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ORIGINAL ARTICLE

A study about the immune-related side effects at SAMOC: incidence, grades of toxicity & relation to past treatment and radiotherapy

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Background: Immunotherapy targeting cytotoxic T-lymphocyte associated antigen 4 (CTLA4) and the programmed death receptor (PD-1) and its ligand (PDL1) is becoming the standard of care for many malignancies. Hence, the number of patients on immunotherapy is increasing as is the probability of developing toxicities secondary to these treatments. This project mainly aims to look at the frequency of ir-AEs at Sir Anthony Mamo Oncology Centre Malta between June 2016 and June 2020.

Method: A cohort of 177 patients were treated with immunotherapy between June 2016 and June 2020 at Sir Anthony Mamo Oncology Centre. These were assessed for immunotherapy related toxicities. These individuals were assessed for the following: age, gender, malignancy diagnosed, immunotherapeutic agents (single or combination therapy) used, systemic anticancer therapy exposure prior to ICI therapy (namely chemotherapy and TKIs), concomitant/ concurrent radiotherapy (radical and palliative RT), line of treatment at which ICI therapy was administered, the CTCAE grade and frequency of ir-AEs studied.

Results: Adverse events occurred in 43.6% of the cohort and none were recorded for 56.4%. The most common ir-AEs in our cohort were dermatological AEs (8%), thyroid-related AEs (19.4%), hepatic AEs (8%) and GI AEs (9.2%). Other data was collected and discussed further below.

Conclusion: The increasing use of immunotherapy for various cancer sites with immune checkpoint inhibitors has resulted in positive primary treatment outcomes. Secondarily, immune-related adverse events have been widely observed, as seen in the cohort assessed for all types of ir-AEs in this study.

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Immunotherapy targeting cytokine T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed death receptor (PD-1) and its ligand (PDL-1) is now becoming an integral part of treatment of many malignancies. However, as the use of these immune-checkpoint inhibitors (ICI) is increasing, so is the probability that patients will develop adverse events related to these treatments. Such adverse events are often immune-related (ir-AEs) and hence are very different to those related to the more commonly used chemotherapy agents. Immune-related adverse events are new and occasionally difficult to diagnose. The incidence of ir-AEs depends on the type and regimen of immunotherapy used. The most common ir-AEs are gastrointestinal, dermatological, hepatic and constitutional symptoms[1-4]. Immune-related adverse events related to other organ systems are not as common but might be more difficult to diagnose and hence may be more severe[5].

Pooled studies have shown that combination immunotherapy (such as ipilimumab/nivolumab) in the context of advanced melanoma, 94.9% will experience at least one irAE1,[4,5]. Additionally, around 55.4% of patients will experience a grade 3/4 toxicity[5]. With single agent anti-CTLA-4 therapy incidence rate of ir-AEs was observed to be around 72% for all grades toxicities and 24% for grade 3/4 toxicities[2]. Moreover, further pooled analysis have shown that incidence of ir-AEs for anti-PD1 agents are just slightly less common when compared to anti CTLA-4; at 50-60% incidence rate for all toxicity grades and <10% for grade 3/4 toxicities[3].

This project mainly aims to look at the frequency of ir-AEs at Sir Anthony Mamo Oncology Centre Malta between June 2016 and June 2020. This study will also assess demographics, patterns of immunotherapy use and emergence of AEs, grades of reported ir-AEs as well as relationship between such adverse events and prior chemotherapy and co-current palliative radiotherapy.

METHOD

A cohort of 177 patients treated with immunotherapy between June 2016 and June 2020 treated at Sir Anthony Mamo Oncology Centre were assessed for immunotherapy related toxicities. These individuals were assessed for the following: age, gender, malignancy diagnosed, immunotherapeutic agents (single or combination therapy) used, systemic anticancer therapy exposure prior to ICI therapy (namely chemotherapy and TKIs), concomitant/ concurrent radiotherapy (radical and palliative RT), line of treatment at which ICI therapy was administered, the CTCAE grade and frequency of ir-AEs studied.

Statistical analysis using the Chi squared test was used to investigate the association between two categorical variables (i.e. previous chemotherapy use/ radiotherapy exposure and ir-AEs observed). The null hypothesis specified that there is no association between two categorical variables and is accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specifies that there is a significant association between the two categorical variables and is accepted if the p-value is less than the 0.05 criterion.

RESULTS

A cohort of 177 patients was reviewed. 72.3% of the group were male and 27.7% were female. The median age was 63 years (range 21-82 years). The majority of the patients were in the 61-70 age group (40.6%) followed by the 51-60 age group (25.4%) and more than 70 age group (21.5%). Demographics can be seen in Table 1.

Immunotherapy was most commonly used in lung tumours, renal tumours, cutaneous melanoma and head and neck malignancies. Immunotherapy was

Table 1 *Demographics*

	n	%
Male	128	72.3%
Female	49	27.7%
20-30 years	4	2.3%
31-40 years	4	2.3%
41-50 years	14	7.9%
51-60 years	45	25.4%
61-70 years	72	40.6%
More than 70 years	38	21.5%

Mean = 62.16 yrs, Median = 63 yrs, Range = 21-82 yrs

used to a lesser extent in other malignancies as shown in Table 2. The majority of patients receiving immunotherapy at SAMOC were given this in the context of metastatic disease (87.6% in the metastatic setting versus 12.4% in the adjuvant/ locally advanced setting).

