxorubicin respectively.

Table 3.8 Oncology medications for pancreatic cancer (n = 27)

Oncology medications at start of study for pancreatic cancer (n = 27)	**n (%)**
Folfirinox	11 (40.7)*
Gemcitabine alone	12 (44.4)*
Gemcitabine and capecitabine	1 (3.7)
Gemcitabine, docetaxel and capecitabine	2 (7.4)
5-fluorouracil/folinic acid (FU/FA)	1 (3.7)*

*Four patients including two who were receiving Folfirnox, another who was receiving gemcitabine and the other patient who was receiving 5FU/FA required treatment switching to gemcitabine, gemcitabine, 5FU/FA and Folfirnox respectively.

Table 3.9 Oncology medications for prostate cancer (n = 21)

Oncology medication at start of study for prostate cancer (n = 21)	**n (%)**
Docetaxel, prednisolone and goserelin	8 (40.7)*
Cyclophosphamide and goserelin	1 (3.7)
Abiraterone, prednisolone and goserelin	1 (3.7)
Enzalutamide and goserelin	2 (7.4)
Goserelin alone	8 (40.7)*
Goserelin and dexamethasone	1 (3.7)*

*Three patients who were receiving docetaxel and goserelin, goserelin, goserelin and dexamethasone required treatment switching to vinorelbine, and the other two patients to goserelin and bicalutamide respectively.

3.7. Monitoring of tumour markers

For the purpose of graphical representation of tumour marker trends, both CA 125 and CA 19-9 tumour marker results were represented as 1 decimal place, while PSA tumour marker results were represented as 2 decimal places as per original results. Since there was a wide range of tumour marker values, secondary axis were added represented as square data markers. The symbol (*) represented treatment switching.

The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the normality assumption of the tumour marker scores, followed by Wilcoxon signed-rank test or one-tailed paired sample t-test depending on the p value generated. This procedure was repeated for the ovarian cancer patients, then for the ovarian cancer patients except treatment switched patients and lastly for the ovarian cancer patients that finished treatment. These statistical tests were repeated for the pancreatic patients, prostate patients, and for the whole sample population i.e. including the three cancer types.

Since after testing for the normality assumption, both tests yield p-values less than 0.05 level of significance indicating that the tumour marker results have a non-normal distribution. For this reason, a non-parametric test i.e. Wilkoxon signed-rank test to compare mean tumour marker results before and after the treatment was used. If the mean post-treatment tumour marker result is expected to be less than the mean pre-treatment tumour marker result, hence p-value was divided by two. A reduction in post-treatment tumour marker result gives an indication that the patient is responding well to treatment.

At first instance, this statistical methodology was applied to the whole study population (Table 3.10). Test for normality to identify statistical test was carried out. When the relevant statistical test was applied, it was shown that there was a significant reduction in the mean tumour marker results post-treatment for all the study population ($p < 0.05$).

Table 3.10 Tumour marker results pre- and post-treatment for the whole study population (N = 67)

	Tests of normality					
	Kolmogorov-Smirnov			**Shapiro-Wilk**		
	Statistic	df	P-value	Statistic	df	P-value
Pre-treatment tumour marker result	0.335	67	0.000	0.506	67	0.000
Post-treatment tumour marker result	0.422	67	0.000	0.232	67	0.000
	Wilcoxon signed-rank test				
	N	Mean	Std.Deviation	Minimum	Maximum
Pre-treatment tumour marker result	67	424.75	932.99	0.01	4727.10
Post-treatment tumour marker result	67	423.68	1865.64	0.01	12826.00

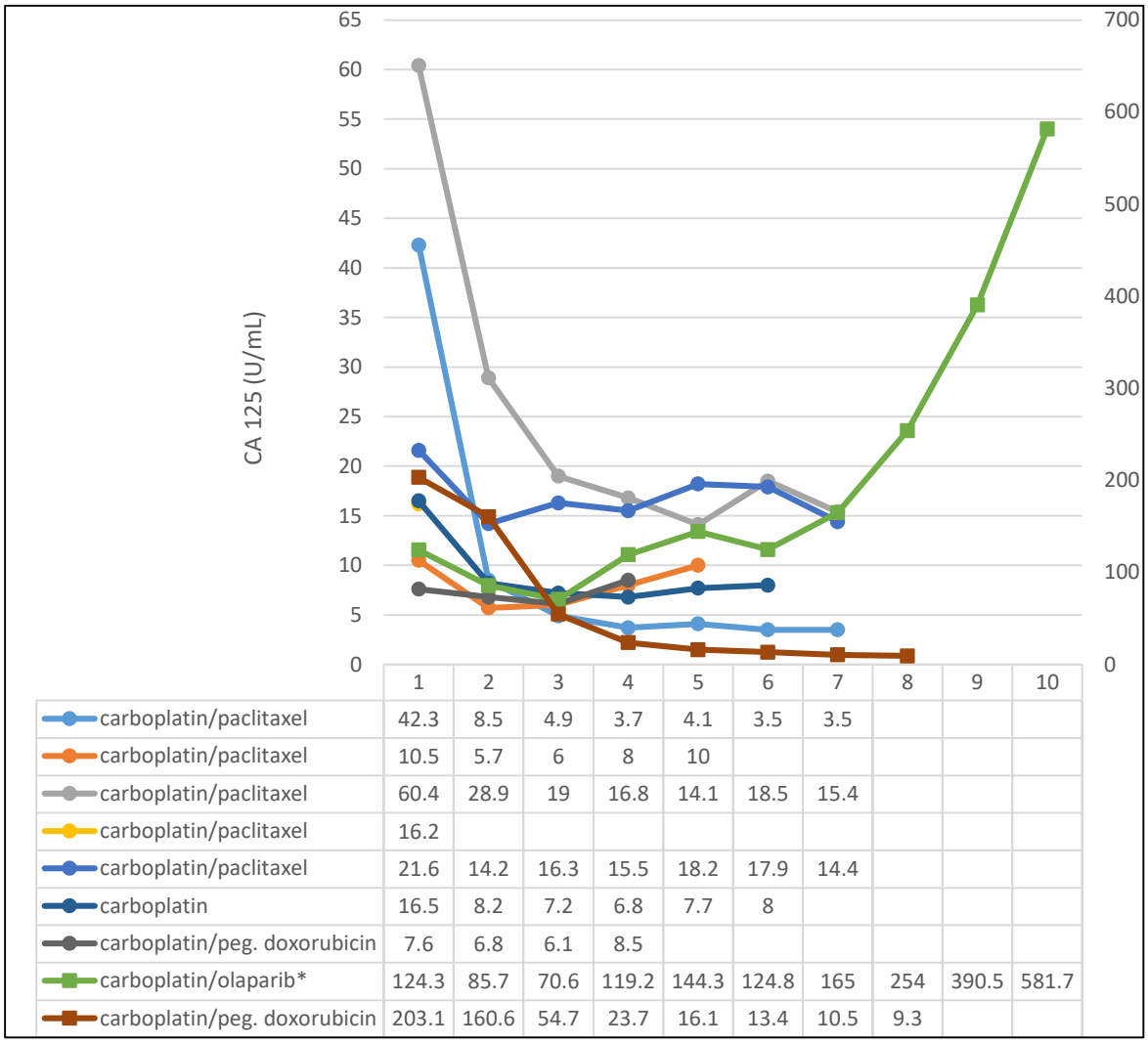
Z = -3.918, **p < 0.001**

For each of the three tumours, a separate statistical analysis using the same statistical procedure was undertaken.

3.7.1. Ovarian tumour markers

In the ovarian cancer group consisting of 19 patients, 9 patients were receiving platinum-based chemotherapy, 7 were receiving non-platinum-based chemotherapy, while the rest, 3 were receiving a combination of chemotherapy and monoclonal antibody.

Figure 3.22, Figure 3.23 and Figure 3.24 provide the tumour marker trends for the patients receiving platinum-based chemotherapy, non-platinum-based chemotherapy and a combination of chemotherapy and bevacizumab respectively.

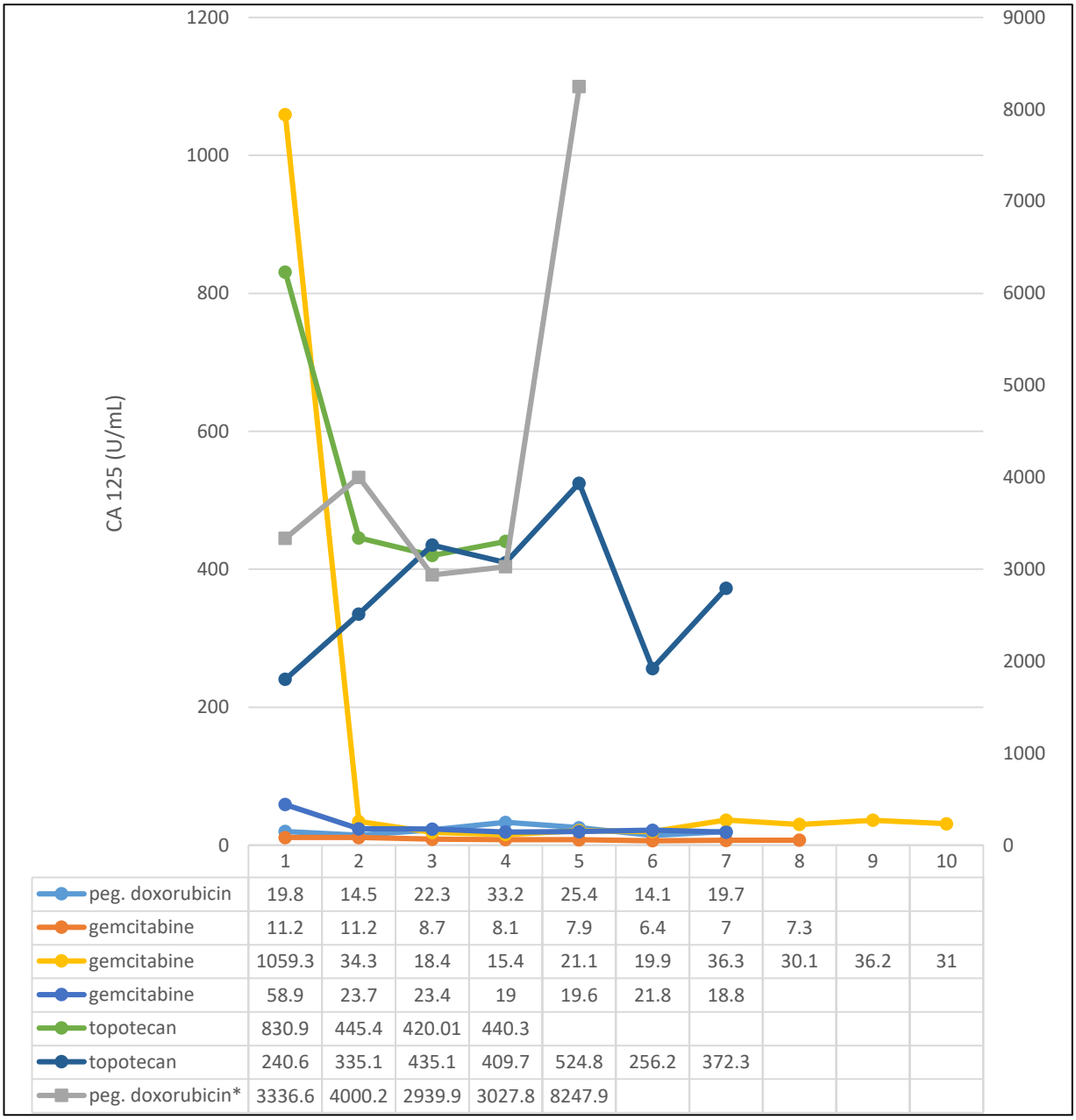


	1	2	3	4	5	6	7	8	9	10
carboplatin/paclitaxel	42.3	8.5	4.9	3.7	4.1	3.5	3.5			
carboplatin/paclitaxel	10.5	5.7	6	8	10					
carboplatin/paclitaxel	60.4	28.9	19	16.8	14.1	18.5	15.4			
carboplatin/paclitaxel	16.2									
carboplatin/paclitaxel	21.6	14.2	16.3	15.5	18.2	17.9	14.4			
carboplatin	16.5	8.2	7.2	6.8	7.7	8				
carboplatin/peg. doxorubicin	7.6	6.8	6.1	8.5						
carboplatin/olaparib*	124.3	85.7	70.6	119.2	144.3	124.8	165	254	390.5	581.7
carboplatin/peg. doxorubicin	203.1	160.6	54.7	23.7	16.1	13.4	10.5	9.3		

The x-axis represents tumour marker tests taken up during the patient monitoring, with 1 denoting the pre-treatment tumour marker test and the others listed course collectively.

Figure 3.22 CA 125 results of patients receiving carboplatin-based chemotherapy (n = 9)

(peg. doxorubicin = pegylated liposomal doxorubicin)

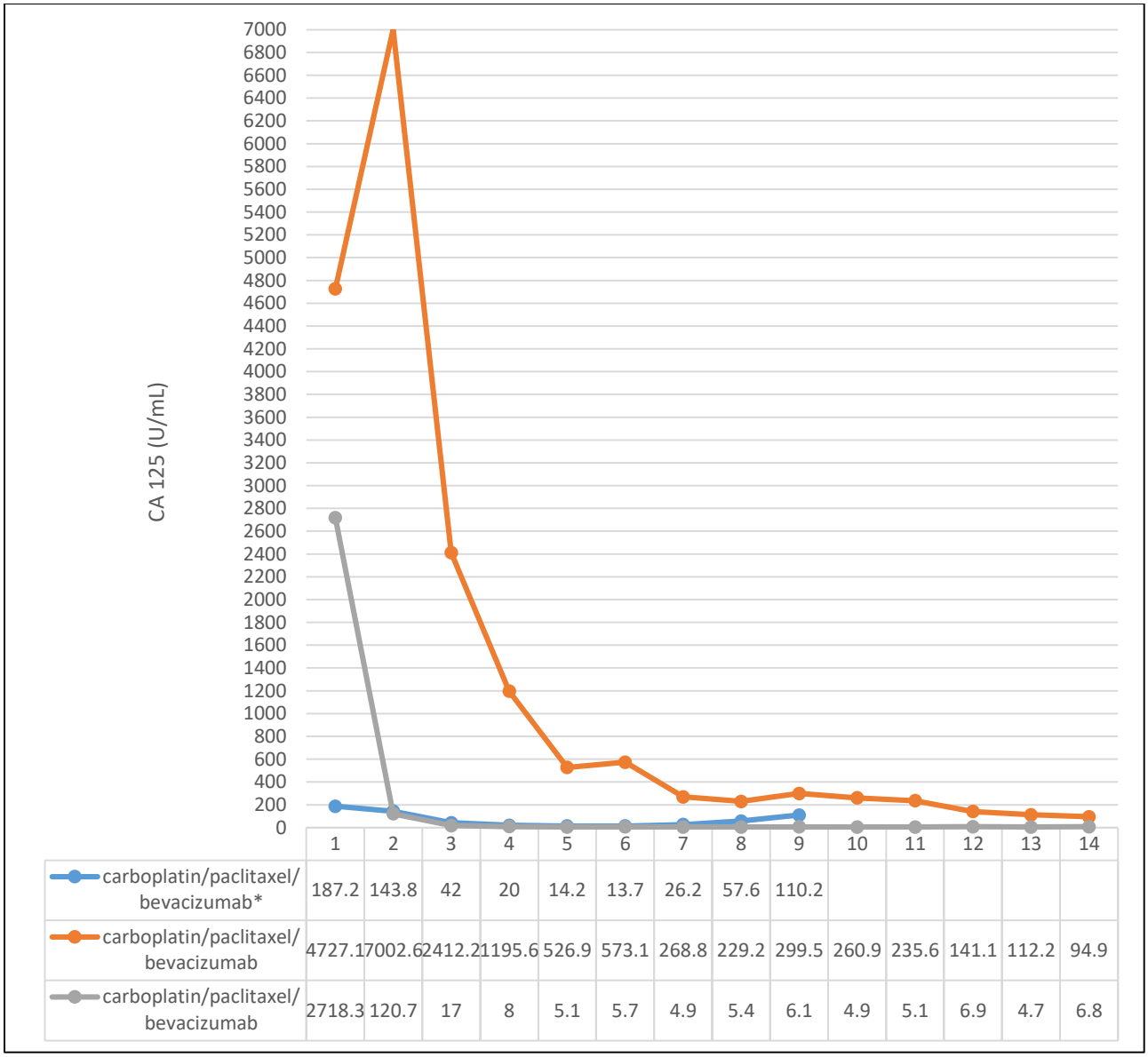


	1	2	3	4	5	6	7	8	9	10
peg. doxorubicin	19.8	14.5	22.3	33.2	25.4	14.1	19.7			
gemcitabine	11.2	11.2	8.7	8.1	7.9	6.4	7	7.3		
gemcitabine	1059.3	34.3	18.4	15.4	21.1	19.9	36.3	30.1	36.2	31
gemcitabine	58.9	23.7	23.4	19	19.6	21.8	18.8			
topotecan	830.9	445.4	420.01	440.3						
topotecan	240.6	335.1	435.1	409.7	524.8	256.2	372.3			
peg. doxorubicin*	3336.6	4000.2	2939.9	3027.8	8247.9					

The x-axis represents tumour marker tests taken up during the patient monitoring, with 1 denoting the pre-treatment tumour marker test and the others listed course collectively.

Figure 3.23 CA 125 results of patients receiving non-platinum-based chemotherapy (n = 7)

(peg. doxorubicin = pegylated liposomal doxorubicin)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
carboplatin/paclitaxel/ bevacizumab*	187.2	143.8	42	20	14.2	13.7	26.2	57.6	110.2					
carboplatin/paclitaxel/ bevacizumab	4727.1	7002.6	2412.2	1195.6	526.9	573.1	268.8	229.2	299.5	260.9	235.6	141.1	112.2	94.9
carboplatin/paclitaxel/ bevacizumab	2718.3	120.7	17	8	5.1	5.7	4.9	5.4	6.1	4.9	5.1	6.9	4.7	6.8

The x-axis represents tumour marker tests taken up during the patient monitoring, with 1 denoting the pre-treatment tumour marker test and the others listed course collectively.

Figure 3.24 CA 125 results of patients receiving carboplatin, paclitaxel and bevacizumab (n = 3)

Test for normality to identify statistical test was carried out. When the relevant statistical test was applied, it was shown that there was a significant reduction in the mean tumour marker results post-treatment ($p < 0.05$).

Table 3.11 Tumour marker results pre- and post-treatment for the ovarian cancer patients (n = 19)

	Tests of normality					
	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	P-value	Statistic	df	P-value
Pre-treatment tumour marker result	0.375	19	0.000	0.598	19	0.000
Post-treatment tumour marker result	0.436	19	0.000	0.300	19	0.000
	Wilcoxon signed-rank test				
	N	Mean	Std.Deviation	Minimum	Maximum
Pre-treatment tumour marker result	19	720.65	1353.45	7.60	4727.10
Post-treatment tumour marker result	19	527.17	1877.39	3.50	8247.90

Z = -1.720, **p = 0.043**

Table 3.12 Tumour marker results pre- and post-treatment for the ovarian cancer patients except treatment switched patients (n = 16)

	Tests of normality					
	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	P-value	Statistic	df	P-value
Pre-treatment tumour marker result	0.367	16	0.000	0.556	16	0.000
Post-treatment tumour marker result	0.419	16	0.000	0.505	16	0.000
	Wilcoxon signed-rank test				
	N	Mean	Std.Deviation	Minimum	Maximum
Pre-treatment tumour marker result	16	627.77	1300.04	7.60	4727.10
Post-treatment tumour marker result	16	67.28	134.64	3.50	440.30

Z = -2.669, **p = 0.004**

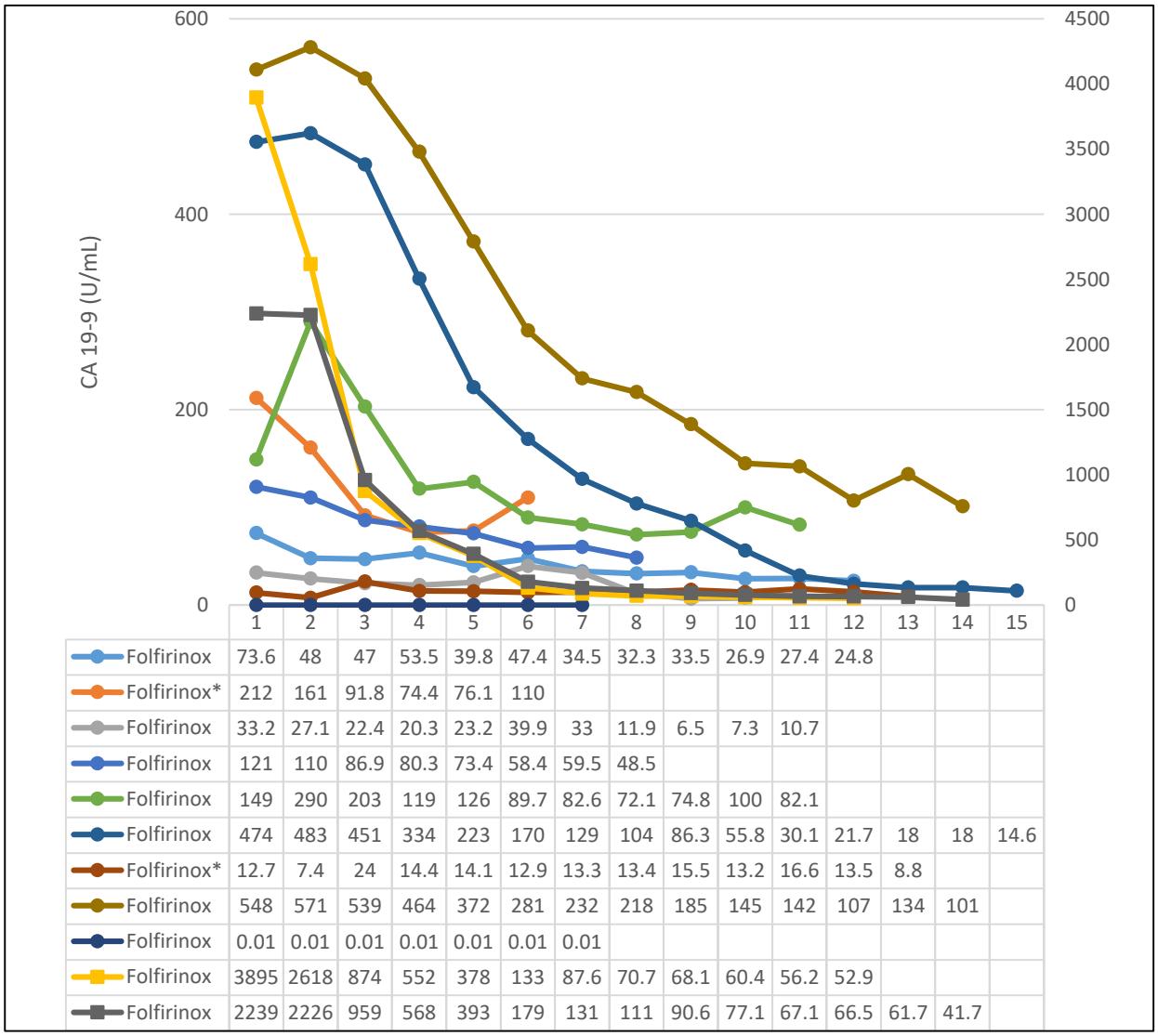
Table 3.13 Tumour marker results pre- and post-treatment for the ovarian cancer patients that finished treatment (n = 11)

	Tests of normality					
	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	P-value	Statistic	df	P-value
Pre-treatment tumour marker result	0.416	11	0.000	0.467	11	0.000
Post-treatment tumour marker result	0.209	11	0.197	0.904	11	0.209
	Wilcoxon signed-rank test				
	N	Mean	Std.Deviation	Minimum	Maximum
Pre-treatment tumour marker result	11	137.38	310.82	7.60	1059.30
Post-treatment tumour marker result	11	13.26	7.75	3.50	31.00

Z = -2.667, **p = 0.004**

3.7.2. Pancreatic tumour markers

In the pancreatic cancer group consisting of 27 patients, 11 patients were receiving Folfirinox treatment, 12 patients were receiving gemcitabine, while 4 patients were receiving a combination of both oral and intravenous treatment. Figure 3.25, Figure 3.26 and Figure 3.27 provide the tumour marker trends for the patients receiving Folfirinox, gemcitabine and combination treatment respectively.

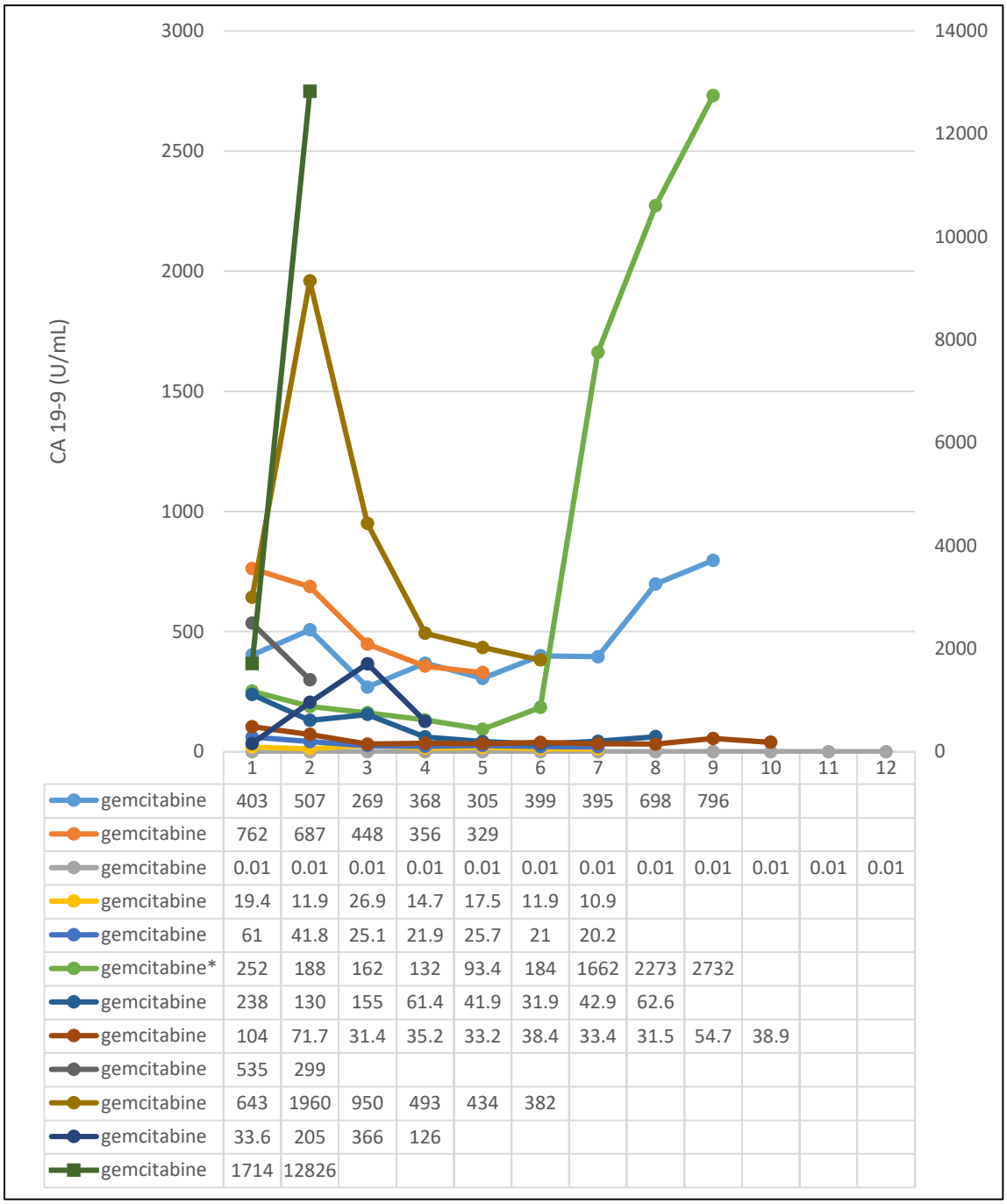


	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Folfirinox	73.6	48	47	53.5	39.8	47.4	34.5	32.3	33.5	26.9	27.4	24.8			
Folfirinox*	212	161	91.8	74.4	76.1	110									
Folfirinox	33.2	27.1	22.4	20.3	23.2	39.9	33	11.9	6.5	7.3	10.7				
Folfirinox	121	110	86.9	80.3	73.4	58.4	59.5	48.5							
Folfirinox	149	290	203	119	126	89.7	82.6	72.1	74.8	100	82.1				
Folfirinox	474	483	451	334	223	170	129	104	86.3	55.8	30.1	21.7	18	18	14.6
Folfirinox*	12.7	7.4	24	14.4	14.1	12.9	13.3	13.4	15.5	13.2	16.6	13.5	8.8		
Folfirinox	548	571	539	464	372	281	232	218	185	145	142	107	134	101	
Folfirinox	0.01	0.01	0.01	0.01	0.01	0.01	0.01								
Folfirinox	3895	2618	874	552	378	133	87.6	70.7	68.1	60.4	56.2	52.9			
Folfirinox	2239	2226	959	568	393	179	131	111	90.6	77.1	67.1	66.5	61.7	41.7	

The x-axis represents tumour marker tests taken up during the patient monitoring, with 1 denoting the pre-treatment tumour marker test and the others listed course collectively.

Figure 3.25 CA 19-9 results of patients receiving Folfirinox (n = 11)

When the tumour marker result was <2.5 U/mL, it was plotted as 0.01 for plotting purposes.

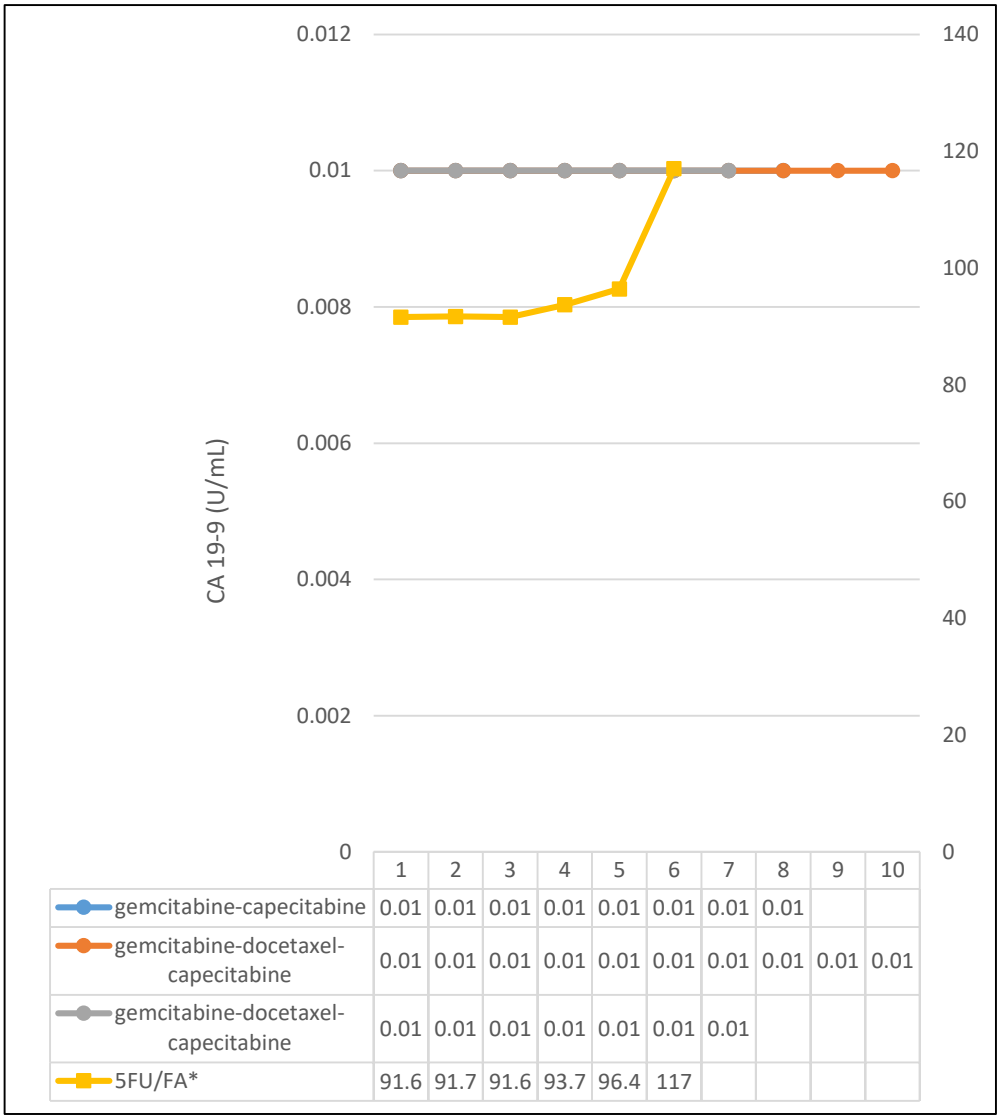


	1	2	3	4	5	6	7	8	9	10	11	12
gemcitabine	403	507	269	368	305	399	395	698	796			
gemcitabine	762	687	448	356	329							
gemcitabine	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
gemcitabine	19.4	11.9	26.9	14.7	17.5	11.9	10.9					
gemcitabine	61	41.8	25.1	21.9	25.7	21	20.2					
gemcitabine*	252	188	162	132	93.4	184	1662	2273	2732			
gemcitabine	238	130	155	61.4	41.9	31.9	42.9	62.6				
gemcitabine	104	71.7	31.4	35.2	33.2	38.4	33.4	31.5	54.7	38.9		
gemcitabine	535	299										
gemcitabine	643	1960	950	493	434	382						
gemcitabine	33.6	205	366	126								
gemcitabine	1714	12826										

The x-axis represents tumour marker tests taken up during the patient monitoring, with 1 denoting the pre-treatment tumour marker test and the others listed course collectively.

Figure 3.26 CA 19-9 results of patients receiving gemcitabine treatment (n = 12)

When the tumour marker result was <2.5 U/mL, it was plotted as 0.01 for plotting purposes.



	1	2	3	4	5	6	7	8	9	10
gemcitabine-capecitabine	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01		
gemcitabine-docetaxel-capecitabine	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
gemcitabine-docetaxel-capecitabine	0.01	0.01	0.01	0.01	0.01	0.01	0.01			
5FU/FA*	91.6	91.7	91.6	93.7	96.4	117				

The x-axis represents tumour marker tests taken up during the patient monitoring, with 1 denoting the pre-treatment tumour marker test and the others listed course collectively.

Figure 3.27 CA 19-9 results of patients receiving combination treatment (n = 4)

When the tumour marker result was <2.5 U/mL, it was plotted as 0.01 for plotting purposes. The patient represented in the light blue round data markers is not visible in the graph since it is overlapped by the patient represented in grey round data markers.

Test for normality to identify statistical test was carried out. When the relevant statistical test was applied, it was shown that there was a significant reduction in the mean tumour marker results post-treatment ($p < 0.05$).

Table 3.14 Tumour marker results pre- and post-treatment for the pancreatic cancer patients (n = 27)

	Tests of normality					
	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	P-value	Statistic	df	P-value
Pre-treatment tumour marker result	0.294	27	0.000	0.578	27	0.000
Post-treatment tumour marker result	0.436	27	0.000	0.288	27	0.000
	Wilcoxon signed-rank test					
	N	Mean	Std.Deviation	Minimum	Maximum	
Pre-treatment tumour marker result	27	467.19	864.46	0.01	3895.00	
Post-treatment tumour marker result	27	675.36	2486.15	0.01	12826.00	

Z = -1.802, **p = 0.036**

Table 3.15 Tumour marker results pre- and post-treatment for the pancreatic cancer patients except treatment switched patients (n = 23)

	Tests of normality					
	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	P-value	Statistic	df	P-value
Pre-treatment tumour marker result	0.286	23	0.000	0.611	23	0.000
Post-treatment tumour marker result	0.455	23	0.000	0.258	23	0.000
	Wilcoxon signed-rank test					
	N	Mean	Std.Deviation	Minimum	Maximum	
Pre-treatment tumour marker result	23	523.73	926.80	0.01	3895.00	
Post-treatment tumour marker result	23	663.78	2657.72	0.01	12826.00	

Z = -2.069, **p = 0.020**

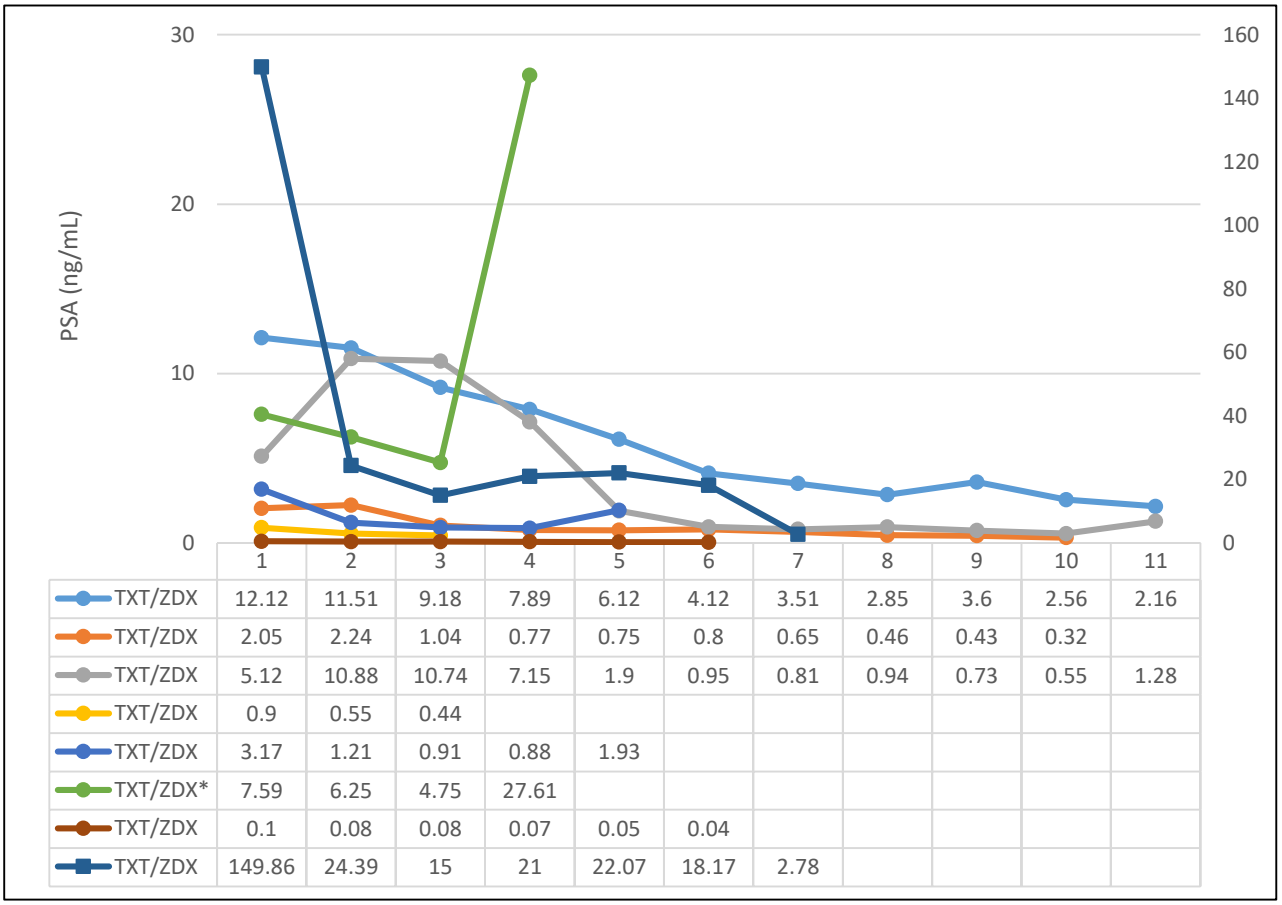
Table 3.16 Tumour marker results pre- and post-treatment for the pancreatic cancer patients that finished treatment (n = 11)

	Tests of normality					
	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	P-value	Statistic	df	P-value
Pre-treatment tumour marker result	0.370	11	0.000	0.626	11	0.000
Post-treatment tumour marker result	0.150	11	0.200	0.950	11	0.643
	Wilcoxon signed-rank test					
	N	Mean	Std.Deviation	Minimum	Maximum	
Pre-treatment tumour marker result	11	710.44	1235.20	0.01	3895.00	
Post-treatment tumour marker result	11	40.86	31.45	0.01	101.00	

Z = -2.803, **p = 0.003**

3.7.3. Prostate tumour markers

In the prostate cancer group consisting of 21 patients, 8 patients were receiving docetaxel treatment, 4 patients were receiving oral treatment, while 9 patients were receiving Zoladex® LA with or without dexamethasone. Figure 3.28, Figure 3.29 and Figure 3.30 provide tumour marker trends for the patients receiving docetaxel treatment, oral treatment, Zoladex® LA 10.8mg with or without dexamethasone respectively.

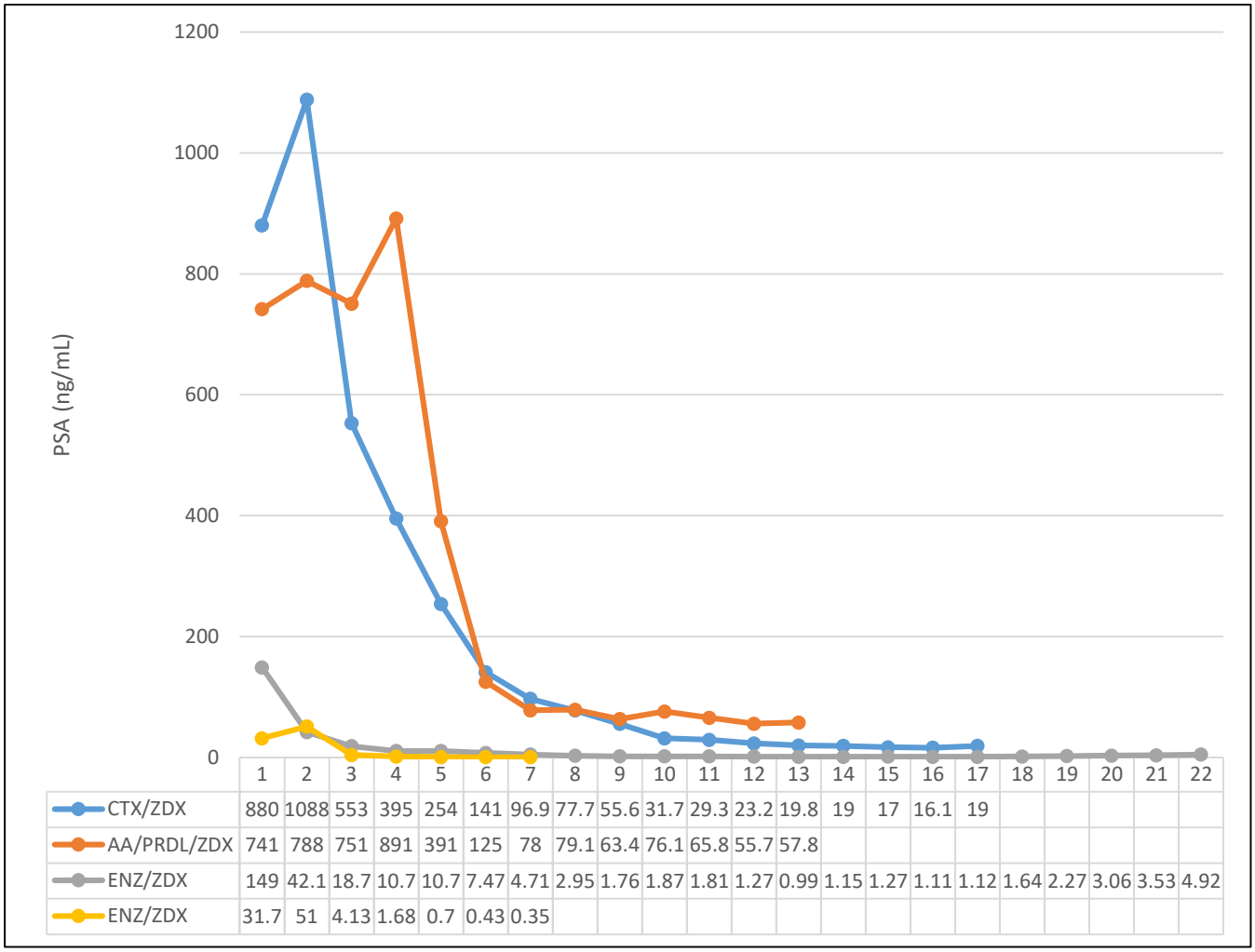


	1	2	3	4	5	6	7	8	9	10	11
TXT/ZDX	12.12	11.51	9.18	7.89	6.12	4.12	3.51	2.85	3.6	2.56	2.16
TXT/ZDX	2.05	2.24	1.04	0.77	0.75	0.8	0.65	0.46	0.43	0.32	
TXT/ZDX	5.12	10.88	10.74	7.15	1.9	0.95	0.81	0.94	0.73	0.55	1.28
TXT/ZDX	0.9	0.55	0.44								
TXT/ZDX	3.17	1.21	0.91	0.88	1.93						
TXT/ZDX*	7.59	6.25	4.75	27.61							
TXT/ZDX	0.1	0.08	0.08	0.07	0.05	0.04					
TXT/ZDX	149.86	24.39	15	21	22.07	18.17	2.78				

The x-axis represents tumour marker tests taken up during the patient monitoring, with 1 denoting the pre-treatment tumour marker test and the others listed course collectively.

Figure 3.28 PSA results of patients receiving docetaxel treatment (n = 8)

(TXT = docetaxel; PRDL = prednisolone; ZDX = Zoladex® LA 10.8mg)

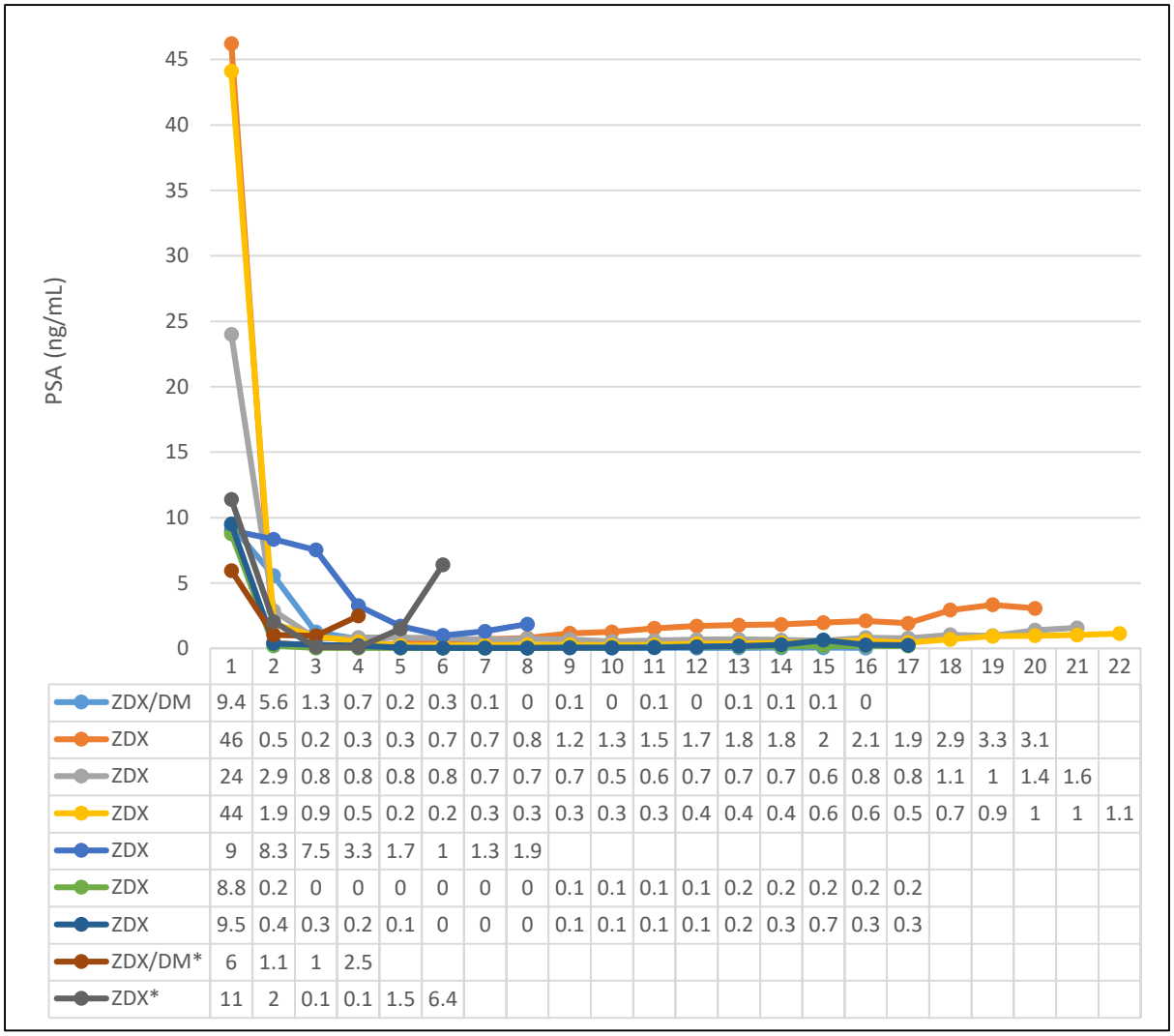


	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
CTX/ZDX	880	1088	553	395	254	141	96.9	77.7	55.6	31.7	29.3	23.2	19.8	19	17	16.1	19					
AA/PRDL/ZDX	741	788	751	891	391	125	78	79.1	63.4	76.1	65.8	55.7	57.8									
ENZ/ZDX	149	42.1	18.7	10.7	10.7	7.47	4.71	2.95	1.76	1.87	1.81	1.27	0.99	1.15	1.27	1.11	1.12	1.64	2.27	3.06	3.53	4.92
ENZ/ZDX	31.7	51	4.13	1.68	0.7	0.43	0.35															

The x-axis represents tumour marker tests taken up during the patient monitoring, with 1 denoting the pre-treatment tumour marker test and the others listed course collectively.

Figure 3.29 PSA results of patients receiving oral treatment (n = 4)

(AA = abiraterone acetate; CTX = cyclophosphamide; ENZ = enzalutamide; PRDL = prednisolone; ZDX = Zoladex® LA 10.8mg)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
ZDX/DM	9.4	5.6	1.3	0.7	0.2	0.3	0.1	0	0.1	0	0.1	0	0.1	0.1	0.1	0						
ZDX	46	0.5	0.2	0.3	0.3	0.7	0.7	0.8	1.2	1.3	1.5	1.7	1.8	1.8	2	2.1	1.9	2.9	3.3	3.1		
ZDX	24	2.9	0.8	0.8	0.8	0.8	0.7	0.7	0.7	0.5	0.6	0.7	0.7	0.7	0.6	0.8	0.8	1.1	1	1.4	1.6	
ZDX	44	1.9	0.9	0.5	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.6	0.6	0.5	0.7	0.9	1	1	1.1
ZDX	9	8.3	7.5	3.3	1.7	1	1.3	1.9														
ZDX	8.8	0.2	0	0	0	0	0	0	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2					
ZDX	9.5	0.4	0.3	0.2	0.1	0	0	0	0.1	0.1	0.1	0.1	0.2	0.3	0.7	0.3	0.3					
ZDX/DM*	6	1.1	1	2.5																		
ZDX*	11	2	0.1	0.1	1.5	6.4																

The x-axis represents tumour marker tests taken up during the patient monitoring, with 1 denoting the pre-treatment tumour marker test and the others listed course collectively.

Figure 3.30 PSA results of patient receiving Zoladex® LA 10.8mg with or without dexamethasone (n = 9)

(DM = dexamethasone; ZDX = Zoladex® LA 10.8mg)

Test for normality to identify statistical test was carried out. When the relevant statistical test was applied, it was shown that there was a significant reduction in the mean tumour marker results post-treatment ($p < 0.05$).

Table 3.17 Tumour marker results pre- and post-treatment for the prostate cancer patients (n = 21)

	Tests of normality					
	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	P-value	Statistic	df	P-value
Pre-treatment tumour marker result	0.402	21	0.000	0.464	21	0.000
Post-treatment tumour marker result	0.360	21	0.000	0.511	21	0.000

	Wilcoxon signed-rank test				
	N	Mean	Std.Deviation	Minimum	Maximum
Pre-treatment tumour marker result	21	102.45	240.30	0.10	880.00
Post-treatment tumour marker result	21	6.46	13.60	0.04	57.82

Z = -1.802, **p = 0.036**

Table 3.18 Tumour marker results pre- and post-treatment for the prostate cancer patients except treatment switched patients (n = 18)

	Tests of normality					
	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	P-value	Statistic	df	P-value
Pre-treatment tumour marker result	0.388	18	0.000	0.503	18	0.000
Post-treatment tumour marker result	0.406	18	0.000	0.425	18	0.000

	Wilcoxon signed-rank test				
	N	Mean	Std.Deviation	Minimum	Maximum
Pre-treatment tumour marker result	18	118.14	257.11	0.10	880.00
Post-treatment tumour marker result	18	5.51	13.76	0.04	57.82

Z = -2.069, **p = 0.020**

Table 3.19 Tumour marker results pre- and post-treatment for the prostate cancer patients that finished treatment (n = 6)

	Tests of normality					
	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	P-value	Statistic	df	P-value
Pre-treatment tumour marker result	0.443	6	0.000	0.557	6	0.000
Post-treatment tumour marker result	0.183	6	0.200	0.942	6	0.675

	Wilcoxon signed-rank test				
	N	Mean	Std.Deviation	Minimum	Maximum
Pre-treatment tumour marker result	6	28.74	59.48	0.10	149.86
Post-treatment tumour marker result	6	1.42	1.08	0.04	2.78

Z = -2.201, **p = 0.014**

3.8. Pharmaceutical Care Issues

In this study, patients were followed throughout the duration of treatment or until the end of the study period, hence multiple PCIs, causes and interventions were identified for each patient. A total of 238 PCIs were identified, ranging from 2 to 5 PCIs per patient. The mean was 3.55 PCIs per patient. The total number of PCIs identified per patient, frequency and ranking of different categories of PCIs identified are tabulated in Table 3.20, Table 3.21, and Table 3.22 respectively.

Table 3.20 Frequency of pharmaceutical care issues (N = 238)

Number of PCIs	Frequency	Percentage (%)
2	8	11.9
3	23	34.3
4	27	40.3
5	9	13.4
Total	67	100.0

Table 3.21 Categories of pharmaceutical care issues (N = 238)

PCI	Frequency	Percentage (%)
Additional medication needs	47	70.1
Inappropriate compliance and failure to receive medicines appropriately	14	20.9
Adverse drug reactions	65	97.0
Interactions	8	11.9
Counselling needs	65	97.0
Monitoring needs	5	7.5
Seamless care needs	34	50.7

Table 3.22 Ranking of pharmaceutical care issues (N = 238)

PCI	Number of patients	Percentage (%)
Counselling needs	65	97.0
Adverse drug reactions	65	97.0
Additional medication needs	47	70.1
Seamless care needs	34	50.7
Inappropriate compliance and failure to receive medicines appropriately	14	20.9
Interactions	8	11.9
Monitoring needs	5	7.5

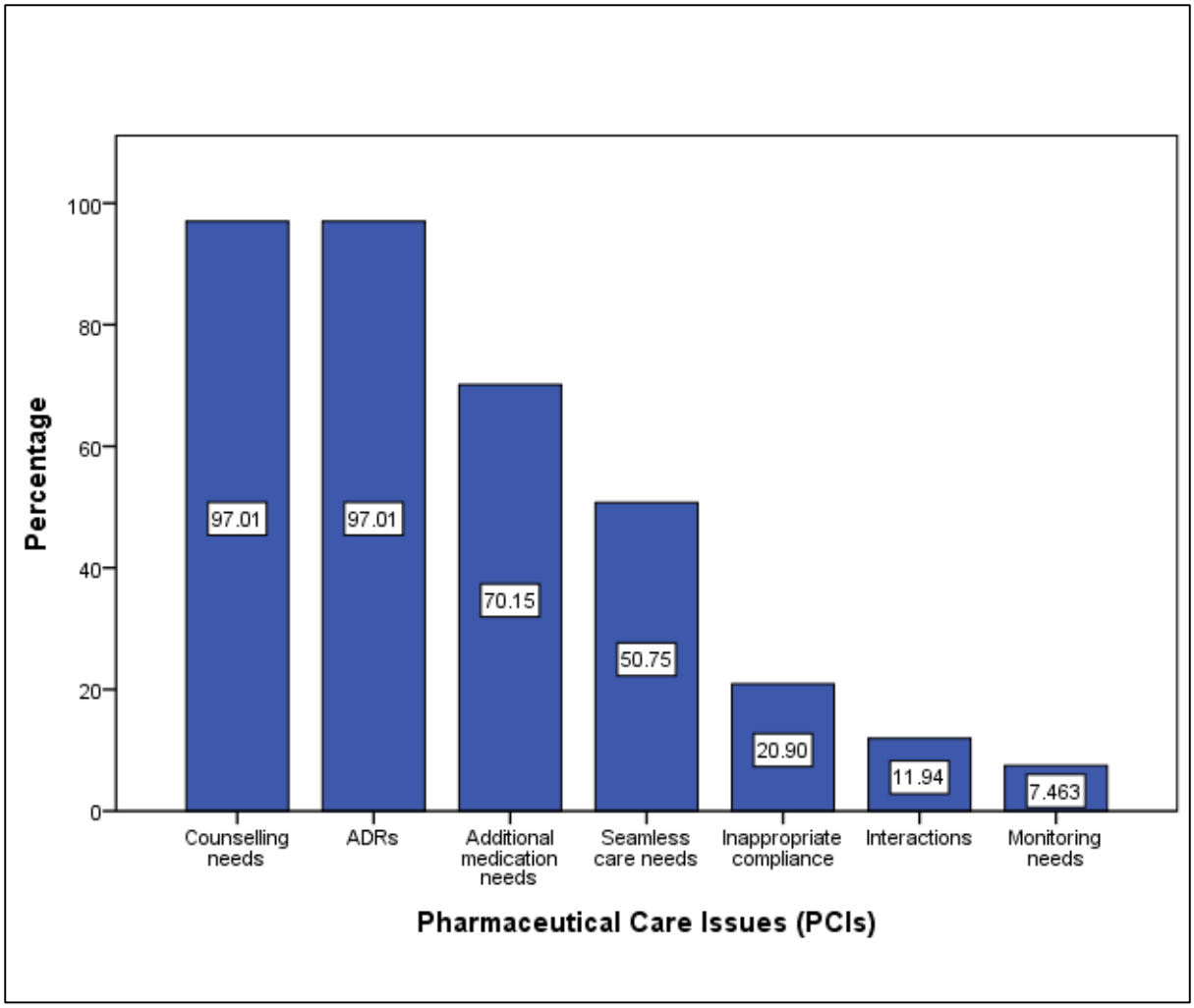


Figure 3.31 Bar graph showing ranking of pharmaceutical care issues (N = 238)

3.8.1. Counselling needs

Counselling needs were identified in sixty-five patients (97%). Counselling needs and ADRs were the most frequently identified. Of these 65 patients, 19, 27 and 19 patients suffered from ovarian, pancreatic and prostate cancer respectively. Counselling aspects were divided into compliance-related, ADRs-related, and interactions-related. The areas identified where patient education and counselling was required included; monitoring of temperature (54), diarrhoea and constipation (30), other such as neutropenic advice (20), good oral hygiene (18), fatigue (17), nausea and vomiting (13), compliance (7), myalgia/arthralgia (5), alopecia (4), hand-foot syndrome (HFS) (4), neuropathy (4) and interactions (2).

Actions/recommendations implemented were categorised as; interviewing and counselling of the patient (55), recommendations of a non-medical measure (43), recommendation of a preventive measure (25), patient awareness importance of compliance and understanding of how and when to take the medication(s) (9), patient awareness of interactions with other drugs (including OTC), food and alcohol (4), patient awareness of ADRs (3) and drug information search (2).

'Other' refers to advice such as neutropenic advice. Patients were counselled about the importance to take precautions to avoid infection and the signs of infection such as pyrexia, productive cough, flu-like symptoms, dysuria, inflamed or discharging wound, diarrhoea, unusual bruising or bleeding. Precautions included good hand-washing practices, frequent hand washing, general good hygiene, washing fruit and vegetables, cooking vegetables and avoiding salads. Patients were advised to avoid crowds and closed places, being near people who have a cold, to avoid sun exposure and to apply sunscreen daily and to avoid injury, even small cuts or tears in the skin. Drinking plenty of water is also beneficial, while consumption

of alcohol should be kept to a minimum. In case of flu-like symptoms, the patient should keep warm with blankets and drink plenty of liquids. The patients were also educated to identify symptoms of oral mucositis/stomatitis, which include pain, redness, swelling or sores in the mouth. The researcher advised on good oral hygiene i.e. rinsing the mouth frequently and effective brushing of the teeth with a soft brush 2-3 times daily, to concentrate on soft food and to drink plenty of fluids. In cases of development of sore throat, saline mouthwash should be used.

Fatigue was ranked as the first ADR experienced in this population. Patients were advised to take breaks and naps. Relaxation techniques help to reduce stress. Maintaining good nutrition is vital. Some patients required counselling about nausea and vomiting. The researcher educated the patient to eat small, frequent meals, liquids before (not with) food and avoiding strong smells. Breathing deeply can also reduce nausea. Dry cereal, toast, crackers especially in the morning help to curb nausea. For myalgia or arthralgia, the researcher advised to rest, and counselled patients on management consisting of NSAIDs to be prescribed by the caring consultant and reassured the patient that it is self-limiting. Alopecia is one of the most distressing side effects of CT. It was advised that if chemotherapy-induced alopecia occurs, it is important to protect the scalp with sunscreen, or a hat or a wig. The patients were educated on how to identify symptoms of neuropathy, such as tingling, numbness or pain in hands/feet especially with taxol. Oncology medications that can cause HFS also called palmar-plantar erythrodysesthesia (PPE), amongst others are capecitabine, 5-FU, pegylated liposomal doxorubicin, paclitaxel and docetaxel. The patients were educated on how to identify symptoms of HFS such as pain, swelling or redness or peeling of the skin in the hands and/or feet which may affect day-to-day activities. To minimize risk of HFS after an infusion, it was advised to keep hands and feet as cool as possible. The patients were

educated not to wear tight-fitting gloves or socks, and to avoid wearing tight-fitting footwear and high-heeled shoes. Patients required awareness about the importance of compliance and understanding how and when to take the medication(s). Apart from compliance with medication, compliance not to miss any appointment was emphasized. Patients were educated and counselled about awareness of interactions especially with other drugs (including OTC), food and alcohol. They were advised not to buy any OTC medications unless advised by their caring consultant.

3.8.2. Adverse drug reactions

ADRs were identified in 65 patients (97%). The most commonly identified ADRs as indicated in Table 3.23 were fatigue (52%), followed by oral (36%), myalgia/arthralgia (33%), diarrhoea (31%), bone marrow suppression (30%), constipation (28%), sensory neuropathy (25%) and nausea (24%). Patient's fear of ADR was identified in eight patients, followed by medication stopped due to unacceptable ADR (3) and presence of allergic reaction (1). The type and frequency of ADRs identified are shown in Table 3.23, while percentage of patients grouped by ADRs are shown in Figure 3.32.

Table 3.23 ADRs identified (N = 67)

Type of ADR	n	%
fatigue	35	52
oral (stomatitis, mouth ulcers, thrush, altered or bad taste)	24	36
myalgia/arthralgia	22	33
diarrhoea	21	31
bone marrow suppression	20	30
constipation	19	28
sensory neuropathy	17	25
nausea	16	24
others	14	21
insomnia	14	21
vomiting	13	19
itching or rash	13	19
loss of appetite/change in weight/anorexia	13	19
motor neuropathy	11	16
lymphoedema	10	15
fever/chills	6	9
alopecia	5	7
anxiety/change in mood or depression	5	7
infusion-related hypersensitivity	4	6
dysuria/urinary symptoms	4	6
hand-foot syndrome (HFS)	3	4
skin toxicity	2	3
menopausal symptoms	2	3
infection	2	3
cough	2	3
dyspnoea	2	3
allergic reactions/ hypersensitivity	1	1
pain or difficulty with swallowing	1	1
thromboembolism	0	0
tumour lysis syndrome	0	0
hyperuricaemia	0	0
pregnancy and reproductive function	0	0
cardiotoxicity	0	0
nephrotoxicity	0	0
ototoxicity	0	0
sexual problems	0	0
flu-like symptoms	0	0

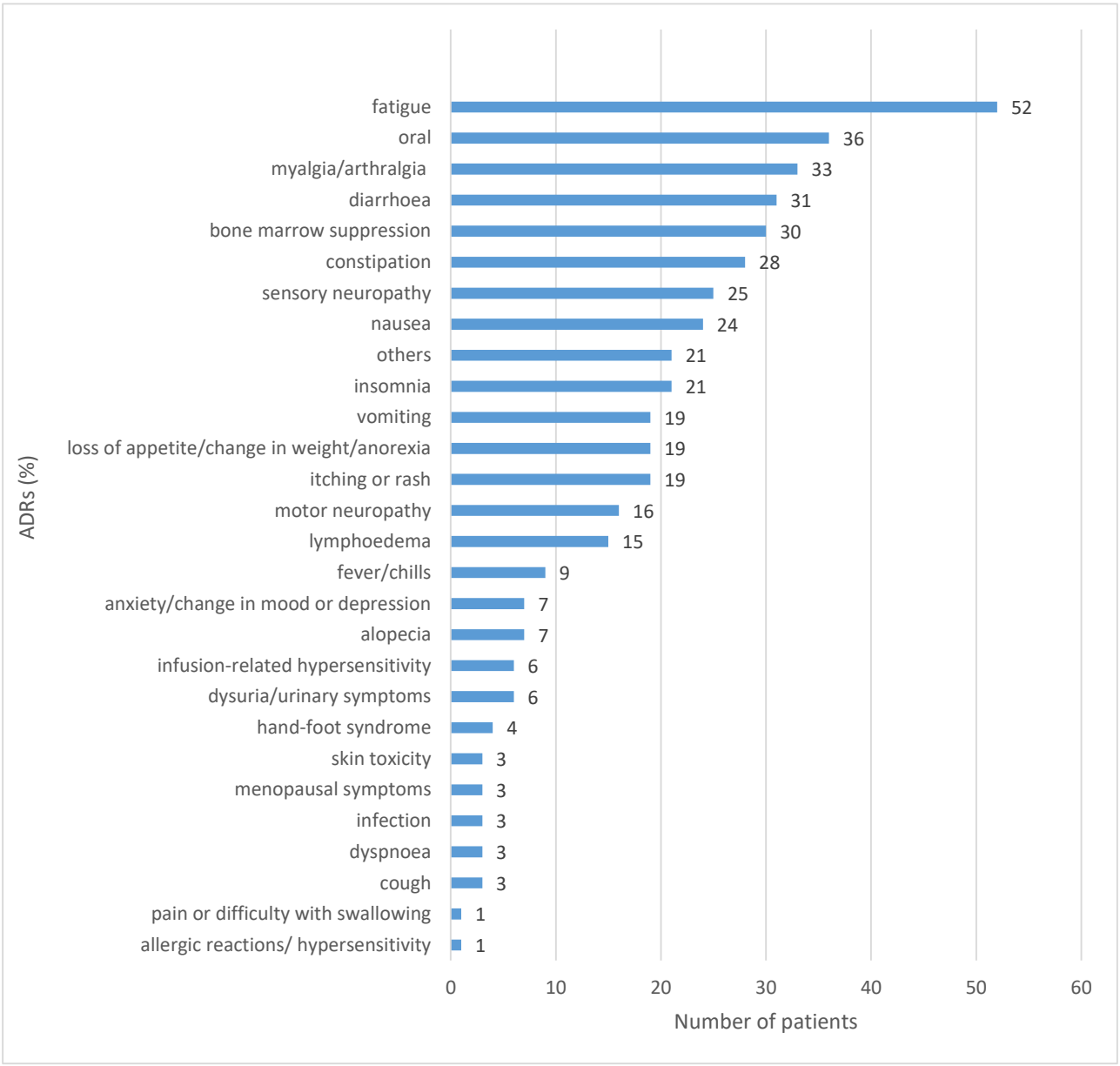


Figure 3.32 Percentage of patients grouped by ADRs (N=67)

Actions taken for counselling patient's fear of ADRs was implemented in 45 patients, followed by identifying ADRs (36), drug information search (7) and others (3).

3.8.3. Additional medication needs

Additional medication needs were identified in 47 (70.1%) patients, including 13, 24 and 10 patients suffering from ovarian, pancreatic and prostate cancer respectively. Causes of this PCI, included; other (43) such as new condition requiring medication related to the malignancy, followed by preventive/prophylactic (11) and synergistic/potentiating (2).

'Other' was defined as additional medication needs related to malignancy. Acid-related disorders preventative measures included eating small, frequent meals, avoiding spicy, fatty and oil-based food, and reducing caffeine and alcohol intake. Raising the head of the bed and not eating a big meal before going to bed are additional help. Two patients required antacids with anti-flatulent such as Maalox plus® oral suspension containing dried aluminium hydroxide (antacid), magnesium hydroxide (antacid) and simeticone (antifoaming agent/ anti-flatulent). A patient required sodium alginate and potassium bicarbonate (Gaviscon®). Another patient required the addition of esomeprazole magnesium trihydrate (Nexium®). Two patients required omeprazole 20mg capsules such as Losec®. The antithrombotic agent enoxaparin sodium (Clexane®) was prescribed to a patient as treatment for venous thromboembolism presenting with pulmonary embolism.

Nine patients required lactulose oral solution (Duphalac®). In some cases, constipation was due to opioid-based analgesics such as codeine preparations. Lactulose solution may be administered diluted or undiluted. Each dose may if necessary be taken with water or fruit juices. During therapy with laxatives, it was recommended to drink sufficient amounts of fluids (1.5-2 litres, equal to 6-8 glasses) during the day. Two patients required Movicol® sachets powder for oral solution, containing macrogol, sodium chloride, sodium bicarbonate and potassium chloride. Each sachet should be dissolved in 125 ml water. Loperamide 2mg

hard capsules (Imodium®) and oral rehydration salts/solution (ORS) (Dioralyte®) were frequently prescribed for diarrhoea. The patients were advised to limit use of loperamide as much as possible and to increase ORS intake. Another patient receiving Folfirinox treatment was prescribed pancreatin capsules (Creon®).

Dermatological conditions observed included rash with or without itching. Preparations prescribed included steroid preparations such as 0.1% w/w hydrocortisone butyrate (Locoid lipocream), 0.0525% w/w clobetasol propionate (Dermovate®) and antihistamine medication hydroxyzine hydrochloride 25mg film-coated tablets (Atarax®). Dry skin was present due to HFS, in which petroleum jelly-based products such as Vaseline® or colloidal oatmeal-based products such as DermaVeen® were used. A patient had high fever, which required paracetamol 500mg tablets (Panadol®), after doctor's consultation. One patient required folic acid tablets due to folic-acid deficiency. Another patient required treatment for hyperkalaemia, and required calcium resonium medication. A patient was commenced on amlodipine 5mg tablets (Amlo®).

Oral mucositis and mouth ulcers were managed with saline or non-alcoholic mouthwash. Oral thrush (candidiasis) was present in two patients, who required nystatin 100,000 units/ml ready mixed oral suspension (Nystan®). The dosage regimen is 4 - 6 ml (400,000 - 600,000 U) four times daily (half dose in each side of the mouth). It was recommended to keep the medication in contact with the affected areas as long as possible. One of these patients was also recommended Betadine® mouthwash. Two patients required hydroxyzine hydrochloride 25mg film-coated tablets (Atarax®) half a tablet daily, which was indicated to treat anxiety disorders and for the treatment of sleep disorders. Five patients required oral complete nutritional supplement with increased level of energy and protein such as Resource Energy®.

These preparations are indicated for malnutrition patients, as enteral feeds containing 1.5kcal/mL and 5g (or more) protein/100mL. Two patients who had iron-deficiency anaemia required iron supplement. The patients were advised to increase the intake of iron-rich foods.

Fifteen patients complained about pain, including arthralgia, abdominal pain, epigastric pain and back pain. Additional medication needs included analgesic gel, paracetamol 500mg tablets (Panadol®), with or without codeine, or in cases of severe pain, morphine sulphate (MST) tablets or tramadol hydrochloride capsules. A patient who had severe generalised pain required various analgesics including morphine sulphate (MST) tablet, morphine sulphate 10mg/5ml oral solution (Oramorph®) and later morphine pump. A patient with left lower limb pain due to a pressure ulcer was prescribed codeine medication. Another patient had oedema where, bumetanide 1mg tablets were prescribed. Some patients had a history of psychiatric issues, while others did not. Medications prescribed included mexazolam (Sedoxil®), escitalopram (Cipralex®) and lorazepam (Ativan®). Another patient was prescribed amitriptyline.

Preventive/prophylactic - Amongst the different scenarios, the following were common;- Antithrombotic agent such as enoxaparin sodium pre-filled syringes (Clexane®) were prescribed to one patient as prophylaxis. Two patients required additional medication for altered or bad taste. Patients were advised to have frequent sips of water, and use antiseptic based toothpaste and mouthwash. Teeth should be brushed for 2 to 3 minutes, at least twice a day, preferably after every meal and before bedtime. It was recommended to use a soft toothbrush along with proper brushing technique. Three patients required additional prophylactic use of recombinant human granulocyte-colony stimulating factor (G-CSF) 30 MIU, such as filgrastim 30 MU (0.3mg/ml) solution for injection (Neupogen®). Three patients

required additional metoclopramide (Maxolon®) 10mg tablets due to severe emetic symptoms. In general, patients were given pre-medications as per protocols, but sometimes change in medications or dose was required. One patient, required different preparations such as metoclopramide (Maxolon®) 10mg tablets and ondansetron hydrochloride dehydrate (Zofran®) 4mg and 8mg tablets. Another patient required aprepitant capsules, which is available as 80mg and 125mg capsules. Another patient required domperidone 10mg tablets (Motilium®).

Synergistic/potentiating - Two patients required increase in dose of their anti-diabetic medication due to steroid medications. One patient required increase in dose of metformin due to dexamethasone medication, while another patient required increase in dose of gliclazide due to steroids. When steroid medications are prescribed, it is important that patients are educated about their nutrition especially if they are already diabetic.

Actions implemented were; clarification with regards to an additional drug (39), followed by recommendation of a preventive measure (36) and drug information search (2).

3.8.4. Seamless care needs

Seamless care needs were identified in 34 patients consisting of 14 patients suffering from pancreatic cancer and 10 patients suffering from ovarian or prostate cancer. Subcategory 10.1 stating 'Issues in lifestyle/behaviour are present such as smoking, alcohol use, weight changes and lack of exercise, emotional and mental health' was positive for 29 patients. The other five patients were classified under the subcategory 'Others'.

Amongst the actions carried out; 'recommending other healthcare professionals such as a general practitioner, a smoking cessation counsellor, dietician, physiotherapist or exercise specialist, psychiatrist, psychologist, counsellor, social worker, chaplain, fertility specialist or

endocrinologist, pain management clinic, palliative care team or others' was recommended for 22 patients followed by 'checking whether there is consistency, continuity, and coordination of care' which was required in 11 patients. 'Information about smoking and alcohol cessation, nutrition and physical training' and 'ensuring a seamless therapy continuation' were both necessary in 2 patients. 'Ensuring a seamless therapy continuation' was chosen in 2 cases; both suffering from prostate cancer. In 1 case, the patient had a fracture right femoral neck, and had a postponement of an appointment and it was important to make sure that the patient understood about the new appointment schedule. In the other case, the physiotherapist who advised to use a topical NSAID cream was following the patient. Hence, therapy continuation is essential.

3.8.5. Compliance

Inappropriate compliance and inappropriate failure to receive medicines appropriately were identified in 14 patients (20.9%). These included 3, 6 and 5 patients suffering from ovarian, pancreatic and prostate cancer respectively. Causes of this PCI were as follows; 'other' in 6 patients, followed by cannot afford drug product (5), patient forgets to take drug (2) and directions not understood (1). For every PCI and its possible cause identified, an action was taken. Action taken were classified as checking whether the prescribed drugs are being taken appropriately (6), searching for the reasons for primary non-compliance (5) followed by drug information search (3).

In the case of ovarian cancer, cause of PCI was listed as 5.2 'Cannot afford drug product' i.e. they had an issue of compliance since they awaited funds. These 3 patients were receiving a combination of carboplatin and paclitaxel with bevacizumab. Carboplatin and paclitaxel medications are available on the hospital formulary list. Bevacizumab is a non-formulary

medication; patients awaited funds from the Malta Community Chest Fund (MCCF) to help compensate for the expense of the medication. Patients suffering from pancreatic cancer had a variety of different causes of PCI. In 4 patients, cause of PCI was 5.7a 'Other'. The patients wished to clarify the dosage regimen administration. Two patients were receiving GTX regimen (gemcitabine, docetaxel and capecitabine) treatment; 1 patient was receiving GemCap regimen (gemcitabine and capecitabine) while the other patient was receiving 5FU/FA treatment. In the case of capecitabine tablets, the usual dosage regimen is based on BSA orally twice daily from Day 1 to 14, followed by 7-day rest (i.e. 21-day cycle). Tablets should be swallowed with water within 30 minutes after a meal. The tablets should never be crushed, broken, opened or chewed. If a dose is missed, it is important not to attempt to double up on the next dose to make up for a missed dose and not to take extra doses at the end of the treatment cycle. If vomiting occurs a few hours from taking the tablet, one should not take another tablet, but wait until the next scheduled dose. Tablets should be stored in a cool dry place, at a temperature less than 30°C. Medication should be handled by the patient only, and ensuring that gloves are always worn by anyone handling the drug. It is important not to miss any hospital appointment. In the case of 5FU/FA, folinic acid is taken orally; the patient re-questioned whether he was taking the medications correctly with regards to timing. Taking more than one tablet at the same time was a bit confusing for the patient and after explaining, the patient looked more confident to continue following the treatment schedule accordingly. The other 2 patients explained that the cause of non-compliance was due to missing an appointment due to a transport issue. In these 2 cases, 5.7 'Other' was chosen.

Five patients suffering from prostate cancer had various different causes of PCI. Two patients were receiving enzalutamide treatment together with Zoladex® LA (goserelin) 10.8mg implant in a pre-filled syringe for subcutaneous use administered every 3 months. Enzalutamide, available as 40mg soft capsule is not yet available in the hospital formulary list, hence treatment could be paid either completely out-of pocket by the patient or else through application for funding through MCCF. These two pensioner patients explained that they could not afford the drug i.e. '5.2 - Cannot afford drug product.' The usual dosage regimen is 160mg (i.e. 4 capsules) orally once daily throughout treatment. Capsules should be swallowed whole with water, with or without food, must not be crushed, chewed or opened or dissolved. Treatment is continuous until disease progression or unacceptable toxicity. Since this is a long-term use medication, it is surely beneficial if these patients are provided some kind of funding. One patient receiving abiraterone together with prednisolone tablets explained that on some occasions, he forgot to take the medication, hence 5.6 – 'Patient forgets to take it' was identified. Abiraterone is available as 250mg tablets. The usual dosage is 1000mg (i.e. 4 x 250mg) orally once daily throughout treatment. Abiraterone is given combined with prednisolone 5mg at a usual dosage of 5mg orally twice daily throughout treatment. Abiraterone should be swallowed whole on an empty stomach i.e. at least one hour before food and at least two hours after any previous food. Taking the tablets with food can dramatically increase the absorption of abiraterone, dependent on the fat content of the food. Treatment is continuous until disease progression or unacceptable toxicity. When abiraterone is discontinued, prednisolone dose should be tapered slowly, and monitoring for adrenocortical insufficiency should occur. Prednisolone should only be taken once daily, with food or after a meal, taken before noon to help promote better sleep. With both medications, if the patient missed a dose, she/he should not double up the next dose but resume normal

dosing the following day. Another patient was receiving docetaxel and prednisolone 5mg orally twice daily throughout treatment and may be omitted on the days that dexamethasone pre-medication is required. He claimed that on some occasions he forgot to take the prednisolone medication, hence 5.6 – 'Patient forgets to take it' was identified. Having to switch from one medication to another may create some unintentional non-compliance, especially if the patient is elderly such as in this case, where the patient was 69 years old. The last patient also receiving docetaxel and prednisolone 5mg orally twice daily throughout the treatment claimed that he did not understand how to take the medications, hence 5.4 – 'Directions not understood' was identified. He was confused when to take the dexamethasone and when to switch to prednisolone medication. This dosage regimen was clearly explained both verbally and the treatment chart was reviewed. The patient repeated the regimen himself to ensure that he had understood it completely.

3.8.6. Interactions

Interactions issues were identified in 8 patients (11.9%), consisting of 3, 2 and 3 patients suffering from ovarian, pancreatic and prostate cancer respectively. The causes of interaction issues were various including patient's fear of an interaction (6), followed by reference to an interaction by literature (1) and other (1). Actions were also implemented. As per other PCIs, more than one required action per patient could be identified. Advice to the patient on fear of the interaction, drug information search, information about possible interactions and countermeasures were identified in 5, 4 and 1 patient respectively. Patients taking psychiatric medications or had a medical history of psychiatric problems were very cautious and expressed fear of interaction. The researcher assured the patients that there was no interaction between the current medications including the antipsychiatric treatment and antineoplastic medications. Drug information search was carried out for the medications.

Patients with polypharmacy also expressed fear of interaction. It was observed that patients were willing to learn about their malignancy and even looked up information on the internet about herbal preparation, including herbal teas that can be added to their current antineoplastic medications. Patients were counselled not to start any herbal preparations or OTC preparations unless discussed and given permission to proceed from their caring consultant. Patients were advised to take paracetamol as the first step in cases of pain. When paracetamol did not provide analgesic relief, the analgesic ladder was followed, and a codeine-containing preparation was prescribed. It was identified in 2 patients who were not aware that paracetamol-containing medications should not be taken at the same time with paracetamol. Applications such as Medscape Drug Interaction Checker and Drugs.com Drug Interactions Checker are reliable sources.

3.8.7. Monitoring needs

Monitoring needs were identified in only 5 patients (7.5%), including 3 and 2 patients suffering from pancreatic and prostate cancer respectively. Two patients were receiving Folfirinox, 1 was receiving gemcitabine and 2 were receiving docetaxel. Incorrect frequent monitoring of tumour markers was identified in 3 patients, followed by 'other' cause (2). Tumour marker was not monitored as advised by the protocol in 3 patients, while monitoring of Mg2+ was not monitored in 2 patients. Actions taken included; to check the frequency of tumour markers (3), followed by drug information search (1) and other (1). 'Others' referred to requirement of checking Mg2+.

In this research, there were different scenarios where treatment switching was required. An ovarian cancer patient who was receiving carboplatin and olaparib had a pre-treatment CA 125 of 124.3 U/mL. At the beginning, there was a positive response to treatment, since there

was a decrease in tumour marker trend but later, there was an increase in tumour marker trend. A PCI related to ADRs was recurrent episodes of neutropenia, thrombocytopenia and leukopenia. Due to this picture, the patient had treatment switching to gemcitabine. Another ovarian cancer patient who was receiving carboplatin and paclitaxel, resulted in a decrease in CA 125 trend. Imaging showed partial response to treatment and she was experiencing worsening of peripheral neuropathy due to paclitaxel. In view of this, treatment was switched to a combination of carboplatin and pegylated liposomal doxorubicin, to which she responded well, resulting in a post-treatment CA 125 of 8.5 U/mL. Another ovarian cancer patient who was receiving pegylated liposomal doxorubicin experienced severe HFS. There was a slight decrease in CA 125 level in the beginning of treatment but then there was a trend of elevated CA 125 values. Considering the trend in CA 125 results and the presence of severe HFS, treatment was switched to gemcitabine. Lastly, an ovarian cancer patient who was receiving a combination of carboplatin, paclitaxel and bevacizumab was not responding very well to this treatment since there was a decrease, but later an increase in tumour marker trend. Even though, the patient had no complaints, imaging showed new metastatic deposits. Treatment was switched to pegylated liposomal doxorubicin.

There were also patients suffering from pancreatic cancer who required treatment switching. Two patients who were receiving Folfirinox required treatment switching to gemcitabine. One patient had a pre-treatment CA 19-9 of 212 U/mL and a post-treatment CA 19-9 of 110 U/mL. Imaging had shown metastasis to the lungs. The patient had experienced drastic weight loss of 11kg and persistent loose stools. The other patient had a pre- and post-treatment CA 19-9 of 12.7 U/mL and 8.8 U/mL respectively. Even though, both CA 19-9 values were within the reference range of CA 19-9 levels, computed tomography imaging had shown mild progression of disease. Patient was feeling well, had good appetite and was pain-free

but was not a candidate for radiotherapy. The way forward was switching to gemcitabine treatment in both cases.

An example of treatment switching in prostate cancer patients is the following. The pre-treatment PSA level was 6 ng/mL and post-treatment was 2.5 ng/mL. The patient had gained weight and developed gross lower limb oedema due to dexamethasone treatment. In view of the above, even though PSA level was within the reference range, treatment switching to bicalutamide was required.

Chapter 4

Discussion

4.1. Main findings

This study indicates that the presence of the researcher helped to identify and resolve the number of PCIs experienced by oncologic patients suffering from ovarian, pancreatic or prostate cancer at SAMOC, ensuring that patients are receiving the highest standard of care. The primary outcome was the type of PCIs encountered by the patients, as identified by the researcher, and classified according to the classification developed. The researcher identified a mean of 3.55 PCIs per patient, indicating that this model can help to identify and resolve PCIs. The developed and implemented individualised PCP was a helpful tool for the clinical pharmacist who can update patient pharmaceutical care records according to the PCIs identified whilst at the same time taking into consideration relevant tumour marker trends and other laboratory investigations. The PCP contributes to optimising patient care within a collaborative management. This research demonstrated the importance of pharmacists working in collaboration within a MDT. Clinical pharmacists have an expanded role in oncology teams, such as introducing individualised treatment plans, monitoring CT and providing patient counselling and education about medications.

This research was the first study implemented at SAMOC about PCIs encountered by oncology patients, and the PCP was the first template to be designed and implemented. Implementation of this model, contributed to a more individualised personalised pharmaceutical care approach leading to an overall better quality of service offered to oncology patients. The pharmacist can work closely with oncology patients and their HCPs to help achieve improved clinical outcomes.

There was an association between gender and cancer type ($p < 0.001$). This was expected since ovarian cancer and prostate cancer are only present in female and male patients

respectively. Pancreatic cancer was present in approximately the same ratio in both male and female oncologic patients. There was a significant association between age and cancer type ($p = 0.003$). Ovarian cancer patients had a higher tendency to be younger in age compared to pancreatic or prostate cancer patients. A higher percentage of patients aged 55 years or less suffered from ovarian cancer. This research highlights the importance to keep abreast of gynaecological follow-up appointments, leading to the identification of cancer-related signs and symptoms at an earlier stage. Patients aged 56-65 years had a higher probability to suffer from pancreatic cancer, while patients aged 66 years or over had a higher probability to suffer from prostate cancer. Some pancreatic cancer patients (11.1%) were older than 76 years. The majority of patients (52.4%) suffering from prostate cancer were older than 66 years.

There was an association between gender and smoking status ($p = 0.003$). There was a higher prevalence of male present smokers and past smokers than females. There was a larger percentage of males (51.4%, 11.4%) compared to females (15.6%, 6.3%), who either were past smokers or smoke at most one packet per day. In the Maltese population, males smoke more than the females, although this trend is changing with time since smoking rate in females is increasing. There was also an association between gender and caffeine consumption ($p = 0.010$). There was a higher prevalence of male who consumed 1 to 2 or more than 2 beverages containing caffeine per day. There were a larger percentage of males (74.3%, 25.7%) compared to females (53.1%, 18.8%), who consumed either 1 to 2 or more than 2 beverages containing caffeine per day. There was association between gender and alcohol consumption ($p = 0.047$). There was a higher prevalence of males with past or current alcohol use. There was a larger percentage of males (28.6%, 14.3%) compared to females

(6.3%, 12.5%), who either had past history of alcohol consumption or consumed less than two units per week.

An association between level of education and age groups ($p < 0.001$) was observed. Only one patient aged 26 years, had a post-secondary vocational level of education. Patients with post-secondary vocational or tertiary level of education were ≤ 65 years.

In Malta, at SAMOC, one can observe that monitoring laboratory parameters, including tumour markers, is very meticulously as advised by clinical guidelines and protocols. Monitoring tumour marker trends was conducted for all treatments and statistical analysis was carried out after testing for the normality assumption. It transpired that, as expected, there was a significant reduction in the mean tumour marker results post-treatment ($p < 0.05$). A reduction in post-treatment tumour marker result gives an indication that the patient is responding well to treatment. Radiological procedures are still required in conjunction with serial monitoring of tumour markers to assess response to treatment.

4.2. Pharmaceutical Care Issues

The clinical pharmacist plays a pivotal role in the pharmacotherapy of cancer and non-cancer medications, by optimizing medication therapy, enhancing compliance through patient education and counselling regarding adverse effect management and prevention, and monitoring laboratory parameters.

The pharmacist is responsible for medication reconciliation, which includes assessment for untreated conditions, duplications in therapy, ADRs and drug interactions. Polypharmacy in oncologic patients is commonly present. MR is a major component of safe patient care in any environment. The researcher conducted standardized comprehensive medication history interview and MR for all the patients. The patient may have had a medication added,

medication stopped or dose reduction by the family doctor and may not have informed the oncology HCT. After reviewing the patient's medical history, the researcher identified a mean of 2.47, 3.33 and 3.43 medications per patient suffering from ovarian, pancreatic and prostate cancer respectively. The researcher compared the patient's medications chart to that written in their hospital file and to what the patients stated during the interview. This reconciliation was done to avoid MEs such as omissions, duplications, dosing errors or drug interactions. An accurate continuous up-to date medication list ensures seamless care.

In a study by Edwards et al. (2014), the authors conducted telephone calls with the community pharmacist of each intervention patient. This procedure resulted in the identification of medications that were not included in the hospital charts and history face-to-face interviews. The mean number of medications obtained after interview or telephone call with the patient's community pharmacy by the SCP increased from 2.57 to 3.96 medications per patient. In the local scenario, this is not current implemented, since the pharmacy only has the details of the medications that the patient collects via the Pharmacy of Your Choice (POYC) scheme, i.e. the pharmacist has no record of other medications that the patient buys via private prescription or OTC medications.

In 2016, Randolph et al. studied the impact of pharmacist interventions on cost avoidance in an ambulatory cancer center. The authors identified that the most common interventions made by the pharmacy resident and the central pharmacist included CT regimen review amounting to 69% and 97% respectively. In a study by Miller and Hoare (2014), it was found out that post CPS implementation in oncology clinics and in an outpatient CT suite, resulted in an increase to 17% of interventions. In more than half of the patients (61%), the pharmacist conducted medicine reconciliation. Edwards et al. (2014) concluded that by the end of the

study period in an oncology clinic, the SCP identified an average of 3.7 DRPs per patient in the intervention arm. Similarly, by the end of this study period, the researcher identified an average of 3.55 PCIs per patient.

4.2.1. Counselling needs

Counselling needs assess whether the patient is being provided with information, advice and assistance. The clinical pharmacist focuses on improving the care of oncologic patients through patient education and counselling. Counselling needs (97%) were the most commonly identified PCI together with ADRs. The clinical oncology pharmacist has a pivotal role in counselling the patients about different aspects such as common ADRs and the importance of monitoring temperature and good oral hygiene. Patients showed interest and admitted that certain information was new for them. They asked questions, listened attentively and were grateful for the time the researcher spent with them. Patients were encouraged and positively motivated and given self-help tips.

Sessions et al. (2010) summarised that in the University of North Carolina Lineberger Comprehensive Cancer Center-North Carolina Cancer Hospital and in the Charles George VA Medical Center, the pharmacist met with oncologic patients who were going to start new oncology medication and counselled them about administration procedure, ADRs, carried out MR and assessed the presence of any drug interactions. In the Moses H. Cone Oncology Clinic and in the Duke Comprehensive Cancer Center, the pharmacist has various roles including patient education, consultation on supportive care measures, such as pain management, nausea/vomiting, myelosuppression; symptom management, toxicity management and drug interactions.

Wang et al. (2015) evaluated the efficacy of pharmaceutical intervention (PI) on CT knowledge-attitude practice (KAP) and QOL. The KAP questionnaire included questions about the knowledge section identified whether patients are aware of common side effects and how they should act. The patients in the PI group received comprehensive pharmaceutical care (face-to-face medication education and psychological counselling) and the self-compiled booklet entitled - Cancer patients medication knowledge guide, which consists of information such as prevention and management of ADRs and cautions. The authors observed that at the end of the study, knowledge scores were significantly increased in the PI group.

In Spoelstra et al. (2015), the patients were given a symptom management toolkit consisting of a notebook of evidence-based information that discusses what is needed to manage the oral anticancer medication safely, compliance to the regimen and common ADRs. The patients received a weekly symptom management message to remember to use the symptom management toolkit as needed to help them manage their symptoms at home. Symptom severity and interference with daily life of 19 symptoms were assessed using the Symptom Experience Inventory at baseline, weekly and exit.

Lingaratnam et al. (2012) reported that the interventions of the use of a patient brochure and form can facilitate self-reporting of drug information and assisted with minimising MEs. The brochure is both a learning tool for the patient to document current medications, and a document, which aids HCP staff undertaking MR on admission. The form, which consisted of a medicines list, encased in an A4 plastic pocket, foldable into wallet size to ensure portability and durability was given to each patient after receiving counselling from the clinical pharmacist. Lingaratnam et al. concluded that both the brochure/form were patient-friendly

and facilitated MR on admission. In this study, the patients had a medication chart compiled by the MDT to serve as a useful educational resource and adherent tool.

In a similar study carried out by Valgus et al. (2011), a clinical pharmacist was integrated into the haematology-oncology clinics at an academic medical center. With the implementation of the new service, the clinical pharmacist counselled all oncologic patients initiated on a new infusion medication. The patients were informed about the agents included in the CT regimen and about the management of treatment-associated adverse events. The clinical pharmacist answered any questions the patient had before initiation of therapy and provided written information to all oncologic patients.

Yamada and Nabeshima (2015) reported that pharmacist-managed clinics (PMCs) for patient education and counselling for cancer chemotherapy have beneficial effects on the patients' adherence, knowledge about the pharmacotherapy and the clinical outcome. The authors found out that the number of inquiries concerning oncology treatment was significantly fewer in the PMC group with PIs, than in the control group (without consultation in the PMC), with percentages being 5.3% and 16.8% respectively.

In a study carried out in an ambulatory oncology clinic by Ruder et al. (2010), consultative interventions accounted for 65%, and consisted of patient education sessions (143), patient visits (124), patient follow-ups (86) and drug information (25). During the initial patient face-to-face interview, the pharmacist planned individualised medication information tailored to each patient. The patients received printed information sponsored by the manufacturer. The pharmacist analysed all information together with the patient and/or family and provided additional verbal patient education in line with the treatment plan, common ADRs, and prevention strategies. The pharmacist monitored patients for development of ADRs during

subsequent visits and if any ADRs were noted, the pharmacist offered OTC treatment recommendations or POM in consultation with the caring prescriber. The patients were seen by the pharmacist in follow-up visits for management. Type of ADRs and management/prevention strategies were documented at each visit.

In this study, the counselling section was found very useful by all the patients that were identified as requiring 'Counselling needs'. It was based specific on the patients' requirements amongst which included counselling about the importance of compliance, interactions, monitoring of temperature and common ADRs such as constipation, diarrhoea and self-care tips. Locally, tailored information in cancer care team booklets[28] are also provided to oncologic patients and are available online. Till today, they are available for a number of cancers including ovarian cancer, early and advanced prostate cancer, breast cancer, CRC and lung cancer in both Maltese and English language.

In this study, patient counselling was ranked as the most commonly identified PCI. The result is similar to a study by Randolph et al. (2016), where highest percentage of interventions documented were also related to patient counselling. The pharmacy resident conducted a weekly CT education class for newly diagnosed patients instead of the nursing staff that traditionally facilitated the class. Patient survey results revealed 100% of the responses being positive. The most common interventions made by the resident pharmacist included patient counselling (n = 102, 24%).

[28] heath.gov.mt [Internet]. Government of Malta: TICC Publications; c2016 [cited 2017 Feb 12]. Available from: https://health.gov.mt/en/SAMOC/Pages/SAMOC-TICC-Publications.aspx

In a study carried out by Delaney et al. (2009) in oncology clinic, counselling was classified under the category direct patient care and the types of interventions were categorized into recommend non-drug treatment, counsel patient on CT treatments, counsel patient on non-chemotherapy treatments, counsel patient on blood work and counsel patient on operation clinic. The percentage of interventions was 4.5% each category.

In a study carried out by Bakitas et al. (2009), advanced practice nurses conducted counselling intervention. Project ENABLE that was a multicomponent, psychoeducational intervention consisted of four weekly educational sessions and monthly follow-up sessions until death or study completion. Quality of life, symptom intensity, and mood were measured by Functional Assessment of Chronic Illness Therapy for Palliative Care, the Edmonton Symptom Assessment Scale and the Center for Epidemiological Studies Depression Scale respectively. The authors found out that patients receiving the intervention had higher scores for QOL and mood, but did not have improvement in symptom intensity scores. Both the clinical pharmacist and the nurses play a significant role in ensuring drug safety. In our local scenario, pharmacists could conduct this too.

In a study by Dohler et al. (2011), a MCMM model, which integrated the pharmacist, was designed and compromised of 38 tasks. These included eleven tasks related to patient education and counselling, and seven tasks related to prevention of DRPs. Examples related to patient education and counselling included patient education on the tumour therapy and possible ADRs; patient information which medication, food and dietary supplements to avoid during tumour therapy; patient information on preventive methods against ADRs of tumour therapy (prophylaxis); and patient support on medication compliance (compliance-enhancement). Examples related to prevention of DRPs included interview to ascertain if

patient adheres to the medication plan (compliance); and detection and documentation of the ADRs of the tumour therapy. In a study by Miller and Hoare (2014), the authors found that post CPS implementation in oncology clinics and in an outpatient CT suite, resulted in an increase to 17% of interventions. In more than half of the patient (61%), the pharmacist conducted patient education and medicine reconciliation.

The importance of patient follow-up by the pharmacist was highlighted in a cross-sectional survey carried out by McKee et al. (2011), where the main outcome was the effect of the pharmacist-patient relationship. This was analysed by observing the interaction between time spent with pharmacist, the understanding of medications and the desire for future pharmacy counselling services. The authors found out that 86% of the interviewees agreed that oncologic patients should discuss their treatment with a pharmacist. Seventy six percent of the respondents requested pharmacists' follow-up through future visits. This study concluded that patients would like to have pharmacist follow-up regularly, whilst also may be willing to pay for pharmacy counselling services. Similarly, in this study, oncologic patients were followed throughout their treatment or until study period completion.

4.2.2. Adverse drug reactions

ADRs are frequent amongst oncologic patients. Routine symptom assessment may help to identify patients who require more comprehensive supportive care. In this study, the majority of PCIs identified were counselling needs (97%) in line with ADRs. Appropriate management of ADRs is important in optimizing therapy. The result is similar to a study by Mancini (2012), where a high percentage of PCIs was related to ADRs. In a multidisciplinary supportive oncology clinic, use of a pharmacist assessment helped to identify PCI such as ADRs (74.7%).

A study by Walsh et al. (2000) conducted in patients on initial referral to the palliative medicine program; found out that fatigue was ranked as one of the most prevalent symptoms with a percentage of 69%. A similar study conducted in ambulatory cancer patients by Feyer et al. (2008), also found out that fatigue was the most frequent side effect, with a percentage of 62% as shown in Table 4.1.

Lau et al. (2004) assessed incidence, predictability, preventability and severity of ADRs in hospitalised oncology patients. They found out that the ten most common ADRs were constipation, nausea ± vomiting, fatigue, alopecia, drowsiness, myelosuppression, skin reactions, anorexia, mucositis and diarrhoea. Similarly, in this study, fatigue was ranked as the most frequently experienced ADR.

Table 4.1 Comparison of ADRs identified in different studies

Walsh et al. (2000)		Feyer et al. (2008)		This research	
Type of ADR	**%**	**Type of ADR**	**%**	**Type of ADR**	**%**
pain	84	*fatigue*	62	*fatigue*	52
fatigue	69	hair loss	55	oral (stomatitis, mouth ulcers, thrush, altered or bad taste)	36
easy weakness	66	nausea	52	myalgia/arthralgia	33
anorexia	66	sleep disturbance	43	diarrhoea	31
lack of energy	61	weight loss	37	bone marrow suppression	30
dry mouth	57	diarrhoea	32	constipation	28
constipation	52	mouth ulcerations	32	sensory neuropathy	25
early satiety	51	pain	30	nausea	24
dyspnoea	50	changes in finger/toe nails	28	others	21
>10% weight loss	50	vomiting	28	insomnia	21
sleep problems	49	increased sweating	25	vomiting	19
depression	41	weight gain	23	itching or rash	19
cough	38	dyspnoea	22	loss of appetite/change in weight/anorexia	19
nausea	36	virility problem	18	motor neuropathy	16
oedema	28	mood/character changes	13	lymphoedema	15
taste changes	28	other adverse events	10	fever/chills	9
hoarseness	24	skin bleeds	6	alopecia	7
anxiety	24			anxiety/change in mood or depression	7
vomiting	23			infusion-related hypersensitivity	6
confusion	21			dysuria/urinary symptoms	6
dizziness	19			hand-foot syndrome (HFS)	4
dyspnoea	19			skin toxicity	3
dysphagia	18			menopausal symptoms	3
belching	18			infection	3
bloating	18			cough	3
wheezing	13			dyspnoea	3
memory problems	12			allergic reactions/ hypersensitivity	1
headache	11			pain or difficulty with swallowing	1
sedation	10			thromboembolism	0
aches	9			tumour lysis syndrome	0
hiccups	9			hyperuricaemia	0
itching	9			pregnancy and reproductive function	0
diarrhoea	8			cardiotoxicity	0
dreams	7			nephrotoxicity	0
hallucinations	6			ototoxicity	0
mucositis	5			sexual problems	0
tremors	5			flu-like symptoms	0
blackout	3				

In the study by Edwards et al. (2014), the DRP 'the patient is experiencing an adverse drug reaction was identified in 36 (9.6%). ADR was defined as not dose related. Examples of such ADRs were not included. This study is similar to a prospective intervention study by Chew et al. (2015), where 9% of the interventions were related to ADRs. Another study conducted at an oncology ward by Bremberg et al. (2006), found that adverse effects were the third most common DRPs, accounting for 11%. DRPs were identified by drug chart reviews based on data from medical files, laboratory tests and interviews with patients and/or relatives. In both these studies, it was not specified whether ADRs were defined as not dose related and examples of ADRs encountered were not mentioned.

In a study by Hong et al. (2016), symptoms were classified into 13 categories as follows; appearance, appetite, bowel, breathing, concentration, cough, fatigue, fear/worry, fever/chills, insomnia, nausea, pain and sexual activity/interest. They found out that at T1 i.e. before treatment, at least 25% of the patients reported moderate-to-severe distress levels for impact of cancer and/or treatment on sexual activity/interest, pain, fear/worry, fatigue, and insomnia. At T2, which was approximately five weeks after the start of the oncology medications, at least 25% of the patients reported moderate-to-severe distress nearly as T1, with the addition of appetite loss and the deletion of fear/worry. In this study, symptoms were analysed during oncology treatment periods and most of the above-mentioned symptoms were also ranked, from highest to lowest frequencies being; fatigue, myalgia/arthralgia, insomnia and appetite loss.

In a study carried out in an ambulatory oncology clinic by Ruder et al. (2010), drug-related interventions accounted for 35%, and consisted of adverse effects (131), MR (52) and dosing (22). The pharmacist documented 131 ADRs, which were organized by affected body system

and type. The four systems and types were as follows; gastrointestinal (diarrhoea, constipation, appetite, stomatitis); dermatological (rash, palmar-plantar erythrodysesthesia (PPE), onycholysis, fixed eruption, extravasation); central nervous system (nausea/vomiting, neuropathy, auditory, blood glucose) and musculoskeletal (myalgias, leg cramps, oedema). The predominant types of ADRs included nausea/vomiting, rash, diarrhoea and myalgias. In this study, these ADRs were also identified with the most frequently ranked.

Spoelstra et al. (2015) assessed symptom severity and interference with daily life of 19 symptoms using the Symptom Experience Inventory, at baseline, weekly and exit. Symptoms were rated "yes" or "no" in relation to their presence in the past week, on a severity scale from 1 (very little) to 9 (worst possible), and in relation to interference with daily life on a scale from 0 (no interference) to 9 (interfered completely). The patients were also given a symptom management toolkit consisting of a bound notebook of evidence-based information that discusses what is needed to manage the oral anticancer medication safely, compliance to the regimen and common ADRs. The patients received a weekly symptom management message to remember to use the symptom management toolkit as needed to help them manage their symptoms at home. Each AVR assessed the 19 symptoms (i.e., anxiety, lack of appetite, constipation, cough, diarrhoea, disturbed sleep, fatigue, fever, headaches, joint or muscle pain, mouth sores, nausea, numbness and tingling, pain, redness, peeling or pain in hands or feet, shortness of breath, skin rashes or sores, swelling in hands or feet and weakness) and use of the toolkit. The mean number of symptoms was 5.8 for the 19 symptoms assessed. No information was provided in the article about the frequency of the symptoms. This finding is very similar to this study where the mean number of ADRs experienced per patient was 4.5.

In 2016, Randolph et al. studied the impact of pharmacist interventions on cost avoidance in an ambulatory cancer center. They found out that interventions related to ADR including; ADR follow up, ADR reported and ADR management or prevention made by the resident pharmacist and centralised pharmacist accounted to approximately 3%. In a prospective, descriptive, observational study in a haematology/oncology inpatient setting by Delpeuch et al. (2015), ADRs were identified in only 2.5% of the prescriptions.

In this study, the patients were followed throughout their duration of treatment or until end of study period and were counselled on the management of treatment-associated ADRs. This is similar to a prospective, multicentre, double-arm, controlled study conducted by Chen et al. (2014), where clinical pharmacist-led guidance teams (CPGTs) provided amongst other, patient follow-up where clinical pharmacist conducted face-to-face or telephone interviews with patient in collaboration with nurses. Evaluations assessed cancer pain control and guided the patient on how to prevent ADRs or deal with ADRs if any occurred. The authors observed that the incidence of gastrointestinal ADRs were significantly lower in the CPGT groups. This is also similar to a prospective, multicentred cohort study carried out by Liekweg et al. (2012), where 76.0% in the intervention group (consisting of additional patient counselling on the management of treatment-associated ADRs and optimization of supportive medication) and 35.4% in the control group (standard care) had a complete response to the antiemetic prophylaxis.

Symptom scores were used in various studies to assess pharmacist intervention. In 2010, Valgus et al. carried out a study in the ambulatory cancer clinic setting. Pharmacist-led interdisciplinary model produced an improvement in symptom scores (assessed on a 5-point Likert-type scale) for nausea and constipation with a reduction from an average of 4.0 to 1.0

and 3.3 to 2.0 respectively. The result was comparable to a study by Yennurajalingam et al. (2011), where it was found that impact of a palliative care consultation team achieved significant symptom improvement in oncologic patents receiving medication. Mean scores at baseline and follow-up visits were fatigue 6.8 and 5.3 ($p < 0.0001$), pain 5.3 and 4.1 ($p < 0.0001$), depression 3.2 and 2.5 ($p < 0.0001$), anxiety 3.7 and 2.8 ($p < 0.0001$), dyspnoea 2.7 and 2.5 ($p = 0.05$), sleep 5 and 4 ($p < 0.0001$), and well-being 5.2 and 4.4 ($p < 0.0001$). Bernard et al. (2010) conducted a study about the use of a pharmacist/nurse model for the delivery of supportive care in adult oncology clinics. Reduction in scores at baseline and second visit were pain 4 and 2.7, nausea 4 and 1.4 and constipation 2 and 1.6. ADRs studied in the above studies, which were also found common in this oncologic population included fatigue, followed by myalgia/arthralgia, constipation, nausea, insomnia, with a percentage of 52, 33, 28, 24 and 21 respectively.

A study conducted at the gynaecologic oncology clinic by Sun et al. (2005) requested oncologic patients to rank order 27 health states using a modified VAS and to complete the Memorial Symptom Assessment Scale (MSAS). Perfect health, clinical remission and complete control of CINV were the most favourable health states. Oncologic patients being administered first-line CT had less symptom distress, and rated sexual dysfunction, fatigue and memory loss more favourably than in patients on second- or third-line CT ($p < 0.05$). Symptom scores in order of most distressful to least distressful included; lack of energy, difficulty in sleeping, numbness in hands/feet, worry, pain, sadness, nervousness, drowsiness, feeling bloated, alopecia, irritability, constipation, concentration, shortness of breath, dry mouth, don't look like myself, sweating, itching, nausea, coughing, changes in way food tastes, lack of appetite, urinary problems, skin changes, mouth sores, dizziness, problems with sex, diarrhoea,

swelling in arms/legs, weight loss, vomiting and difficulty in swallowing. In line with this study, fatigue was also highlighted as the most distressful ADR.

4.2.3. Additional medication needs

Some patients were given take-home medications both pre-treatment and post-treatment. Oncologic patients might still encounter the requirement of additional medication needs. In fact, the PCI – 'additional medication needs' was identified in forty-seven (70.1%). In a prospective intervention study conducted by Chew et al. (2015), five percent of the intervention involved symptom management. The definition of symptom management was not defined and no examples of symptom management were mentioned in the article. This result is similar to a study carried out by Randolph et al. (2016), where supportive care and disease state recommendation interactions were identified in 5 and 7 respectively, accounting to approximately 3% of the total pharmacy resident interventions.

In a study carried out in haematology/oncology clinical pharmacy in outpatient setting by Shah et al. (2006), amongst the major drug interventions identified, drug additions accounted to 41%. The majority of drug additions (64%) were due to supportive care issues. Supportive care issues consisted mainly of management of anaemia, pain, constipation/diarrhoea and nausea/vomiting. They found out that 54% of the prescriptions were for supportive care and 25% were for CT. The other agents prescribed included antibiotics, antifungal, antiviral, antidepressant, antitussive, antihypertensive or diabetic medications. Some of the supportive care medications prescribed were for erythropoietic agents, pain management, iron supplementation, nausea/vomiting, constipation/diarrhoea, sleep, heartburn, appetite, mucositis and anticoagulation. Bernard et al. (2010) conducted a study about the use of a

pharmacist/nurse model for the delivery of supportive care in adult oncology clinics. The authors found that recommendations leading to additional medications amounted to 32%.

4.2.4. Seamless care needs

Seamless care continuation is an essence for oncologic patients. Occupational therapy, physiotherapy, psychological services and social work services are amongst the most commonly required referrals for seamless care continuation. Other referrals that might be required include referral to dermatologist or ophthalmologist. Whenever the patient experiences fever, the patients were advised to refer to A&E immediately and not await until fever subsides or take any antipyretic medication.

'Seamless care needs' had been identified in 34 patients. A common scenario for the requirement of occupational therapy and physiotherapy assistance is due to neuropathy (motor or sensory) as a result of treatment side effects such as paclitaxel. This ADR can be devastating and the importance of working within a MDT is crucial. Physiotherapy requirements was the most commonly mentioned. Amongst other HCPs requirement include; occupational therapist, dietician and endocrinologist/diabetologist. It was observed that not all patients had the knowledge of good nutrition. They expressed interest in knowing which food has which vitamins, which foods are good for the immune system and which food should be avoided. A number of patients were diabetics and referral to a diabetologist was required in certain cases. Some medications such as steroids alter glucose level and so it is vital that the patient is aware to be careful what type of food to eat and to monitor blood glucose more frequent.

Checking whether there is consistency, continuity, and coordination of care was required in eleven patients. Patients that were making use of Hospice Malta service were very pleased

with the services and had no complaints. Patients made use of different services such as transport, physiotherapy, psychotherapist and respite care. As explained clearly in their website, "Hospice Malta is a non-profit organisation, provides and promotes palliative care to patients with cancer, motor neuron disease and other life threatening illnesses. Care is delivered by an inter-disciplinary team to provide professional palliative care, advice, support to patients and their families."[29] Amongst the service provided, include home care, day care facilities such as physiotherapy; psychosocial and spiritual support and transport; family support and bereavement support. The services are all free of charge and the Malta Hospice Movement is caring for over 1000 patients. Patients, who expressed that sometimes they are having transport issues, were advised that transport service could be provided either through SAMOC or through Hospice Malta.

Action 'Information about smoking and alcohol cessation, nutrition and physical training' was required in two patients. One patient suffering from ovarian and another suffering from pancreatic cancer were very interested when the researcher explained to them that the health promotion unit organizes classes about smoking cessation and which are free of charge. The classes are carried out once a week for a duration of eight weeks and are located in some health centres located in Malta and Gozo. The application is available through their website page online, and one can send it by post or fill it online through their link www.ehealth.gov.mt. Both patients were not aware of these services and were willing to give it another trial to quit smoking. The researcher explained the location of the directorate and provided the contact number. The Health Promotion and Disease Prevention Directorate is

[29] hospicemalta.org [Internet]. Malta: Hospice Malta; c2012 [updated 2017; cited 2017 Jan 18]. Available from: http://hospicemalta.org/

situated in Msida, Malta[30]. This directorate strives to achieve various aims amongst which through building and leading alliances with public, private, non-governmental and international organisations and civil society to create sustainable actions for health. They organise various campaigns, produce a vast range of publications including various educational online leaflets and posters.

In a study carried out by Delaney et al. (2009) in oncology clinics, coordination of care was sub-categorized into the following types of interventions;- patient preparation, provide information to dispensary, enter pertinent information into computer, monitor laboratory results and therapeutic drug levels and contact community pharmacy with percentage of interventions amounted to 4.5%, 4.5%, 4.5%, 4.5% and 0% respectively. A study carried out by Edwards et al. (2014), assessed the impact of a SCP on clinical outcomes. The pharmacist conducted a MR interview for all the oncologic patients in the intervention group. The pharmacist carried out a medication safety check, including drug interaction check and carried out a counselling session while identifying and resolving DRPs. Overall, the SCP identified an average of 3.7 DRPs per intervention patient. Patient not receiving or taking a medication for which there is an indication, were found to be the most common DRPs observed. In this study, the researcher followed a similar pattern. The patients were counselled and MR was carried out. The researcher identified an average of 3.55 PCIs per patient.

4.2.5. Compliance

Compliance is a multidimensional phenomenon. In a review by Partridge et al. (2002), the authors found out that few published studies had focused on compliance to oral

[30] Health Promotion Malta [Internet]. Government of Malta: The Health Promotion Unit; c2016 [updated 2017; cited 2017 Feb 2]. Available from: https://health.gov.mt/en/health-promotion/Pages/home.aspx

antineoplastic therapy, in part because the vast majority of oncology therapy is delivered intravenously in hospitals. As stated by Gebbia et al. (2012), data published in medical literature about the issue of compliance to new oral chemotherapeutic and/or biologic agents are quite limited. In a review by Ruddy et al. (2009), it was demonstrated that compliance and persistence ranged from 16% to 100% with different therapies and different measurements of compliance. MDT need to identify those at risk of non-persistence and develop strategies to combat this barrier to treatment success.

Since the majority of the antineoplastic treatments are administered intravenously, compliance rate is usually very high since oncologic patients very rarely miss an appointment. Only approximately 28% of the study patient population were prescribed oral medications. In this study, the PCI stating 'inappropriate compliance and failure to receive medicines appropriately' was identified in 14 patients (20.9%). In fact, in this study, two patients (3%) stated that had missed appointment due to transport issue. The cause of the PCI was selected from the statements 5.1 to 5.7. In this study, the statement 'patient forgets to take a drug' defined non-compliance to medications. In the study carried out in an oncology clinic by Edwards et al. (2014), the DRP 'the patient is not taking/receiving the prescribed drug appropriately' was identified in 56 (15.2%).

In a study by Kozma et al. (2014), compliance to abiraterone acetate was evaluated by assessing the mean medication consistency/MPR was greater than 90%. The mean daily dose was within 1% of the recommended daily dose i.e. 1000mg. In this research population, only one patient was receiving abiraterone. He stated that the cause of PCI – 'inappropriate compliance and failure to receive medicines appropriately' was 5.6 - 'Patient forgets to take drug'. Lafeuille et al. (2014) also showed similar results to Kozma et al. (2014). Mean MPR

was 93% in both study population 1 and 2. The mean daily abiraterone acetate dose per person per prescription was 998.8mg and 994.2mg for Dataset 1 and Dataset 2 respectively.

Compliance was assessed differently by Spoelstra et al. (2015) study which was carried out in two community cancer centers. Compliance was measured by patient report of whether medications were taken as directed in the past seven days during weekly AVR calls and exit interview, as well as by returned texts in the intervention group. Patients received daily texts for compliance for a duration of 21-28 days. The patients received text message reminders to take the anticancer medications. They had to reply "taken" when they have taken the medication. This study found out that the patients had a high satisfaction with the texts and adherence improved after the intervention. This could be implemented locally in community pharmacies since lately, some of the oncology medications are also being dispensed via the POYC scheme so that patients can be dispensed all the medications they require including medications for chronic conditions and also the oncology medications from one-stop i.e. their pharmacy of their choice.

In a study by Walter et al. (2014) carried out in cancer clinics, adherence was defined as >80% of adherence according to the three methods of measurement i.e. self-report, pill count and MEMS and the overall adherence rates were 99, 100 and 61% respectively. Ten patients (53%) were classified as non-adherent. In a multicentre, non-randomised interventional study by Simons et al. (2011), adherence to capecitabine medication was measured using MEMS. They found out that the mean daily adherence was significantly higher in the intervention group (i.e. received intensified pharmaceutical care consisting of written and spoken information), 96.8% vs 87.2%. In this study, the three patients receiving capecitabine expressed, so that

the dosage regimen will be clarified again. It might be an indication of lack of compliance to treatment. Hence, pharmacist interventions have a positive impact on patient care.

One would expect that cancer patients would have a high compliance rate rather that patients that are less seriously ill or suffering from chronic conditions. In a retrospective study, Nilsson et al. (2006) found out that oncologic patients on oral long-term medications have a non-adherence rate similar to that of patients receiving medications for chronic conditions. In fact, no statistically significant difference was found between the number of patients underusing for cancer medications (<80% use of prescribed cancer medications) and that of patients underusing all other medications.

As highlighted also in this study, the clinical pharmacist has an important role in educating, counselling and clarifying misunderstandings or fears that might contribute to drug non-adherence. In a review carried out by Verbrugghe et al. (2013), the authors observed that younger age, older age, higher out-of-pocket costs and lower income were associated with non-adherence to oral anticancer medications.

In a study carried out by Yennurajalingam et al. (2011), the most frequent pharmacological intervention in medication changes included opioids, laxatives, antiemetic, anti-depressants, hypnotics, corticosteroids, neuroleptics, anti-inflammatory, psychostimulants and anti-psychotics. Similarly, the researcher noted that many of these classes of medications were also present in this study.

4.2.6. Interactions

Drug interactions can be pharmaceutical, pharmacokinetic or pharmacodynamic. They can also be between cytotoxic drugs, cytotoxic drugs and non-cytotoxic drugs or with pharmaceutical vehicles. Potential interactions between anticancer drugs and over-the-

counter or alternative medicines and herbal preparations should not be underestimated. MR is of utmost importance in the hospital setting especially in an oncology setting. Patients are more susceptible to ADRs and might be immunocompromised; the importance of MR should be continuously highlighted. The clinical oncology pharmacist has the responsibility to update the patient's treatment chart including taking notice of any medications that have been started or any change in dose whether increase or decrease in dose.

WHO has developed a three-step "ladder" for cancer pain relief in adults. WHO's cancer pain ladder for adults as illustrated below in Figure 4.1, states that if pain occurs, prompt oral administration of drugs should take place in the following order: non-opioids such as aspirin and paracetamol; then, as necessary, mild opioids such as codeine; then strong opioids such as morphine, until the patient is free of pain. Additional medications known as adjuvants can be prescribed to calm the patient's anxiety and fear[31]. Patients were counselled on the importance to avoid interactions between paracetamol-containing medications.

[31] who.int. [Internet]. WHO's cancer pain ladder for adults. WHO; c2017 [cited 2016 July 2]. Available from: http://www.who.int/cancer/palliative/painladder/en/

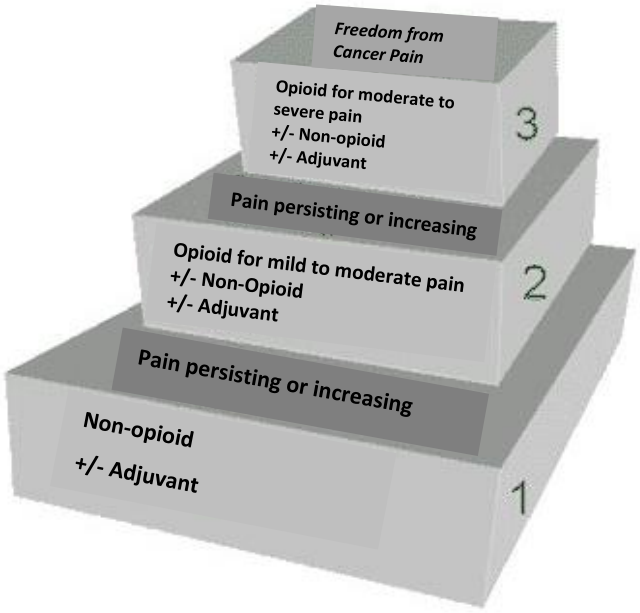


Figure 4.1 WHO's cancer pain ladder for adults. Adapted from: WHO's cancer pain ladder for adults. WHO, c2017.

In this study, interactions issues were identified in eight patients (11.9%). Randolph et al. (2016) study was carried out in the ambulatory cancer centre. Both the pharmacy resident and the central pharmacist did not identify any drug interactions. This is in line with this study, where no drug interactions were identified. Various studies reported about the frequency of DDIs, with different frequencies. In the study carried out in an oncology clinic by Edwards et al. (2014), the DRP 'The patient is experiencing a drug-drug, drug-disease, drug-food, or drug-laboratory interaction' was identified in 37 (9.6%). Interaction check was also carried out in this study.

In 2015, Stoll and Kopittke assessed the frequency of DDIs throughout the hospital stay of 113 cancer patients. It was found out that all patients had at least one potential DDI. Only 13.7% of all interactions involved antineoplastic agents. In an observational prospective study of 100 adult patients being admitted to the cancer center for infusion CT, Tenti et al. (2015),

identified seventy-seven drug interactions that required a dosage adjustment or close monitoring detected. In a prospective, descriptive, observational study in a haematology/oncology inpatient setting by Delpeuch et al. (2015), DRP DDIs were identified in 14.3% of the prescriptions.

Higher percentage of interactions were identified in other studies. Tavakoli-Ardakani et al. (2013) conducted a cross-sectional study by reviewing charts of 224 consecutive in hospitalized patients in haematology-oncology ward of a hospital in a developing country. Two hundred and twenty-eight potential interactions were detected. The result is similar to a study by Mancini (2012), where a high percentage of PCIs were related to drug interactions. In a multidisciplinary supportive oncology clinic, use of a pharmacist assessment helped to identify PCIs such as drug interactions (44%). Riechelmann et al. (2005) retrospective study evaluated hospitalized patients for solid and haematological tumours, and reported that 63% of patients were exposed to potential DDI. Riechelmann et al. (2007) cross-sectional study carried out in an ambulatory center for patients suffering from solid tumour and patients on active cancer-directed therapy, found out that 27% of patients were exposed to potential DDIs, mostly medications to treat comorbid illnesses.

In another retrospective study by Riechelmann et al. (2008) carried out in an ambulatory setting evaluated oncologic patients suffering from solid and haematological tumours, patients at the end of life and receiving supportive care exclusively. The authors found that 29% of patients were exposed to potential DDIs, mostly drugs to treat comorbid illnesses. A study conducted at an oncology ward by Bremberg et al. (2006), found that drug interactions were the third most common DRPs, accounting for 17%. DRPs were identified by drug chart

reviews based on data from medical files, laboratory tests and interviews with patients and/or relatives.

4.2.7. Monitoring needs

The pharmacist has a role to identify whether there is continuous or frequent periodic clinical and laboratory assessment. Regular blood investigations and scanning such as computed tomography scan are the keys to monitoring response to treatment. In this research population, monitoring needs were identified in only five patients. HCPs follow meticulously the protocol for each medication.

In a prospective, descriptive, observational study in a haematology/oncology inpatient setting by Delpeuch et al. (2015), DRP lack of monitoring was identified in 9.6% of the prescriptions. Interventions led to therapeutic drug monitoring. In a study carried out by Randolph et al. (2016), no data was included about monitoring recommendation identified through the pharmacy resident and central pharmacist interventions. Farias et al. (2016) implemented a CPS in haematology, consisting of an antineoplastic prescription validation (analysis of patients' characteristics, laboratory tests, compliance with the therapeutic protocol and with pharmacotechnical parameters). Laboratory tests parameters included checking the need to adjust dose of the medication, as per result of the biochemical and haematological tests. The authors found out that at period B (presence of a CPS), adjustment of dose for laboratory tests was identified in 6%.

In this study, the patient's laboratory parameters were also analysed and tumour marker results trends were reviewed. In line with the PCP designed for this study, which included laboratory parameters monitoring section, a study carried out by Chung et al. (2011) also highlighted labs section in the development of standardised CT forms. Chung et al. study

included the development and implementation of an interdisciplinary oncology program in a community hospital, amongst which developed standardised CT monitoring form and CT order set. In the monitoring form, the section for lab parameters was included where the date and value of the tests had to be documented, while in the order set form, labs section included information about the various tests to be carried out and their frequency. In a study carried out by Delaney et al. (2009) in oncology clinics, tasks performed by the pharmacist were divided into three categories; direct patient care, direct contact with the HCT and coordination of care. Monitoring laboratory results and therapeutic drug levels were categorised under coordination of care with a frequency of 13 (4.5%). In a study carried out in haematology/oncology clinical pharmacy in outpatient setting by Shah et al. (2006), amongst the major drug interventions identified, laboratory monitoring accounted for 10% of total interventions.

4.3. Limitations

There are some limitations to this study. The time frame of the research was not long enough, and some patients had not finished the treatment until the end of the study period. Some patients had treatment switching since they were not responding well to treatment.

Another limitation is the sample size. If the study period was longer, this would have led to a larger sample size. The researcher identified all the patients treated within the study period. Patients suffering from prostate cancer receiving only Zoladex® LA 10.8mg injection, do not access SAMOC day care unit; the medication can be administered either through their private family doctor or through any health centre located in Malta. These settings were not included in the design setting criteria, and these patients could not be included in the implemented sample population. The patients enrolled who received Zoladex® LA 10.8mg injection, were

those patients who had an appointment for the afternoon clinics and would also have been receiving either zoledronic acid infusion and/or oral oncology medication.

In Malta, only one governmental oncology centre is available, and patient recruitment had to be limited to this center only. Since Malta's population is small, and various oncology medications are currently available, this led to a lower possibility of capturing a large number of patients receiving the same medication. Even though in Malta, a cancer registry is available, it is not up-to-date, and so patient identification took longer. If an up-to-date registry would have been in place, this may have facilitated patient recruitment. The HCPs were very willing to help and support me and so this limitation had been overcome.

4.4. Recommendations

In view of the above limitations, a longer time frame would be ideal so that the patients will be enrolled at the start of their treatment and followed up until they finish treatment. This will lead to the feasibility of a larger number of patients receiving the same medication, and can compare other parameters.

Since this is the first study implemented at SAMOC about PCIs encountered by oncologic patients, surely further research needs to be conducted. A recommendation would be to follow a larger sample of patients receiving the same medications and assess the similarities and PCIs encountered through the use of that particular oncology medication. Statistical analysis will be carried out accordingly. Different solid tumours can be identified and the results obtained can be compared to this study.

4.5. Conclusion

Incorporating tumour makers monitoring within a pharmaceutical care plan represents a fundamental pillar for optimal management of cancer patients.

The researcher identified an average of 3.55 PCIs per patient, indicating that this model can help to identify and resolve PCIs. The developed and implemented individualised PCP was a helpful tool for the clinical pharmacist who can update patient pharmaceutical care records according to the PCIs identified whilst at the same time taking into consideration relevant tumour marker trends as well as other laboratory investigations. The PCP contributes to optimising patient care within a collaborative management.

Since ovarian cancer patients had a higher tendency to be younger in age compared to pancreatic or prostate cancer patients, this research highlighted the importance to keep abreast to gynaecological follow-up appointments, leading to the identification of cancer-related signs and symptoms at an earlier stage.

References

Adusumilli P, Adepu R. Drug related problems: An overview of various classification systems. Asian J Pharm Clin Res. 2014;7(4):7-10.

Aetna. Tumor markers. Medical Clinical Policy Bulletins. 2016; Number 0352.

AHRQ. Lo L, Kwan J, Fernandes O, Shojania K. Medication reconciliation supported by clinical pharmacists. In: Making health care safer II: An updated critical analysis of the evidence for patient safety practices. Evidence report/Technology assessment 2013;211.

Ahmad A, Nijpels G, Dekker J, Kostense P, Hugtenburg J. Effect of a pharmacist medication review in elderly patients discharged from the hospital. Arch Intern Med. 2012;172(17):1346-7.

Al-Quteimat O. Oncology pharmacist: Role and expectations. J Cancer Sci Ther. 2014;6(10):107.

Amayo A, Kuria J. Clinical application of tumour markers: A review. East Afr Med J. 2009;86(12):S76-83.

Amling C, Bergstralh E, Blute M, Slezak J, Zincke H. Defining prostate specific antigen progression after radical prostatectomy: What is the appropriate cutpoint? J Urol. 2001;165(4):1146-51.

ASHP guidelines on a standardized method for pharmaceutical care. In: Deffenbaugh J, ed. Best practices for health-system pharmacy. Bethesda, MD: American Society of Health-System Pharmacists; 1996:109-11.

Baig J, Alam J, Mahmood S, Baig M, Shaheen R, Sultana I. Hepatocellular carcinoma (HCC) and diagnostic significance of A-fetoprotein (AFP). J Ayub Med Coll Abbottabad. 2009;21(1):72-5.

Bakitas M, Lyons KD, Hegel MT, Balan S, Brokaw FC, Seville J, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer. (Clinical report). JAMA. 2009;302(7):741-9.

Ballehaninna U, Chamberlain R. Serum CA 19-9 as a biomarker for pancreatic cancer - A comprehensive review. Indian J Surg Oncol. 2011;2(2):88-100.

Barnett M, Frank J, Wehring H, Newland B, VonMuenster S, Kumbera P, et al. Analysis of pharmacist-provided medication therapy management (MTM) services in community pharmacies over 7 years. J Manag Care Pharm. 2009;15(1):18-31.

Basger B, Moles R, Chen T. Critical analysis of seven Drug Related Problem (DRP) classification system, resulting in an aggregated system for classifying causes of DRPs. Res Social Adm Pharm. 2014;10(5):e14-5.

Basger B, Moles R, Chen T. Development of an aggregated system for classifying causes of drug-related problems. Ann Pharmacother. 2015;49(4):405-18.

Bast R, Badgwell D, Lu Z, Marquez R, Rosen D, Liu J, et al. New tumor markers: CA125 and beyond. Int J Gynecol Cancer. 2005;15(Suppl 3):274-81.

Batchelder K, Miller P. A change in the market, investing in diagnostics. Nat Biotechnol. 2006;24(8):922-6.

Beijnen J. Drug interactions in oncology. Lancet Oncol. 2004;5(8):489-96.

Beney J, Bero L, Bond C. Expanding the roles of outpatient pharmacists: Effects on health services utilisation, costs, and patient outcomes. Cochrane Database Syst Rev; 2000 CD000336(2).

Berard C, Mahoney C. Cost-reducing treatment algorithms for antineoplastic drug-induced nausea and vomiting. Am J Health Syst Pharm. 1995;52(17):1879-85.

Bernard S, Valgus J, Jarr S, Rice M, Schwartz R. Use of a pharmacist/nurse model for the delivery of supportive care in adult oncology clinics at the University of North Carolina Hospital. J Clin Oncol. 2010;28(15).

Bero L, Grilli R, Grimshaw J, Harvey E, Oxman A, Thomson M. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. BMJ. 1998;317(7156):465-8.

Bladh L, Ottosson E, Karlsson J, Klintberg L, Wallerstedt S. Effects of a clinical pharmacist service on health related quality of life and prescribing of drugs: A randomised controlled trial. BMJ Qual Saf. 2011;20(9):738-46.

Bondesson A, Holmdahl L, Midlöv P, Höglund P, Andersson E, Eriksson T. Acceptance and importance of clinical pharmacists' LIMM-based recommendations. Int J Clin Pharm. 2012;34(2):272-6.

Bondesson A, Eriksson T, Kragh A, Holmdahl L, Midlov P, Hoglund P. In-hospital medication reviews reduce unidentified drug-related problems. Eur J Clin Pharmacol. 2013;69(3):647-55.

Bremberg E, Hising C, Nylén U, Ehrsson H, Eksborg S. An evaluation of pharmacist contribution to an oncology ward in a Swedish hospital. J Oncol Pharm Pract. 2006;12(2):75-81.

Carelle N, Piotto E, Bellanger A, Germanaud J, Thuillier A, Khayat D. Changing patient perceptions of the side effects of cancer chemotherapy. Cancer. 2002;95:155-63.

Caselnova D, Dzierba S, O'Neill M, Dillon K, Farley P. Implementing clinical pharmacy services in an outpatient oncology clinic. Am J Hosp Pharm. 1985;42(6):1348-52.

Castelino R, Bajorek B, Chen T. Are interventions recommended by pharmacists during home medicines review evidence-based? J Eval Clin Pract. 2011;17(1):104-10.

Chabner B, Chabner Thompson E. Merck Manuals. Diagnosis of Cancer. USA: Merck; 2017.

Chan D, Chen J, Kuo H, We C, Lu I, Chiu L, et al. Drug-related problems (DRPs) identified from geriatric medication safety review clinics. Arch Gerontol Geriatr. 2012;54(1):168-74.

Chan D, Chen J, Wen C, Chiu L, Wu S. Effectiveness of the medication safety review clinics for older adults prescribed multiple medications. J Formos Med Assoc. 2014;113(2):106-13.

Chandrashekar K, Vinayak M, Saritha M, Anil P. Adherence to medication. Inter J Res Ayurveda Pharm. 2013;4(2):291-3.

Chen J, Lu X, Wang W, Shen B, Ye Y, Jiang H, et al. Impact of a clinical pharmacist-led guidance team on cancer pain therapy in China: A prospective multicenter cohort study. (Clinical report). J Pain Symptom Manage. 2014;48(4):500-9.

Cheung K, Graves C, Robertson J. Tumour marker measurements in the diagnosis and monitoring of breast cancer. Cancer Treat Rev. 2000;26(2):91-102.

Chew C, Chiang J, Yeoh T. Impact of outpatient interventions made at an ambulatory cancer centre oncology pharmacy in Singapore. J Oncol Pharm Pract. 2015;21(2):93-101.

Christensen A, Holmbjer L, Midlöv P, Höglund P, Larsson L, Bondesson Å, et al. The process of identifying, solving and preventing drug related problems in the LIMM-study. Int J Clin Pharm. 2011;33(6):1010-8.

Chua S, Kok L, Md Yusof F, Tang G, Lee S, Efendie B, et al. Pharmaceutical care issues identified by pharmacists in patients with diabetes, hypertension or hyperlipidaemia in primary care settings. BMC Health Serv Res. 2012;12(1):388-97.

Chung C, Collins A, Cui N. Development and implementation of an interdisciplinary oncology program in a community hospital. Am J Health Syst Pharm. 2011;68(18):1740-7.

Cipolle R, Strand L, Morley P. Pharmaceutical Care Practice. New York; NY: McGraw-Hill; 1998.

Cipolle R, Strand L, Morley P. Pharmaceutical Care Practice: The Clinician's Guide. 2nd ed. New York, NY: McGraw-Hill; 2004.

Cipolle R, Strand L, Morley P. Pharmaceutical Care Practice: The patient centered approach to medication management services. 3rd ed. New York, NY: McGraw-Hill; 2012.

Coates A, Abraham S, Kaye S, Sowerbutts T, Frewin C, Fox R, et al. On the receiving end-patient perception of the side-effects of cancer chemotherapy. Eur J Cancer Clin Oncol. 1983;19(2):203-8.

Cohen M, Anderson R, Attilio R, Green L, Muller R, Pruemer J. Preventing medication errors in cancer chemotherapy. Am J Health Syst Pharm. 1996;53(7):737-46.

Colombo N, Peiretti M, Garbi A, Carinelli S, Marini C, Sessa C. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2012;23(Suppl 7):vii20-6.

Cooper B, Sood A, Davis C, Ritchie J, Sorosky J, Anderson B, et al. Preoperative CA 125 levels: An independent prognostic factor for epithelial ovarian cancer. Obstet Gynecol. 2002;100(1):59-64.

Cornetta K, Brown C. Perspective: Balancing personalized medicine and personalized care. Acad Med. 2013;88(3):309-13.

Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN, et al. Unintended medication discrepancies at the time of hospital admission. Arch Intern Med. 2005;165(4):424-9.

Council on Credentialing in Pharmacy, Albanese NP, Rouse MJ, Schlaifer M. Scope of contemporary pharmacy practice: Roles, responsibilities, and functions of pharmacists and pharmacy technicians. J Am Pharm Assoc. 2010;50(2):e35-69.

Crisp G, Burkhart J, Esserman D, Weinberger M, Roth M. Development and testing of a tool for assessing and resolving medication-related problems in older adults in an ambulatory care setting: the individualised Medication Assessment and Planning (iMAP) tool. Am J Geriatr Pharmacother. 2011;9(6):451-60.

Crooke M. Appropriate use of tumour markers. Best Tests. 2010;7:8-13.

Custem E, Cervantes A, Nordlinger B, Arnold D. ESMO Guidelines Working Group. Metastatic Colorectal Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):iii1-9.

Davies N, Spaven J, Chambers C. Comprehensive clinical pharmacy documentation in an out-patient cancer facility. Can J Hosp Pharm. 1992;45(3):107-11.

Delaney L, Chambers C, Roldán G, De Robles P, Cairncross G, Forsyth P, et al. A feasibility study to assess the integration of a pharmacist into neurooncology clinic. J Oncol Pharm Pract. 2009;15(2):79-85.

Delpeuch A, Leveque D, Gourieux B, Herbrecht R. Impact of clinical pharmacy services in a hematology/oncology inpatient setting. Anticancer Res. 2015;35(1):457-60.

de Sa Borges A, Guidoni C, Ferreira L, de Freitas O, Pereira L. The pharmaceutical care of patients with type 2 diabetes mellitus. Pharm World Sci. 2010;32(6):730-6.

Diamandis E, Hoffman B, Sturgeon C. National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines for the Use of Tumor Markers. Clin Chem. 2008;54(11):1935-9.

Dohler N, Krolop L, Ringsdorf S, Meier K, Ko Y, Kuhn W, et al. Task allocation in cancer medication management - Integrating the pharmacist. Patient Educ Couns. 2011;83(3):367-74.

Dranitsaris G, Warr D, Puodziunas A. A randomized trial of the effects of pharmacist intervention on the cost of antiemetic therapy with ondansetron. Support Care Cancer. 1995;3(3):183-9.

Dranitsaris G, Leung P, Warr D. Implementing evidence based antiemetic guidelines in the oncology setting: Results of a 4-month prospective intervention study. Support Care Cancer. 2001;9(8):611-8.

Duffy M. Clinical uses of tumor markers: A critical review. Crit Rev Clin Lab Sci. 2001;38(3):225-62.

Duffy M. Carcinoembryonic antigen as a marker for colorectal cancer: Is it clinically useful? Clin Chem. 2001;47(4):624-30.

Duffy M, van Dalen A, Haglund C, Hansson L, Klapdor R, Lamerz R, et al. Clinical utility of biochemical markers in colorectal cancer: European Group on Tumour Mark ers (EGTM) guidelines. Eur J Cancer. 2003;39(6):718-27.

Duffy M, Bonfrer J, Kulpa J, Rustin G, Soletormos G, Torre G, et al. CA 125 in ovarian cancer: European Group on Tumor Markers (EGTM) guidelines for clinical use. Int J Gynecol Oncol. 2005;15(5):679-91.

Duffy M. Role of tumor markers in patients with solid tumors: A critical review. Eur J Intern Med. 2007;18(3):175-84.

Duffy M, Van Dalen A, Haglund L, Hansson L, Holinski-Feder E, Klapdor R, et al. Tumour markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines for clinical use. Eur J Cancer. 2007;43(9):1348-60.

Duffy M, Crown J. A personalized approach to cancer treatment: How biomarkers can help. Clin Chem. 2008;54(11):1770-9.

Duffy M, McGing P. The Association of Clinical Biochemists in Ireland (ACBI) - Guidelines for the use of tumour markers. 4th ed; 2010.

Duffy M, Sturgeon C, Lamerz R, Haglund C, Holubec V, Klapdor R, et al. Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. Ann Oncol. 2010;21(3):441-7.

Duffy M. Tumor markers in clinical practice: A review focusing on common solid cancers. Med Princ Pract. 2013;22(1):4-11.

Duffy M, Lamerz R, Haglund C, Nicolini A, Kalousová M, Holubec L, et al. Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European Group on Tumor Markers 2014 guidelines update. Int J Cancer. 2014;134(11):2513-22.

Eddlemon J, Hayman J, Breland B. Establishment and operation of an oncology satellite pharmacy. Am J Hosp Pharm. 1984;41(10):2045-7.

Edwards SJ, Abbott R, Edwards J, LeBlanc M, Dranitsaris G, Donnan J, et al. Outcomes assessment of a pharmacist-directed seamless care program in an ambulatory oncology clinic. J Pharm Pract. 2014;27(1):46-52.

Eichenberger P, Lampert M, Kahmann I, van Mil J, Hersberger K. Classification of drug-related problems with new prescriptions using a modified PCNE classification system. Pharm World Sci. 2010;32(3):362-72.

Elf M, Wikblad K. Satisfaction with information and quality of life in patients undergoing chemotherapy for cancer. The role of individual differences in information preference. Cancer Nurs. 2001;24(5):351-6.

Engstrom C, Hernandez I, Haywood J, Lilenbaum R. The efficacy and cost effectiveness of new antiemetic guidelines. Oncol Nurs Forum. 1999;26(9):1453-8.

Excellus Health Plan. Serum tumor markers for diagnosis and management of cancer. 2015.

Faulkner D, Meldrum C. Abnormal laboratory results: Tumour markers. Aust Prescr. 2012;35(4):125-8.

Farias TF, Aguiar K, Rotta I, Belletti K, Carlotto J. Implementing a clinical pharmacy service in haematology. Einstein. 2016;14(3):384-90.

Felton M, van Londen G, Marcum Z. Medication adherence to oral cancer therapy: The promising role of the pharmacist. J Oncol Pharm Pract. 2016;22(2):378-81.

Feyer P, Kleeberg U, Steingräber M, Günther W, Behrens M. Frequency of side effects in outpatient cancer care and their influence on patient satisfaction - a prospective survey using the PASQOC® questionnaire. Support Care Cancer. 2008;16(6):567-75.

Finkers F, Maring J, Boersma F, Taxis K. A study of medication reviews to identify drug-related problems of polypharmacy patients in the Dutch nursing home setting. J Clin Pharm Ther. 2007;32(5):469-76.

Forsmark C, Lambiase L, Vogel S. Diagnosis of pancreatic cancer and prediction of unresectability using the tumor-associated antigen CA 19-9. Pancreas. 1994;9(6):731-4.

Fritsche H, Bast R. CA 125 in ovarian cancer: advances and controversy. Clin Chem. 1998;44(7):1379-80.

Gavhane Y, Shete A, Bhagat A, Shinde V, Bhong K, Khairnar G, et al. Solid Tumors: Facts, challenges and solutions. Int J Pharma Sci Res. 2011;2(1):1-12.

Gebbia V, Bellvia G, Ferrau F, Valerio M. Adherence, compliance and persistence to oral therapy: a review focused on chemotherapeutic and biologic agents. Expert Opin Drug Saf. 2012;11(Suppl 1):S49-59.

Gilbert A, Roughead E, Beilby J, Mott K, Barratt J. Collaborative medication management services: improving patient care. Med J Aust. 2002;177(4):189-92.

Gillespie U, Alassaad A, Henrohn D, Garmo H, Hammarlund-Udenaes M, Toss H, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. Arch Intern Med. 2009;169(9):894-900.

Gisev N, Bell J, O'Reilly C, Rosen A, Chen T. An expert panel assessment of comprehensive medication reviews for clients of community mental health teams. Soc Psychiatry Psychiatr Epidemiol. 2010;45(11):1071-9.

Gogas H, Lofts F, Evans T, Daryanani S, Mansi J. Are serial measurements of CA19-9 useful in predicting response to chemotherapy in patients with inoperable adenocarcinoma of the pancreas? Br J Cancer. 1998;77(2):325-8.

Granas A, Berg C, Hjellvik V, Haukereid C, Kronstad A, Blix H, et al. Evaluating categorisation and clinical relevance of drug-related problems in medication reviews. Pharm World Sci. 2010;32(3):394-403.

Grech L. An evaluation of a pharmaceutical care model in patients with rheumatological disorders. [PhD dissertation]. Department of Pharmacy (Msida): University of Malta; 2015.

Grem J. The prognostic importance of tumor markers in adenocarcinomas of the gastrointestinal tract. Curr Opin Oncol. 1997;9(4):380-7.

Grupo de Investigacíon en Aténcion Farmacéutica. The second Granada consensus on drug-related problems. Ars Pharm. 2002;43:175-84.

Gupta R, Kim J, Spiegel J, Ferguson S. Developing products for personalized medicine: NIH research tools policy applications. Per Med. 2004;1(1):115-24.

Hall D, Pater K. Implementation of a medication therapy management program in a hospital-based outpatient pharmacy. Hosp Pharm. 2011;46(7):512-8.

Hanlon J, Schmader K, Samsa G, Weinberger M, Uttech K, Lewis I, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992;45(10):1045-51.

Hanlon J, Schmader K, Landsman P, Samsa G, Lewis I, Weinberger M. Inappropriate prescribing and health outcomes in elderly veteran outpatients. Ann Pharmacother. 1997;31(5):529-33.

Harris I, Westberg S, Frakes M, Van Vooren J. Outcomes of medication therapy review in a family medicine clinic. J Am Pharm Assoc. 2009;49(5):623-7.

Harrison J, Wang J, Cervenko J, Jackson L, Munyal D, Hamandi B, et al. Pilot study of a pharmaceutical care intervention in an outpatient lung transplant clinic. Clin Transplant. 2012;26(2):E149-57.

Hatah E, Tordoff J, Duffull S, Braund R. Pharmacists performance of clinical interventions during adherence support medication reviews. Res Social Adm Pharm. 2014;10(1):185-94.

Hepler C, Strand L. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm. 1990;47(3):533-43.

Holle L, Boehnke Michaud L. Oncology pharmacists in health care delivery: vital members of the cancer care team. J Oncol Pract. 2014;10(3):e142-5.

Hong F, Blonquist T, Halpenny B, Berry D. Patient-reported symptom distress, and most bothersome issues, before and during cancer treatment. Patient Relat Outcome Meas. 2016;7:127-35.

Hooper R, Adam A, Kheir N. Pharmacist-documented interventions during the dispensing process in a primary health care facility in Qatar. Drug Health Patient Saf. 2009;1:73-80.

Hudson S, Macintyre J, Dalrymple H, Maclean H, Lannigan N. Development of a system for reporting pharmaceutical care issues in cancer patients receiving chemotherapy. Pharm J. 2003;271(7264):266-7.

Hudson S, Mc Anaw J, Johnson B. The changing roles of pharmacists in society. Int J Sci Med Educ. 2007;1(1):22-34.

Hutchison L, Castleberry A. The pharmacist's new role as part of an interdisciplinary care team. J Am Soc Aging. 2011;35(4):62-8.

Hutten B, Prins M, Gent M, Ginsberg J. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol. 2000;18:3078-83.

Isetts B, Brown L, Schondelmeyer S, Lenarz L. Quality assessment of a collaborative approach for decreasing drug-related morbidity and achieving therapeutic goals. Arch Intern Med. 2003;163(15):1813-20.

Isetts B, Schondelmeyer S, Artz M, Lenarz L, Heaton A, Wadd W, et al. Clinical and economic outcomes of medication therapy management services: the Minnesota experience. J Am Pharm Assoc. 2008;48(2):203-11.

Isetts B, Brummel A, Ramalho de Oliveira D, Moen D. Managing drug-related morbidity and mortality in the patient-centered medical home. Med Care. 2012;50(11):997-1001.

Jaehde U, Liekweg A, Simons S, Westfeld M. Minimising treatment-associated risks in systemic cancer therapy. Pharm World Sci. 2008;30(2):161-8.

Kaboli P, Hoth AB, Mcclimon B, Schnipper J. Clinical pharmacists and inpatient medical care - A systematic review. Arch Intern Med. 2006;166(9):955-64.

Kato P, Cole S, Bradlyn A, Pollock B. A video game improves behavioral outcomes in adolescents and young adults with cancer: a randomized trial. Pediatrics. 2008;122(2):e305-17.

Kim G, Chen A, Arceci R, Mitchell S, Kokoszka K, Daniel D, et al. Error reduction in pediatric chemotherapy: computerized order entry and failure modes and effects analysis. Arch Pediatr Adolesc Med. 2006;160(5):495-8.

Kozma C, Slaton T, Ellis L, Mckenzie R, Lafeuille M, Grittner A, et al. Prostate cancer patients' adherence to medication while on abiraterone acetate (AA) therapy. J Clin Oncol. 2014;32(4):Suppl14 Ab267.

Krska J, Cromarty J, Arris F, Jamieson D, Hansford D. Providing pharmaceutical care using a systematic approach. Pharm J. 2000;265(7120):656-60.

Krska J, Jamieson D, Arris F, McGuire A, Abbott S, Hansford D, et al. A classification system for issues identified in pharmaceutical care practice. Int J Pharm Pract. 2002;10(2):91-100.

Lafeuille M, Gritter A, Lefebvre P, Ellis L, McKenzie R, Slaton T, et al. Adherence patterns for abiraterone acetate and concomitant prednisone use in patients with prostate cancer. J Manag Care Pharm. 2014;20(5):477-84.

Lampert M, Kraehenbuehl S, Hug B. Drug-related problems: evaluation of a classification system in the daily practice of a Swiss university hospital. Pharm World Sci. 2008;30(6):768-76.

Lau P, Stewart K, Dooley M. The ten most common adverse drug reactions (ADRs) in oncology patients: do they matter to you? Support Care Cancer. 2004;12(9):626-33.

Ledermann J, Raja F, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl6):vi24-32.

Lee C, Nicholson P, Ledermann J, Rustin G. Patient compliance with prolonged oral altretamine treatment in relapsed ovarian cancer. Eur J Gynaecol Oncol. 1996;17(2):99-103.

Leendertse A, de Koning F, Goudswaard A, Belitser S, Verhoef M, de Gier H, et al. Preventing hospital admissions by reviewing medication (PHARM) in primary care: an open controlled study in an elderly population. J Clin Pharm Ther. 2013;38(5):379-87.

Leikola S, Virolainen J, Tuomainen L, Tuominen R, Airaksinen M. Comprehensive medication reviews for elderly patients: findings and recommendations to physicians. J Am Pharm Assoc. 2012;52(5):630-3.

Leman E, Gonzalgo M. Prognostic features and markers for testicular cancer management. Indian J Urol. 2010;26(1):76-81.

Levine A, Richardson J, Marks G, Chan K, Graham J, Selser J, et al. Compliance with oral drug therapy in patients with hematologic malignancy. J Clin Oncol. 1987;5(9):1469-76.

Liekweg A, Westfeld M, Jaehde U. From oncology pharmacy to pharmaceutical care: new contributions to multidisciplinary cancer care. Support Care Cancer. 2004;12(2):73-9.

Liekweg A, Westfeld M, Braun M, Zivanovic O, Schink T, Kuhn W, et al. Pharmaceutical care for patients with breast and ovarian cancer. Support Care Cancer. 2012;20(11):2669-77.

Lin S, Hatoum HT, Buchner D, Cox D, Balu S. Impact of 5-HT sub 3 receptor antagonists on chemotherapy-induced nausea and vomiting: a retrospective cohort study. BMC Health Serv Res. 2012;12(1):215-23.

Lin Q, Wang G, Ma G, Shen Q. The role of pharmaceutical care in the oncology department. Eur J Hosp Pharm. 2015;22(3):128-31.

Lingaratnam S, Aranda S, Pearce T, Kirsa S. A controlled before and after study to evaluate a patient and health professional partnership model towards effective medication reconciliation. J Oncol Pharm Pract. 2012;19(1):48-56.

Locker G, Hamilton S, Harris J, Jessup J, Kemeny N, Macdonald J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol. 2006;24(33):5313-27.

Ma C. Role of pharmacists in optimizing the use of anticancer drugs in the clinical setting. Integr Pharm Res Pract. 2014;3(1):11-24.

Mackie CA. Randomised controlled trial of medication review. In: Repeat prescribing in general practice: the development and evaluation of methodologies to improve the quality and cost-effectiveness of repeat prescribing [dissertation]. Glasgow (UK): University of Strathclyde; 2002.

Mancini R. Implementing a standardized pharmacist assessment and evaluating the role of a pharmacist in a multidisciplinary supportive oncology clinic. J Support Oncol. 2012;10(3):99-106.

Mannheimer B, Ulfvarson J, Eklöf S, Bergqvist M, Andersén-Karlsson E, Pettersson H, et al. Drug-related problems and pharmacotherapeutic advisory intervention at a medicine clinic. Eur J Clin Pharmacol. 2006;62(12):1075-81.

McDonnell M. An audit of tumour marker requests in Northern Ireland. Ann Clin Biochem. 2004;41:378-84.

McGinley P, Kilpatrick E. Tumour markers: their use and misuse by clinicians. Ann Clin Biochem. 2003;40:643-7.

McGivney M, Meyer S, Duncan-Hewitt W, Hall D, Goode J, Smith R. Medication therapy management: Its relationship to patient counseling, disease management, and pharmaceutical care. J Am Pharm Assoc. 2007;47(5):620-8.

McKee M, Frei BL, Garcia A, Fike D, Soefje SA. Impact of clinical pharmacy services on patients in an outpatient chemotherapy academic clinic. J Oncol Pharm Pract. 2011;17(4):387-94.

Mekonnen A, Yesuf E, Odegard P, Wega S. Implementing ward based clinical pharmacy services in an Ethiopian university hospital. Pharm Pract (Granada). 2013;11(1):51-7.

Meyboom R, Lindquist M, Egberts A. An ABC of drug-related problems. Drug Saf. 2000;22:415-23.

Meyer T, Rustin G. Role of tumour markers in monitoring epithelial ovarian cancer. Br J Cancer. 2000;82(9):1535-8.

Miller L, Hoare C. Clinical pharmacy service in oncology clinics and an outpatient chemotherapy suite. PC43 - NHS Highland; 2014.

Milos V, Rekman E, Bondesson A, Eriksson T, Jakobsson U, Westerlund T, et al. Improving the quality of pharmacotherapy in elderly primary care patients through medication reviews: a randomised controlled trial. Drugs Aging. 2013;30(4):235-46.

Moen E, Godley L, Zhang W, Dolan M. Pharmacogenomics of chemotherapeutic susceptibility and toxicity. Genome Med. 2012;4(11):90.

Montgomery R, Hoffman J, Riley L, Rogatko A, Ridge J, Eisenberg B. Prediction of recurrence and survival by post-resection CA 19-9 values in patients with adenocarcinoma of the pancreas. Ann Surg Oncol. 1997;4(7):551-6.

Naunton M, Peterson G. Evaluation of home-based follow-up of high-risk elderly patients discharged from hospital. J Pharm Pract Res. 2003;33(3):176-82.

NCCN. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Besh S, Chao J, et al. Gastric Cancer, Version 3.2016, National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2016;14(10):1286-1312.

Nicholas A, Divine H, Nowak-Rapp M, Roberts K. University and college of pharmacy collaboration to control health plan prescription drug costs. J Am Pharm Assoc. 2007;47(1):86-92.

Nickel C, Ruedinger J, Messmer A, Maile S, Peng A, Bodmer M, et al. Drug-related emergency department visits by elderly patients presenting with non-specific complaints. Scand J Trauma Resusc Emerg Med. 2013;21:15.

Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence (Review). Cochrane Database Syst Rev [CD000011]. 2014(11):1-730.

Nilsen E, Myrhaug H, Johansen M, Oliver S, Oxman A. Methods of consumer involvement in developing healthcare policy and research, clinical practice guidelines and patient information material (Review). Cochrane Database Syst Rev [CD004563]. 2006(3):1-3.

Nilsson J, Andersson K, Bergkvist A, Björkman I, Brismar A, Moen J. Refill adherence to repeat prescriptions of cancer drugs to ambulatory patients. Eur J Cancer Care. 2006;15(3):235-7.

Nishtala P, McLachlan A, Bell J, Chen T. A retrospective study of drug-related problems in Australian aged care homes: medication reviews involving pharmacists and general practitioners. J Eval Clin Pract. 2011;17(1):97-103.

Norton PG, Baker G. Patient safety in cancer care: a time for action. J Natl Cancer Inst. 2007;99(8):579-80.

Ntaios G, Hatzitolios A, Chatzinikolaou A, Karalazou P, Savopoulos C, Karamouzis M, et al. An audit of tumour marker utilization in Greece. Eur J Intern Med. 2009;20(3):e66-9.

O'Donnell P, Ratain M. Germline pharmacogenomics in oncology: Decoding the patient for targeting therapy. Mol Oncol. 2012;6(2):251-9.

Öberg K, Knigge U, Kwekkeboom D, Perren A, on behalf of the ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):vii124-30.

Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487-97.

Palmer C, Pratt J, Basu B, Earl H. A study to evaluate the use of CA125 in ovarian cancer follow-up: A change in practice led by patient preference. Gynecol Oncol. 2006;101(1):4-11.

Parker C, Gillessen S, Heidenreich A, Horwich A, on behalf of the ESMO Guidelines Committee. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v69-77.

Partridge A, Avorn J, Wang P, Winer E. Adherence to therapy with oral antineoplastic agents. J Natl Cancer Inst. 2002;94(9):652-61.

Pastel D, Fay P, Lee D. Effect of implementing a cancer chemotherapy order form on prescribing habits for parenteral antineoplastics. Hosp Pharm. 1993;28(12):1192-5.

Pharmaceutical Care Network Europe (PCNE) Foundation: PCNE Classification for drug related problems. Available from: http://www.pcne.org/working-groups/2/drug-related-problem-classification

Pharmaceutical Care Network Europe (PCNE) Foundation: PCNE Classification for drug related problems. V6.2. 2010. Available from: http://www.pcne.org/upload/files/11_PCNE_classification_V6-2.pdf.

Pharmaceutical Care Network Europe (PCNE) Foundation: PCNE Classification for drug related problems. V7.0. 2016. Available from: http://www.pcne.org/upload/files/152_PCNE_classification_V7-0.pdf

Pon D. Service plans and clinical interventions targeted by the oncology pharmacist. Pharm Pract Manag Q. 1996;16(1):18-30.

Pound C, Partin A, Eisenberger M, Chan D, Pearson J, Walsh P. Natural history of progression after PSA elevation following radical prostatectomy. JAMA. 1999;281(17):1591-7.

Preusser M. Neuro-oncology: A step towards clinical blood biomarkers of glioblastoma. Nat Rev Neurol. 2014;10(12):681-2.

Ramalho de Oliveira D, Brummel A, Miller D. Medication therapy management: 10 years of experience in a large integrated health care system. J Manag Care Pharm. 2010;16(3):185-95.

Randolph L, Walker C, Nguyen A, Zachariah S. Impact of pharmacist interventions on cost avoidance in an ambulatory cancer center. J Oncol Pharm Pract. 2016;0(0):1-6.

Rao D, Gilbert A, Strand L, Cipolle R. Drug therapy problems found in ambulatory patient populations in Minnesota and South Australia. Pharm World Sci. 2007;29(6):647-54.

Rashed A, Neubert A, Tomlin S. Epidemiology and potential associated risk factors of drug-related problems in hospitalised children in the United Kingdom and Saudi Arabia. Eur J Clin Pharmacol. 2012;68(12):1657-66.

Rashed A, Neubert A, Alhamdan H, Tomlin S, Alazmi A, AlShaikh A, et al. Drug-related problems found in children attending an emergency department in Saudi Arabia and in the United Kingdom. Int J Clin Pharm. 2013;35(3):327-31.

Riechelmann R, Moreira F, Smaletz Ò, Saad E. Potential for drug interactions in hospitalized cancer patients. Cancer Chemother Pharmacol. 2005;56(3):286-90.

Riechelmann R, Tannock I, Wang L, Saad E, Taback N, Krzyzanowska M. Potential drug interactions and duplicate prescriptions among cancer patients. J Natl Cancer Inst. 2007;99(8):592-600.

Riechelmann R, Zimmermann C, Chin S, Wang L, O'Carroll A, Zarinehbaf S, et al. Potential drug interactions in cancer patients receiving supportive care exclusively. J Pain Symptom Manage. 2008;35(5):535-43.

Riechelmann R, Del Giglio A. Drug interactions in oncology: how common are they? Ann Oncol. 2009;20(12):1907-12.

Ross L, Bloodworth L. Patient-centered health care using pharmacist-delivered medication therapy management in rural Mississippi. J Am Pharm Assoc. 2012;52(6):802-9.

Rough S, Carro G. Developing and implementing oral 5-HT3 receptor antagonist guidelines: a multidisciplinary process. Pharm Pract Manag Q. 1998;18(2):48-58.

Roughead E, Barratt J, Gilbert A. Medication-related problems commonly occurring in an Australian community setting. Pharmacoepidemiol Drug Saf. 2004;13(2):83-7.

Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. Ca Cancer J Clin. 2009;59(1):56-66.

Ruder AD, Smith DL, Madsen MT, Kass FH. Is there a benefit to having a clinical oncology pharmacist on staff at a community oncology clinic? J Oncol Pharm Pract. 2010;17(4):425-32.

Rustin G, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Gynecological Cancer Intergroup. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011;21(2):419-23.

Ruths S, Straand J, Nygaard H. Multidisciplinary medication review in nursing home residents: what are the most significant drug-related problems? The Bergen district nursing home (BEDNURS) study. Qual Saf Health Care. 2003;12(3):176-80.

Ruths S, Viktil K, Blix H. Classification of drug-related problems. Tidsskr Nor Laegeforen. 2007;127:3073-76.

Samoy L, Zed P, Wilbur K, Balen R, Abu-Laban R, Roberts M. Drug-related hospitalizations in a tertiary care internal medicine service of a Canadian hospital: a prospective study. Pharmacotherapy. 2006;26(11):1578-86.

Sano HS, Waddell J, Solimando DA, Doulaveris P, Myhand R. Study of the effect of standardized chemotherapy order forms on prescribing errors and anti-emetic cost. J Oncol Pharm Pract. 2005;11(1):21-30.

Schaefer M. How indispensable are pharmacists? Results of a study on documenting drug-related problems in the pharmacy German. Dtsch Apoth Ztg. 1995;33:3019-27.

Schaefer M. Discussing basic principles for a coding system of drug-related problems: The case of PI-Doc. Pharm World Sci. 2002;24(4):120-7.

Schlieman M, Ho H, Bold R. Utility of tumor markers in determining resectability of pancreatic cancer. Arch Surg. 2003;138(9):951-6.

Schmoll H, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol. 2012;23(10):2479-516.

Schwartz R, Eng K, Frieze D, Gosselin T, Griffith N, Seung A, et al. NCCN Task Force Report: Specialty Pharmacy. J Natl Compr Canc Netw. 2010;8(Suppl 4):S1-S12.

Scripture CD, Figg WD. Drug interactions in cancer therapy. Nat Rev Cancer. 2006;6(7):546-58.

Semjonow A, Schmid H. The rise and fall of PSA: clinical implications of prostate specific antigen kinetics. Urol Res. 2002;30(2):85-8.

Serrano-Fabia A, Albert-Marí A, Almenar-Cubell D, Jiménez-Torres N. Multidisciplinary system for detecting medication errors in antineoplastic chemotherapy. J Oncol Pharm Pract. 2010;16(2):105-12.

Sessions J, Valgus J, Yowell B, SY, Lacovelli L. Role of oncology clinical pharmacists in light of the oncology workforce study. J Oncol Pract. 2010;6(5):270-2.

Shah S, Dowell J, Greene S. Evaluation of clinical pharmacy services in a hematology/ oncology outpatient setting. Ann Pharmacother. 2006;40(9):1527-33.

Sharma R, Tobin P, Clarke S. Management of chemotherapy-induced nausea, vomiting, oral mucositis and diarrhoea. Lancet Oncol. 2005;6(2):93-102.

Sharma S. Tumour markers in clinical practice: General principles and guidelines. Indian J Med Paediatr Oncol. 2009;30(1):1-8.

SHB-SEP. Proposals for adaptation of the SEP-codes. (Dutch). Houten, the Netherlands: SHB PlusPunten. 2003 Jan 14:15.

Sherman M. Current status of alpha-fetoprotein testing. Gastroenterol Hepatol. 2011;7(2):113-4.

Sikaris K. Prostate specific antigen. Aust Prescr. 2011;34(6):186-8.

Simons S, Ringsdorf S, Braun M, Mey U, Schwindt P, Ko Y, et al. Enhancing adherence to capecitabine chemotherapy by means of multidisciplinary pharmaceutical care. Support Care Cancer. 2011;19(7):1009-18.

Skalla KA, Bakitas M, Furstenberg CT, Ahles T, Henderson JV. Patients' need for information about cancer therapy. Oncol Nurs Forum. 2004;31(2):313-9.

Smith M, Giuliano M, Starkowski M. In Connecticut: Improving patient medication management in primary care. Health Aff (Millwood). 2011;30(4):646-54.

Song P, Wu Q, Huang Y. Multidisciplinary team and team oncology medicine research and development in China. Biosci Trends. 2010;4(4):151-60.

Spoelstra SL, Given CW, Sikorskii A, Coursaris CK, Majumder A, DeKoekkoek T, et al. Feasibility of a text messaging intervention to promote self-management for patients prescribed oral anticancer agents. (Report). Oncol Nurs Forum. 2015;42(6):647-57.

Stratton T, Cernohous T, Hager K, Bumgardner M, Traynor A, Worley MM, et al. College of pharmacy-based medication therapy management program for a university system. J Am Pharm Assoc. 2012;52(5):653-60.

Stoll P, Kopittke L. Potential drug-drug interactions in hospitalized patients undergoing systemic chemotherapy: a prospective cohort study. Int J Clin Pharm. 2015;37(3):475-84.

Strand L, Cipolle R, Morley P, Frakes M. The impact of pharmaceutical care practice on the practitioner and the patient in the ambulatory practice setting: twenty-five years of experience. Curr Pharm Des. 2004;10(31):3987-4001.

Stratton T, Cernohous T, Hager K, Bumgardner M, Traynor A, Worley M, et al. College of pharmacy-based medication therapy management program for a university system. J Am Pharm Assoc. 2012;52(5):653-60.

Stuijt C, Franssen E, Egberts A, Hudson S. Appropriateness of prescribing among elderly patients in a Dutch residential home: observational study of outcomes after a pharmacist-led medication review. Drugs Aging. 2008;25(11):947-54.

Sturgeon C. National Academy of Clinical Biochemistry (NACB). Practice guidelines for tumour markers use in the clinic. Clin Chem. 2002;48(8):1151-9.

Sturgeon C, Duffy M, Stenman U, Lilja H, Brunner N, Chan D, et al. National Academy of Clinical Biochemistry (NACB) Laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast and ovarian cancers. Clin Chem. 2008;54(12):e11-79.

Sturgeon C, Diamandis E. The National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines. Use of tumor markers in clinical practice: quality requirements. 2009.

Sturgeon C, Lai L, Duffy M. Serum tumour markers: how to order and interpret them. BMJ. 2009;339:852-8.

Sturgeon C, Duffy M, Hofmann B, Lamerz R, Fritsche H, Gaarenstroom K, et al. National Academy of Clinical Biochemistry (NACB) Laboratory medicine practice guidelines for use of tumor markers in liver, bladder, cervical, and gastric cancers. Clin Chem. 2010;56(6):e1-e48.

Sun C, Bodurka D, Weaver C, Rasu R, Wolf J, Bevers M, et al. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. Support Care Cancer. 2005;13(4):219-27.

Taegtmeyer A, Curkovic I, Rufibach K, Corti N, Battegay E, Kullak-Ublick G. Electronic prescribing increases uptake of clinical pharmacologists' recommendations in the hospital setting. Br J Clin Pharmacol. 2011;72(6):958-64.

Taegtmeyer A, Curkovic I, Corti N, Rosen C, Egbring M, Russmann S, et al. Drug-related problems and factors influencing acceptance of clinical pharmacologists' alerts in a large cohort of neurology inpatients. Swiss Med Wkly. 2012;142:w1361.

Tam V, Knowles S, Cornish P, Fine N, Marchesano R, Etchells E. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. Can Med Assoc J. 2005;173(5):510-5.

Tavakoli-Ardakani M, Kazemian K, Salamzadeh J, Mehdizadeh M. Potential of drug interactions among hospitalized cancer patients in a developing country. Iran J Pharm Res. 2013;12(Suppl S):171-8.

Tenti E, Schirone A, Passardi A, Casadei Gardini A. Medication reconciliation in oncology and monitoring of preventable drug interactions. Int J Mol Med. 2015;36(S26).

Thorn D, Sexton M, Lemay A, Sarigianis J, Melita D, Gustafson N. Effect of a cancer chemotherapy prescription form on prescription completeness. Am J Hosp Pharm. 1989;46(9):1802-6.

Tollefson M, Slezak J, Leibovich B, Zincke H, Blute M. Stratification of patient risk based on prostate-specific antigen doubling time after radical retropubic prostatectomy. Mayo Clin Proc. 2007;82(4):422-7.

Toner G, MacCallum P. Early identification of therapeutic failure in nonseminomatous germ cell tumors by assessing serum tumor marker decline during chemotherapy: still not ready for routine clinical use. J Clin Oncol. 2004;2(19):3842-5.

Touchette D, Massica A, Dolor R, Schumock G, Choi Y, Kim Y, et al. Safety-focused medication therapy management: a randomized controlled trial. J Am Pharm Assoc. 2012;52(5):603-12.

Triller D, Clause S, Briceland L, Hamilton R. Resolution of drug-related problems in home care patients through a pharmacy referral service. Am J Health Syst Pharm. 2003;60(9):905-10.

Trusheim M, Berndt E, Douglas F. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nat Rev Drug Discov. 2007;6(4):287-93.

Tuffaha H, Abdelhadi O, Omar S. Clinical pharmacy services in the outpatient pediatric oncology clinics at a comprehensive cancer center. Int J Clin Pharm. 2012;34(1):27-31.

Valgus J, Jarr S, Schwartz R, Rice M, Bernard SA. Pharmacist- led, interdisciplinary model for delivery of supportive care in the ambulatory cancer clinic setting. J Oncol Pharm Pract. 2010;6(6):e1-4.

Valgus J, Faso A, Gregory KM, Jarr S, Savage S, Caiola S, et al. Integration of a clinical pharmacist into the hematology-oncology clinics at an academic medical center. Am J Health Syst Pharm. 2011;68(7):613-9.

van Mil J, Tromp T. Coding frequently asked questions during the pharmaceutical care process with the PAS System. J Appl Ther. 1997;1:351-5.

van Mil J, Westerlund L, Hersberger K, Schaefer M. Drug-related problem classification systems. Ann Pharmacother. 2004;38(5):859-67.

van Mil J. Drug-related problems: a cornerstone for pharmaceutical care. J Malta College Pharm Pract. 2005;10:5-8.

van Roozendaal B, Krass I. Development of an evidence-based checklist for the detection of drug related problems in type 2 diabetes. Pharm World Sci. 2009;31(5):580-95.

Verbrugghe M, Verhaeghe S, Lauwaert K, Beeckman D, Van Hecke A. Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review. Cancer Treat Rev. 2013;39(6):610-21.

Verheijen R, von Mensdorff-Pouilly S, van Kamp G, Kenemans P. CA 125: fundamental and clinical aspects. Semin Cancer Biol. 1999;9(2):117-24.

Viktil KK, Blix HS. The Impact of clinical pharmacists on drug-related problems and clinical outcomes. Basic Clin Pharmacol Toxicol. 2008;102(3):275-80.

Villa L, Von Chrismar A, Oyarzun C, Eujenin P, Fernandez M, Quezada M. Pharmaceutical care program for dyslipidemic patients at three primary health care centers: impacts and outcomes. Lat Am J Pharm. 2009;28(3):415-20.

Vollmer R, Egawa S, Kuwao S, Baba S. The dynamics of prostate specific antigen during watchful waiting of prostate carcinoma: a study of 94 Japanese men. Cancer. 2002;94:1692-8.

Waight C. Electronic pharmaceutical care plans in oncology. Hosp Pharm Eur. 2011(54).

Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender and performance status in 1,000 patients. Support Care Cancer. 2000;8(3):175-9.

Walter T, Wang L, Chuk K, N P, Tannock IF, Krzyzanowska MK. Assessing adherence to oral chemotherapy using different measurement methods: Lessons learned from capecitabine. J Oncol Pharm Pract. 2014;20(4):249-56.

Wang Y, Wu H, Xu F. Impact of clinical pharmacy services on KAP and QOL in cancer patients: a single-center experience. Biomed Res Int. 2015:1-8.

Waterhouse D, Calzone K, Mele C, Brenner D. Adherence to oral tamoxifen: A comparison of patient self-report, pill counts, and microelectronic monitoring. J Clin Oncol. 1993;11(6):1189-97.

Weingart S, Cleary A, Seger A, Eng T, Saadeh M, Gross A, et al. Medication reconciliation in ambulatory oncology. Jt Comm J Qual Patient Saf. 2007;33(12):750-7.

Wermeille J, Bennie M, Brown I, McKnight J. Pharmaceutical care model for patients with type 2 diabetes: integration of the community pharmacist into the diabetes team: a pilot study. Pharm World Sci. 2004;26(1):18-25.

Westberg S, Sorensen T. Pharmacy-related health disparities experienced by non-English-speaking patients: impact of pharmaceutical care. J Am Pharm Assoc. 2005;45(1):48-54.

Westerlund T, Almarsdottir A, Melander A. Drug-related problems and pharmacy interventions in community pharmacy. Int J Pharm Pract. 1999;7(1):40-50.

Westerlund T. Drug-related problems: identification, characteristics and pharmacy interventions [dissertation]. Department of Social Medicine (Sweden): Göteborg University; 2002.

Westerlund T, Gelin U, Pettersson E, Skärlund F, Wågström K, Ringbom C. A retrospective analysis of drug-related problems documented in a national database. Int J Clin Pharm. 2013;35(2):202-9.

Williams M, Peterson G, Tenni P, et al. Drug-related problems detected in Australian Community Pharmacies: The PROMISe trial. Ann Pharmacother. 2011;45:1067-76.

Wong W, Ignoffo R. If there an expert systems and dose checks, why do we still need the clinical pharmacist? Pharm Pract Manag Q. 1996;16(1):50-8.

Wong S, Gray E. Clinical pharmacy services in oncology clinics. J Oncol Pharm Pract. 1999;5(1):49-54.

Wu E, Zhou S, Bhat K, Ma Q. CA 19-9 and pancreatic cancer. Clin Adv Hematol Oncol. 2013;11(1):53-5.

Wu Z, Kuntz A, Wadleigh R. CA 19-9 tumor marker: is it reliable? A case report in a patient with pancreatic cancer. Clin Adv Hematol Oncol. 2013;11(1):50-2.

Yamada K, Nabeshima T. Pharmacist-managed clinics for patient education and counseling in Japan: current status and future perspectives. J Pharm Health Care. 2015;1:2-9.

Yennurajalingam S, Urbauer DL, Casper KLB, Reyes-Gibby C, Chacko R, Poulter V, et al. Impact of a palliative care consultation team on cancer-related symptoms in advanced cancer patients referred to an outpatient supportive care clinic. J Pain Symptom Manage. 2011;41(1):49-56.

Young S, Bishop L, Conway A. Interventions performed by community pharmacists in one Canadian province: a cross-sectional study. Ther Clin Risk Manag. 2012;8:415-21.

Zaal R, Jansen M, Duisenberg-van Essenberg M, Tijssen C, Roukema J, van Den Bemt P. Identification of drug-related problems by a clinical pharmacist in addition to computerised alerts. Int J Clin Pharm. 2013;35(5):753-62.

Zaman Huri H, Fun Wee H. Drug related problems in type 2 diabetes patients with hypertension: a cross-sectional retrospective study. BMC Endocr Disord. 2013;13(1):2-12.

Appendices

Appendix A

Study Information Sheet in English and in Maltese

Study Information Sheet

Who is doing this study?

The study is being carried out by Charyl Fava, a pharmacist as part of a PharmD thesis entitled *"The implication of monitoring tumour markers: A personalised medicine approach."* The study is being undertaken under the supervision of the Pharmacy Department at the University of Malta.

What are the aims of the study?

This study aims to provide a pharmaceutical personalised approach within the pharmacotherapy of cancer patients incorporated in a multidisciplinary team approach. The research will be based on the implementation of a pharmaceutical care model incorporating the clinical relevance of tumour markers in order to further optimize the pharmacotherapy offered to oncology patients.

Who can participate in the study?

Patients suffering from ovarian cancer, prostate cancer or pancreatic cancer attending the Oncology Clinic at Sir Anthony Mamo Oncology Centre and who are under the care of the participating consultants.

What will happen if I decide to participate in the study?

As a routine you will be asked about your oncology treatment and pharmaceutical care issues related.

Will I have to take part in questionnaires?

No. A one-to one interview will be carried out.

Will the study affect my treatment?

The study will not affect your treatment. You will not undergo additional procedures to current routine. You will continue your regular visits to the clinic and will continue being under the care of your current oncologist.

Who will view the information?

The information will only be accessed by the researcher. Addresses and contact numbers will only be used to contact you.

You are free to withdraw from the study at any point in time.

If you require further information, please do not hesitate to contact me on _____.

Thank you

Charyl Fava

Fuljett ta' tagħrif dwar l-istudju

Min qed jagħmel dan l-istudju?

Dan l-istudju qed isir minn Charyl Fava, spiżjara bħala parti mit-teżi tagħha li twassal għal PharmD. L-istudju jismu *"The implication of monitoring tumour markers: A personalised medicine approach".* Dan l-istudju qed isir taħt is-superviżjoni tad-Dipartiment tal-Farmaċija ta' l-Universita` ta' Malta.

X'inhu l-skop ta' dan l-istudju?

L-istudju jivvalidizza u jistħarreġ "pharmaceutical personalised approach" fil-qasam tal-kura farmaċewtika tal-kanċer. Fi kliem ieħor, l-ispiżjara jimplementa mudell ta' kura farmaċewtika billi janalizza it-tumour markers biex jipprovdi l-aħjar kura farmaċewtika.

Min jista' jieħu sehem?

Pazjenti li jbatu minn kanċer ta' l-ovarji, tal-prostata u tal-frixa li regolarment jiġu l-Oncology Clinic f'Sir Anthony Mamo Oncology Centre u li qegħdin taħt il-kura tal-konsulenti li qed jieħdu sehem fl-istudju jistgħu jieħdu sehem fl-istudju.

X'jiġri jekk niddeċiedi li nieħu sehem?

Inti tkun mistoqsi dwar il-mediċini li qed tieħu biex l-ispiżjara tkun tista' tagħtik pariri u għajnuna fuqhom fejn meħtieġa.

Ikun hemm bżonn niehu sehem f'xi kwestjonarji?

Le. Il-parteċipanti jiġu mistiedna għal intervista qasira.

L-istudju se jkollu effett fuq il-kura li qed niehu?

Le, l-istudju mhux se jkollu effett fuq il-kura li qed tieħu jew tuża'. Minħabba l-istudju m'intix se tkun mitlub/a tagħmel testijiet iżjed milli qed tagħmel bhalissa. Inti tibqa' tara' lil konsulent li jieħu ħsiebek issoltu.

Min jista' jara l-informazzjoni?

L-informazzjoni tkun biss għand l-ispiżjara li qed tagħmel l-istudju. L-indirizz u n-numru tat-telefon tiegħek ikunu biss użati jekk ikun hemm bżonn ta' xi kuntatt miegħek.

Inti tista' tieqaf tieħu sehem mill-istudju meta trid.

Jekk tixtieq aktar informazzjoni tista' iċċempilli fuq _____.

Grazzi

Charyl Fava

Appendix B

Consent Form in English and in Maltese

CONSENT FORM

I am a Maltese citizen and am over eighteen (18) year of age.
I have been asked to participate in a research study entitled:
The implication of monitoring tumour markers: A personalised medicine approach.

The purpose and details of the study have been explained to me by Charyl Fava and any difficulties which I raised have been adequately clarified.

I give my consent to the Principal Investigator and his delegate either make the appropriate observation/tests or both or take the necessary samples. I am aware of the inconveniences which this may cause.

I understand that the results of this study may be used for medicine or scientific purposes and that the results achieved from this study in which I am participating may be reported or published: however, I shall not be personally identified in any way, either individually or collectively, without my express written permission.

I am under no obligation to participate in this study and am doing so voluntarily.

I may withdraw from this study at any time, without giving any reason. This will not influence if any way the care and attention and treatment normally given to me *(applicable only in the case of patients receiving treatment).*

I understand that any complications and/or adverse effects which may arise during or as a consequence of the study will be recorded and any treatment which this may entitle will be given within the Government Health Services.

I am not receiving any remuneration for participating in this study.

In case of queries during the study I may contact Charyl Fava Tel No: _____

Signature of participant _____

Name of participant _____
ID No _____ *(capital letters)*

Signature of Researcher _____

Name of Researcher _____
ID No _____ *(capital letters)*

PROPOSTA GĦALL-FORMULA TAL-KUNSENS

Jien/a ċittadin/a Malti/ja u għalaqt tmintax (18)-il sena.
Talbuni biex nieħu sehem fi studju riċerka bl-isem ta'
The implication of monitoring tumour markers: A personalised medicine approach.

L-istudju ġie spjegat u mfiem sew minn Charyl Fava u kull diffikulta li kelli gew klerifikati.

Nagħti l-kunsent tiegħi lill-persuna responsabli għal din ir-riċerka biex tagħmel l-osservazjonijiet li hemm bżonn.

Jien nifhem li r-riżultat ta'dan l-istudju jistgħu jintużaw għal skopijiet xjentifiċi u jista' jigi ppublikat rapport bil-miktub: jekk isir hekk b'ebda mod ma nista' nkun identifikat/a, individwalment jew bħala parti minn group, mingħajr il-kunsent miktub.

Jiena ma għandi l-ebda dmir li nieħu sehem f'dan l-istudju u dan qed nagħmlu minn rajja. Jiena nista', meta rrid, ma nkopmplix nieħu sehem fl-istudju, u mingħajr ma nagħti raġuni.

Jiena mhux qed nitħallas beix nieħu sehem f'dan l-istudju.

Jekk ikolli xi diffukult' waqt l-istudju, nista nikuntatja lil:
Charyl Fava Tel: _____

Firma tal-parteċipant: _____
Isem tal-parteċipant: _____
ID Card_____
Isem u firma tal-persuna responsabbli għal din ir-riċerka: _____
Data:_____

Appendix B Consent Form in English and in Maltese

Appendix C

Approvals

- Approval letter endorsed by Dr Mario Vassallo
- Chairperson UREC - Prof Helen Grech
- Dr Laspina
- Dr Brincat
- Dr Magri
- Dr Micallef
- Dr Refalo
- Ms Sharon Young
- Mr Ivan Falzon
- Data Protection Form

L-UNIVERSITÀ TA' MALTA

Msida – Malta
Skola Medika
Sptar Mater Dei

UNIVERSITY OF MALTA

Msida – Malta
Medical School
Mater Dei Hospital

Ref No: **18/2016**

Thursday 26th May 2016

Ms. Charyl Fava
44, Fleur Maison
School Street
Zabbar, ZBR1373

Dear Ms. Fava,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

The implication of monitoring tumour markers: A personalised medicine approach

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

UNIVERSITY OF MALTA
L-Università ta' Malta

Charyl Fava <charyl.fava.04@um.edu.mt>

urec meeting - Friday 6th May

Helen Grech <helen.grech@um.edu.mt> 26 May 2016 at 18:54
To: Charyl Fava <charyl.fava.04@um.edu.mt>
Cc: Michelle Caruana Montebello <michelle.montebello@um.edu.mt>, UNIVERSITY RESEARCH ETHICS COMMITTEE <research-ethics.committee@um.edu.mt>, Louise Grech <louise.grech@um.edu.mt>, "Lilian M. Azzopardi" <lilian.m.azzopardi@um.edu.mt>

Dear Ms Fava,
Further to your revised forms I am pleased to inform you that your proposal has been approved.
Good luck with the study.

Sincerely,

Professor Helen Grech
Chairperson, University Research Ethics Committee
Head, Department of Communication Therapy
Deputy Dean, Faculty of Health Sciences
University of Malta, MSD 2090
Tel: +356 2340 1858
Displaying Banner for Auto signature IALP Dublin 2016.png

The implication of monitoring tumour markers:

A personalised medicine approach

Charyl Fava

PharmD (2015-2017)

Research Proposal

Supervisor: Prof Lilian M. Azzopardi

Co-supervisor: Dr Louise Grech

Approved.

DR. S. CASPINA

23/2/16.

From: Brincat Stephen at SAMOC-Health
Sent: Tuesday, 09 February 2016 11:23
To: West Lorna M at SAMOC-Health
Cc: Fava Charyl at MEH-DPA-Health
Subject: Re: research proposal

Agreed

Sent from my iPhone

RE: research proposal Inbox x

Magri Claude at SAMOC-Health <claude.magri@gov.mt> 01/02/2016
to West, me

Fine by me – do not hesitate to get in touch if you need guidance.

Warm regards
Claude Magri

From: Micallef Rachel at SAMOC-Health
Sent: Monday, 01 February 2016 09:37
To: West Lorna M at SAMOC-Health
Subject: RE: research proposal

ok from my end
r

West Lorna M at SAMOC-Health <lorna.m.west@gov.mt> 01/02/2016
to Refalo, Fava, me

Dear Charyl,

I have spoken with Dr Refalo and gives you his approval to carry out the research and access data of the patients at SAMOC.

Regards
Lorna

Data Protection at MDH <datapro.mdh@gov.mt> 24/02/2016

to Aquilina, Buhagiar, me

Dear Ms Fava
On the basis of the documentation you submitted, from the MDH data protection point of view you have been cleared to proceed with your study provided that you obtain approval from MDH CEO and the University Ethics Committee.
Please contact Ms. Nadine Buhagiar on 2545 5334 or Ms. Graziella Aquilina on 2545 5346 to present a copy of your approvals and fill in the appropriate Data Protection Form.
Remember that in no way should you retain any personal details you obtain from your research and this should be destroyed at the end of your study.
All medical records are to be viewed at the Medical Records Department MDH.
You are requested to submit a copy of your findings to this office at the end of your study.
Regards
Sharon Young
Data Protection Officer
Mater Dei Hospital

Falzon Ivan at MDH-Health <ivan.falzon@gov.mt> 24/02/2016

to Caruana, Satariano, me

Dear Ms Fava,

No objection for you to proceed with this project in line with applicable protocols regulating such.

Ivan

Ivan Falzon
Chief Executive Officer | TeaMDH

SPTAR MATER DEI

T +356 2545 4102
M +356 9995 0393
E ivan.falzon@gov.mt

Mater Dei Hospital, Triq tal-Qroqq, Msida, Malta MSD 2090 | Tel +356 2545 0000 | www.materdeihospital.org.mt

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MATER DEI

Information Management & Technology Department
Mater Dei Hospital
Telephone: 2545 5346

POLICY ON ACCESS TO PATIENT DATA ON MATER DEI HOSPITAL (MDH) SYSTEMS

Access to patient data recorded on MDH systems, whether in paper or electronic form, is permitted solely for the purpose of delivering or supporting delivery of health care, as part of the performance of official working duties.

All patient data on MDH systems is 'personal data' or 'personal sensitive data' in terms of the Data Protection Act. Therefore, access to patient data is subject to compliance with the provisions of the Data Protection Act, as well as those of the Professional Secrecy Act and other relevant legislation and regulations, including the computer misuse provisions of the Criminal Code.

Person identifiable patient data may not be copied, oriented or otherwise exported from MDH-based systems (paper or electronic) except as part of the performance of official working duties.

DECLARATION ON ACCESS TO PATIENT DATA

I hereby declare that I will respect the confidentiality and privacy of any personal data or information that I will come across at Mater Dei Hospital or on Mater Dei Hospital systems and will in no circumstance disclose any such information to third parties not directly involved in the patient's care without the patient's prior and informed consent.

I also declare that I am aware of the provisions of the Data Protection Act (ref: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8906&I=1), the computer Misuse provisions of the Criminal Code (ref: http://justiceservices.gov.mt/DownloadDocument.aspx?appIom&itemid=8574&I=1), and the Professional Secrecy Act (ref: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8844&I=1), and that I will abide by all Government and hospital regulations related to data, information and use of IT systems and services (ref: http://ictpolicies.gov.mt , http://www.kura.gov.mt).

Signature: _____

Full name: CHARYL FAVA

ID / Passport number: 191336 M

INFORMATION MANAGEMENT & TECHNOLOGY DIRECTORATE MATER DEI HOSPITAL MSD 2090

Graziella VA

26/02/2016.

Appendix C Approvals

Appendix D

Pharmaceutical Care Plan (PCP)

Date:	Care plan No:

Sir Anthony Mamo Oncology Centre (SAMOC)

Pharmaceutical Care Plan

PATIENT DETAILS						
Surname				**Patient Reference No**		
Name				**Patient Phone**		
Date of birth (DOB)	____/____/____	**Age**		**Consultant**		**Ward**
Gender	□ Male	□ Female		**Ethnic origin**		
Marital status	□ Single	□ Widow		□ Married/partner	□ Separated/Divorced	
Current living situation	□ Living with family/partner			□ Living alone	□ Other	
Family history of cancer	□ Yes	□ No				
Genetic/hereditary risk factor(s) or predisposing conditions						
Smoking status	□ Past History	□ None		□ 0-1 pack/day	□ >1 pack/day	
Caffeine consumption	□ Past History	□ None		□ 1-2 bev/day	□ >2 bev/day	
Alcohol consumption	□ Past History	□ None		□ <2 U/week	□ 2-6 U/week	□ >6 U/week
Level of Education				**Occupation**		
□ Pre-Primary □ Primary □ Secondary	□ Post-secondary □ Vocational	□ Tertiary □ Other		□ Housewife □ Worker □ Employee	□ Self-employed □ Public servant □ Pensioner	□ Craftsman □ Other

DIAGNOSIS		
Cancer type/location/histologic subtype:		**Diagnosis date:** ____/____/____
Tumour size:	**Lymph nodes:**	**Metastasis:**
Stage □ **I** □ **II** □ **III** □ **IV** □ **Not applicable**		
Other information about the cancer:		

RELEVANT MEDICAL HISTORY					
Approx. date		**Problem description**	**Approx. date**		**Problem description**
1			**4**		
2			**5**		
3			**6**		
Known drug sensitivities:					

CURRENT MEDICATIONS															
Drug name		**Dose**	**Form**	**Frequency**	**Route**	**Dates**		**Drug name**		**Dose**	**Form**	**Frequency**	**Route**	**Dates**	
						start	**stop**							**start**	**stop**
1								**7**							
2								**8**							
3								**9**							
4								**10**							
5								**11**							
6								**12**							
ADR's/ OTC medications (including herbals):															

PREVIOUS TREATMENT(s) FOR CANCER				
Systemic therapy (chemotherapy, hormonal therapy, other)		**Date**	**No. of cycles**	**Response / toxicities / cumulative doses**
1				
2				
3				
Radiotherapy: (body area treated)		**Date**	**No. Fractions**	**Response / toxicities**
1				
2				
Other treatments (including surgery – surgery date(s)/surgical procedure/location/findings):				

ANTINEOPLASTIC THERAPY: (drug name, frequency)							
Cycle Number		**1**	**2**	**3**	**4**	**5**	**6**
Dates of cycles		__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Height (m)	**Weight (kg)**						
Body Surface Area (BSA) (m^2)							
Dose (mg/m^2)							
Dose reduction		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No

MONITORING									
Test			**Range**	**Dates**					
FBC	**White Blood Cell Count (WBC)**		4.30-11.40 x 10^9/L						
	Neutrophils (Neut)		2.10-7.20 x 10^9/L						
	Immature Granulocytes		0.00-0.09 x 10^9/L						
	Lymphocytes		1.30-3.60 x 10^9/L						
	Monocytes		0.40-1.10 x 10^9/L						
	Eosinophils		0.10-0.70 x 10^9/L						
	Basophils		0.00-0.10 x 10^9/L						
	Red Cell Count		4.60-5.90 x 10^{12}/L						
	Haemoglobin (Hb)		14.1-17.2 g/dL						
	Haematocrit		40.4-50.4%						
	Mean Cell Volume (MCV)		79.0-93.0 fL						
	Mean Cell Hb (MCH)		27.0-32.0 pg						
	Mean Cell Hb Conc (MCHC)		33.0-36.0 g/dL						
	Red Cell Distribution Width		11.9-14.6 %						
	Platelets (PLT)		146-302 x 10^9/L						
	Mean Platelet Volume		9.2-12.6 fL						
LFT`s	**Alkaline Phosphatase (AlkP) (Serum)**		40-129 U/l						
	Alanine Aminotransferase (ALT) (Serum)		5-41 U/l						
	Gamma Glutamyl Transferase (GGT) (Serum)		8-61 U/l						
	Bilirubin (Serum)		0-21 µmol/L						
U&E	**Chloride (Serum)**		98-106 mmol/L						
	Creatinine (Creat) (Serum)		59-104 µmol/L						
	Potassium (K) (Serum)		3.5-5.1 mmol/L						
	Sodium (Na) (Serum)		135-145 mmol/L						
	Urea (Serum)		1.7-8.3 mmol/L						
	eGFR		>60mls/min/1.73m^2						
Tumour markers (serum)	**AFP**	**alphafetoprotein**	0-6.64 IU/mL						
	CA 125	**cancer antigen 125**	0-30.2 U/mL						
	CA 19-9	**cancer antigen 19-9**	0-33 U/mL						
	CEA	**carcinoembryonic antigen**	0-2.5 ng/mL						
	HCG	**human chorionic gonadotrophin**	0-2.7 mIU/mL						
	LDH	**lactate dehydrogenase**	135-220 U/l						
	PSA	**prostate specific antigen**	0-4 ng/mL						
Others									

PHARMACEUTICAL CARE ISSUES				
Pharmaceutical Care Issues (PCIs)		**Possible cause of PCIs**		**Action**
1	**Additional medication needs**	1.1 1.2 1.3 1.4	Untreated condition Synergistic/potentiating Preventive/prophylactic Other	□ Clarification with regards to an additional drug □ Recommendation of a preventive measure □ Drug information search □ Contacting the physician
2	**Unnecessary medication use**	2.1 2.2 2.3 2.4	No medical indication Duplicate therapy Treat avoidable ADR Other	□ Identifying unnecessary drug therapy □ Information about the risk of drug use without appropriate indication □ Drug information search □ Contacting the physician
3	**Dose is too high**	3.1 3.2 3.3 3.4 3.5	Wrong dose Frequency inappropriate Duration inappropriate; Pharmacokinetic problem requiring dose adjustment Other	□ Advice to the patient with regard to dosing □ Clarification with regard to the correct strength □ Clarification with regard to an overdosage □ Clarification with regard to an underdosage □ Clarification with regard to suitable dosage intervals □ Advice with regard to optimal duration of use □ Drug information search □ Contacting the physician
4	**Dose is too low**	4.1 4.2 4.3 4.4 4.5 4.5	Wrong dose Frequency inappropriate Incorrect storage Incorrect administration Duration inappropriate Other	
5	**Inappropriate compliance and failure to receive medicines appropriately**	5.1 5.2 5.3 5.4 5.5 5.6 5.7	Drug product not available Cannot afford drug product Cannot swallow/administer Directions not understood Patient prefers not to take Patient forgets to take drug Other	□ Searching for the reasons for primary non-compliance and counselling □ Checking whether the prescribed drugs are being taken appropriately □ Drug information search □ Contacting the physician
6	**Adverse drug reactions (ADR's)**	6.1 6.2 6.3 6.4 6.5 6.6 6.7 6.8	Unsafe drug for patient Allergic reaction Incorrect administration Dosage change too rapid Patient's fear of ADR's Medication stopped due to unacceptable ADR Undesirable effect such as; Other	□ Identifying ADR's □ Counselling patient fearing ADR's □ Documentation of symptoms of an ADR □ Drug information search □ Contacting the physician □ Suggesting a change in medication to the physician
	□ bone marrow suppression □ oral mucositis/stomatitis □ nausea □ vomiting □ diarrhoea □ constipation □ alopecia □ thromboembolism □ infusion-related hypersensitivity □ tumour lysis syndrome	□ hyperuricaemia □ pregnancy and reproductive function □ myalgia/arthralgia □ cardiotoxicity □ nephrotoxicity □ neuropathy – motor □ neuropathy – sensory □ ototoxicity □ skin toxicity □ hand-foot syndrome	□ itching or rash □ allergic reactions/ hypersensitivity □ insomnia □ loss of appetite/change in weight/anorexia □ fatigue □ dysuria/urinary symptoms □ anxiety/change in mood or depression □ menopausal symptoms	□ sexual problems □ lymphoedema □ flu-like symptoms □ infection □ fever/chills □ cough □ pain or difficulty with swallowing □ dyspnoea □ Others
7	**Interactions**	7.1 7.2 7.3 7.4 7.5 7.6 7.7 7.8 7.9 7.10 7.11	Drug-drug (includes herbal) Drug-allergy Drug-food Drug-ethanol Drug-laboratory Drug-tobacco Drug-disease Reference to an interaction by literature Patient's fear of an interaction Symptoms of an interaction Other	□ Attempt to clarify the clinical relevance of a drug interaction □ Advice to the patient in fear of an interaction □ Observation of the symptoms of an interaction □ Information about possible interactions and countermeasures □ Drug information search □ Contacting the physician

8	**Counselling needs**	8.1 8.2 8.3 8.4 8.5 8.6 8.7 8.8 8.9 8.10 8.11 8.12	Compliance Interactions Monitoring of temperature Good oral hygiene Nausea and vomiting Diarrhoea and constipation Hair loss Myalgia/arthralgia Neuropathy Hand-foot syndrome Fatigue Other	□ Interviewing and counselling of the patient □ Interview and counselling of the patient's relatives □ Patient awareness importance of compliance and understanding how and when to take the medication(s) □ Patient awareness of ADR's □ Patient awareness of interactions with other drugs (inc. OTC), food and alcohol etc. □ Recommendation of a preventive measure □ Recommendation of a non-medical measure □ Drug information search □ Contacting the physician
	Drug-related patient education and counselling and self-care tips			
	□ **Oral mucositis/stomatitis**: Identify symptoms of oral mucositis/stomatitis: pain, redness, swelling or sores in the mouth. Advice for good oral hygiene i.e. rinsing the mouth frequently and effective brushing of the teeth with a soft brush 2-3 times daily. Concentrate on soft food and drink plenty of fluids. Once a sore mouth has developed, saline mouthwash should be used. □ **Nausea and vomiting:** Educate re management consisting of anti-emetic drugs. Smaller frequent meals, liquids before (not with) food and avoiding strong smells will help too. Breathing deeply can also reduce nausea. Dry cereal, toast, crackers especially in the morning help curb nausea.	□ **Diarrhoea and/or constipation**: For diarrhoea; it is advised to avoid caffeine-containing beverages, high-fiber foods and milk products. For constipation, it is advised so as to get some exercise, drink fluids and eat high-fiber fruits (prunes, pears kiwi), cereals and vegetables. □ **Hair loss:** Advice that if the hair comes out, it is important to protect the head with sunscreen, or a hat or wig. □ **Myalgia/arthralgia**: i.e. muscle or joint pain - Advice to rest, counsel re management consisting of NSAIDs and reassuring patient that it is self-limiting. □ **Neuropathy**: Identify symptoms of neuropathy: tingling, numbness or pain in hands/feet.	□ **Fatigue:** Advice to take breaks or naps. Relaxation technique reduce stress. Maintain good nutrition. □ **Hand-foot syndrome** Identify symptoms of hand-foot syndrome: pain, swelling or redness in the hands and/or feet which might affect day-to-day. To minimize risk of hand-foot syndrome after an infusion; Keep hands & feet as cool as possible. Do not wear tight fitting gloves or socks, and avoid wearing tight-fitting footwear and high heeled shoes. Avoid exposing the skin to very hot water, such as the bath or washing up. Do not rub the skin vigorously or use abrasive washcloths. Pat skin dry after washing. Avoid the use of topical anaesthetics as they can worsen skin reactions.	□ **Menopausal symptoms**: It is advised to dress in cotton clothing and removable layers since it is useful for hot flushes. A vaginal lubricant or cream may help in vaginal dryness. □ For **flu-like symptoms**, Keep warm with blankets and drink plenty of liquids. □ **Monitoring temperature**; fever (often accompanied with unwellness). A significant fever (≥38°C) requires immediate first aid. □ **Precautions to avoid infection**; Identify signs of infection: pyrexia; productive cough, flu-like symptoms, dysuria, inflamed or discharging wound, diarrhoea; unusual bruising or bleeding. Promote good hand-washing practices. Avoid injury, even small cuts or tears in the skin.
9	**Monitoring needs**	9.1 9.2 9.3 9.4 9.5	Full Blood Count (FBC) Liver Function (LFT's) Renal Function (U&E) Tumour marker(s) (serum) Other	□ Check frequency and results □ Check FBC □ Check LFT's □ Check Renal Function □ Check Tumour marker(s) □ Drug information search □ Contacting the physician
10	**Seamless care needs**	10.1 10.2	Issues in lifestyle/behaviour are present such as smoking, alcohol use, weight changes and lack of exercise, emotional and mental health Other	□ Checking whether there is consistency, continuity, and coordination of care □ Refer a patient to self-help groups □ Recommending other health care professionals such a general practitioner, a smoking cessation counsellor, dietician, physiotherapist or exercise specialist, psychiatrist, psychologist, counsellor, social worker, chaplain, fertility specialist or endocrinologist, pain management clinic, palliative care team or others □ Information about smoking and alcohol cessation, nutrition and physical training □ Ensuring a seamless therapy continuation
11	**Other**	11.1 11.2	Other cause; specify No obvious cause	

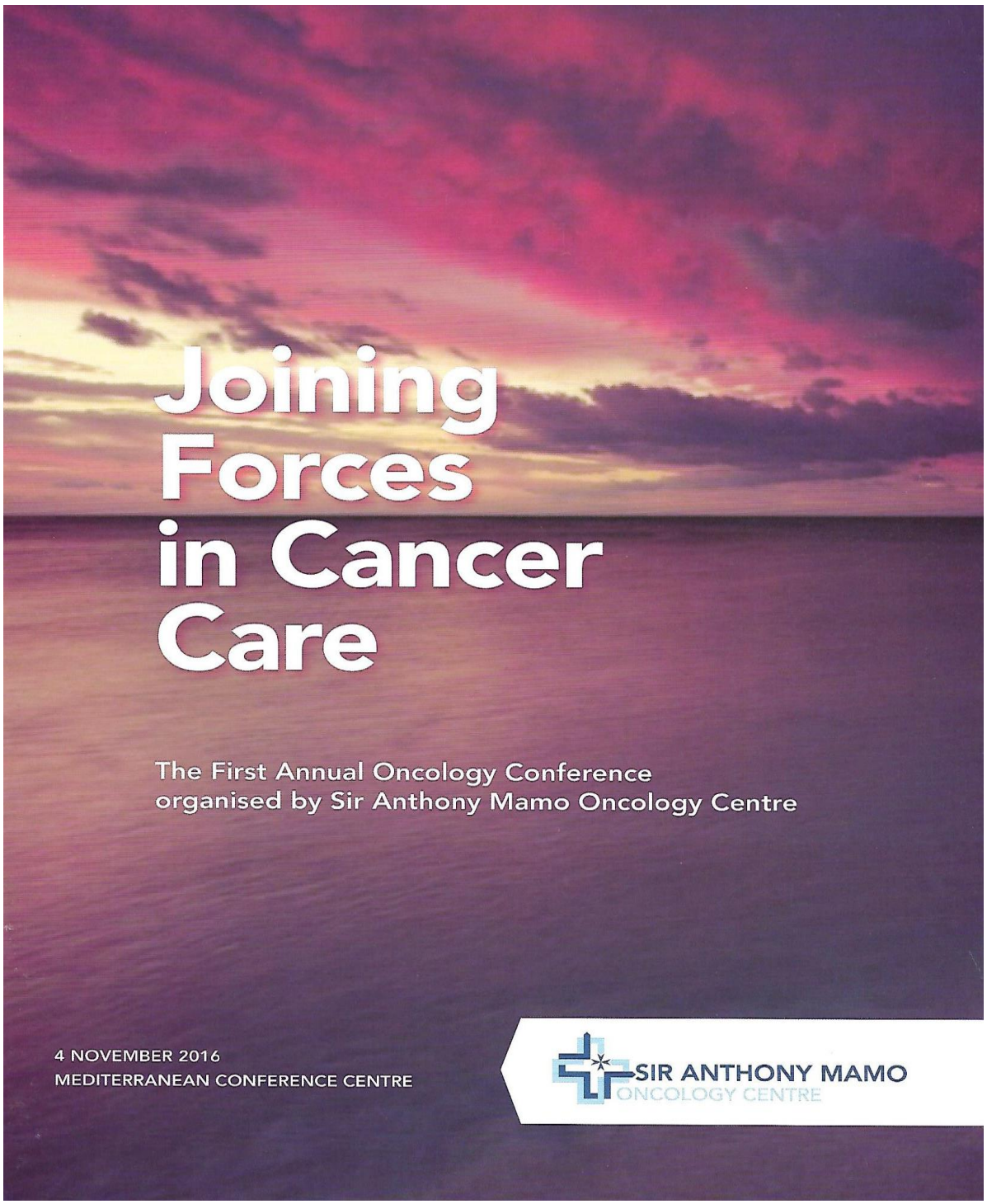
INDIVIDUALISED CARE ISSUES			
Date	**Pharmaceutical Care Issue (PCI)**	**Action**	**Output**

Appendix D Pharmaceutical Care Plan (PCP)

Appendix E

1st Oncology Conference (Malta) –

Joining Forces in Cancer Care



In Malta, the First Annual Oncology Conference entitled 'Joining Forces in Cancer Care' for HCPs organised by SAMOC, was carried out on the 4th November 2016 at the Mediterranean Conference Centre (MCC). There were concurrent workshops including innovative treatments; coping during cancer treatment, the way forward in breast cancer and colon cancer and managing side effects. This research was included as one of the oral presentations in this conference.

The implication of monitoring tumour markers: A personalised medicine approach

Charyl Fava[1], Louise Grech[1,2], Stefan Laspina[3,4], Christopher Barbara[4,5], Rachel Micallef[6], Lilian M Azzopardi[1]

[1]Department of Pharmacy, Faculty of Medicine & Surgery, University of Malta, Malta
[2]Clinical Pharmacy Practice Unit, Department of Pharmacy, Mater Dei Hospital, Malta
[3]Department of Haematology & Oncology, Mater Dei Hospital, Malta
[4]Department of Pathology, Faculty of Medicine & Surgery, University of Malta, Malta
[5]Molecular Diagnostics Unit, Department of Pathology, Mater Dei Hospital, Malta
[6]Department of Oncology, Sir Anthony Mamo Oncology Centre

Introduction: The availability of tumour markers in managing oncology patients contributes to developing personalised pharmacotherapy. The aim of this research is to develop a pharmaceutical personalised approach through the design and implementation of a pharmaceutical care plan (PCP) incorporating tumour markers for patients suffering from ovarian, pancreatic or prostate cancer.

Method: Guidelines, recommendations and standards of care for the management of ovarian, pancreatic or prostate cancer were reviewed. The classification systems for drug therapy problems developed and validated by Cipolle et al. (2004) and the Pharmaceutical Care Network Europe version 6.2 (PCNE, 2010) were reviewed. These classifications were amended and adapted to accommodate local service requirements and include tumour marker results within a newly designed Pharmaceutical Care Plan (PCP) template for cancer patients.

Results: The developed PCP template consists of two sections. The first section records patient's details, carer's details, diagnosis, past medical history, previous cancer treatments, current medications including non-oncologic therapy, chemotherapy cycles prescribed, relevant laboratory investigations and tumour marker results.

The second section of the PCP template categorises individualised pharmaceutical care issues (PCIs) identified for each patient subsequently screened. These care issues are further classified according to the newly developed classification of the drug therapy problems designed specifically by the researcher which includes counselling needs, monitoring needs and transitional care. The pharmacist's actions are also documented in this section.

Conclusion: The developed individualised PCP is intended as a helpful tool for the clinical pharmacist who can update patient pharmaceutical care records according to the PCIs identified whilst at the same time taking into consideration relevant tumour marker trends as well as other laboratory investigations.

Appendix E First Annual Oncology Conference (Malta) - booklet cover and abstract

Appendix F

77th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2017

This research had been accepted by the scientific committee for poster presentation for the 77th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2017, to be held in Seoul, South Korea from 10th to 14th September 2017.

Abstract:

My preferred method of presentation is: Poster Presentation

Background: The availability of tumour markers in managing oncology patients contributes to developing personalised pharmacotherapy.

Purpose: To develop and implement a pharmaceutical personalised approach based on pharmaceutical care plan (PCP) incorporating tumour markers for patients suffering from ovarian, pancreatic or prostate cancer.

Methods: Drug therapy problems classifications were used in the development of a newly designed PCP template, which was implemented at Sir Anthony Mamo Oncology Centre. The PCP template consists of two sections. The first section records amongst others patient's details, diagnosis, current medications including non-oncologic therapy, chemotherapy cycles prescribed and tumour marker results. The second section categorises individualised pharmaceutical care issues (PCIs) identified and documented the pharmacist's actions. All data collected was analysed.

Results: A total of 67 patients (35 male, 32 female) were enrolled in this study. The mean age was 65 years (range 26-83 years). Oncologic patients suffering from ovarian, pancreatic and prostate cancer were 19, 27 and 21 respectively. A total of 238 PCIs were identified, ranging from 2 to 5 PCIs per patient. The most common PCIs identified were classified as counselling needs (65), adverse drug reactions (65) and additional medication needs (47). There was statistical correlation between age and cancer type and between pre-post treatment tumour marker results ($P<0.05$ for both).

Conclusion: The developed individualised PCP was intended as a helpful tool for the clinical pharmacist who can update patient pharmaceutical care records according to the PCIs identified whilst at the same time taking into consideration relevant tumour marker trends.

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Abstract Submission Number: FIP-896
Abstract topic: Hospital Pharmacy
Abstract title: The implication of monitoring tumour markers: a personalised medicine approach

Dear Dr. Grech,

Thank you for having submitted the abstract listed above for the 77th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2017, to be held in Seoul, South Korea from 10-14 September 2017.
On behalf of the Scientific Committee, it is our great pleasure to inform you that this abstract **has been accepted** for **POSTER presentation.**
Further information regarding the display dates of your poster and the poster guidelines will be communicated at a later stage.

Please note that the presenting author needs to register **before 15 May 2017** to keep your abstract in the Congress programme. If you have not yet registered, we kindly invite you to register as soon as possible. For registration and more information on the various fees and deadlines, please visit the Congress website: http://www.fip.org/seoul2017/registration.

Please also note that residents from some countries require a visa. An official support letter can be requested during online registration. We recommend that you start the visa process as soon as possible. Do not hesitate to contact us if you encounter any difficulty.

For questions regarding your presentation or registration, please contact fip@mci-group.com.

We look forward to meeting you in Seoul, South Korea and remain at your disposal for any further information you may require.

Sincerely yours,

Ymke Pol
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Appendix F 77th FIP World Congress of Pharmacy and Pharmaceutical Sciences - abstract and acceptance email