Table 2 *% Malignancies in which ICI used*

	n	%
Colon	2	1.1%
Head and Neck	19	10.7%
Renal	31	17.5%
Bladder	12	6.8%
Lung	68	38.4%
Uveal melanoma	4	2.3%
Cutaneous Melanoma	20	11.3%
Choroidal melanoma	4	2.3%
Mucosal melanoma	1	0.6%
HCC	4	2.3%
Cholangiocarcinoma	1	0.6%
Testes	1	0.6%
Penile	1	0.6%
Astrocytoma	1	0.6%
Breast	7	4.0%
Mesothelioma	1	0.6%
Oesophagus	1	0.6%
SCC unknown primary	1	0.6%

Table 3 *Type of immunotherapy*

n	%	
Pembrolizumab	81	45.8%
Nivolumab	78	44.1%
Ipilimumab & Nivolumab	16	9.0%
Ipilimumab	2	1.1%

Table 4 *Number of cycles*

	n	%
1-5	68	38.7%
6-10	50	28.4%
11-15	25	14.2%
>16	33	18.7%

With regards to patterns of immunotherapy administration and emergence of ir-AEs, only 23.7% of patients received immunotherapy as first line treatment while in 76.3% immunotherapy was used as second line treatment. Single agent pembrolizumab (45.8%) and nivolumab (44.1%) were the most commonly used ICIs and combination ipilimumab/nivolumab was used in 9% of cases. Table 3 shows a summary of this.

The majority of patients in our cohort has 15 cycles of treatment or less (1-5 cycles 38.7%, 6-10 cycles 28.4% and 11-15 cycles 14.2%). 1.7% had more than 41 cycles. The median number of cycles was 7 (range 1-54). This is summarised in Table 4. Adverse events occurred in 43.6% of the cohort and none were recorded for 56.4%. Ir-AEs in this study occurred mostly in cycles 1-5 (24.9%) followed by in cycles 6-10 (14.1%). Median number of cycles at which ir-AEs occurred was at cycle 4 (range 1-31), as shown in Table 5.

Table 6 shows the frequency of ir-AEs and related grades in our cohort over a 3-year period. The most common ir-AEs in our cohort were dermatological AEs (8%), thyroid-related AEs (19.4%), hepatic AEs (8%) and GI AEs (9.2%). Respiratory AEs, fatigue and renal AEs were slightly less common at 6.9%, 3.4% and 4% respectively. Pituitary, neurological, rheumatological, ocular and haematological AEs as well as diabetes were very uncommon. Grade 1 AEs were the most common followed closely by Grade 2 events. Grade 3/4 events were uncommon.

Additionally, we also looked at the relationship between prior chemotherapy/Tyrosine-kinase inhibitors (TKIs) and an increased number of adverse

Table 5 *Number of cycles prior to event*

	n	%
1-5	44	24.9%
6-10	25	14.1%
11-15	2	1.1%
16-20	3	1.7%
21-25	1	0.6%
26-30	1	0.6%
31-35	1	0.6%
No adverse events	100	56.4%

Table 6 *Frequency of ir-SEs and related grades*

Organ	IR-AEs	n	%	G1	G2	G3	G4
Constitutional	Fatigue	6	3.4%	1.7%	1.1%	0	0.6%
Skin	All	15	8.6%				
	Rash	12	6.8%	2.8%	4.0%	0	0
	Pruritus	1	0.6%	0.6%	0	0	0
	Other	2	1.2%	0.6%	0.6%	0	0
Thyroid	All	32	19.4%				
	Hypothyroid	26	14.8%	11.4%	3.4%	0	0
	Hyperthyroid	6	4.6%	4%	0.6%	0	0
Pituitary	All	4	2.4%	0.6%	1.2%	0	0.6
Pancreas	All (DMT1)	1	0.6%	N/A	N/A	N/A	N/A
Liver	All (hepatitis)	14	8%	4%	2.3%	1.1%	0.6%
GI	All	16	9.2%				
	Diarrhoea	9	5.1%	2.8%	0.6%	1.7%	0
	Blood PR	1	0.6%	0.6%	0	0	0
	Abdominal Pain	4	2.3%	0.6%	1.1%	0.6%	0
	Vomiting	1	0.6%	0	0	0.6%	0
	Other	1	0.6%	0	0.6%	0	0
Lung	All	12	6.9%				
	SOB	3	1.7%	0	1.1%	0.6%	0
	Cough	5	2.9%	0	2.3%	0.6%	0
	Radiological Changes	3	1.7%	0	1.1%	0.6%	0
	Other	1	0.6%	0	0	0.6%	0
Neurological	All	2	1.2%	0	0.6%	0.6%	0
Cardiac	All	0	0	0	0	0	0
Rheumatology	All	4	2.3%	0	1.7%	0.6%	0
Kidney	All	7	4%	1.1%	2.3%	0.6%	0
Eyes	All	3	1.7%	0.6%	1.1%	0	0
Haematology	All	2	1.2%	0	0.6%	0	0.6%

events. There seemed to be no increased number of AEs in the group that had prior treatment. Conversely, there was an association between the patients who were on co-current palliative radiotherapy and an increased number of AEs. Pt who were on co-current radiotherapy seemed to have an increased number of AEs (p=0.028).

Finally, with regards to effect of AEs on continuation of treatment, in 85.9% treatment was stopped only in view of disease progression or death unrelated to immunotherapy. Treatment was stopped due to ir-AEs in 9% of patients in our cohort and in 5% treatment was stopped until AE was treated and then restarted.

DISCUSSION

Immune check point inhibitors (ICIs) have revolutionised cancer therapy. In comparison to conventional chemotherapy or even tyrosine kinase inhibitors, ICI's have a favourable side effect profile. However, their mode of action may lead to immune-related adverse effects. Our study delves into the prevalence of these effects, and any correlation between their occurrence on a background of radiation exposure or even use of prior SACT (systemic anti-cancer therapy).

Mode of Action of Immunotherapy

CTLA-4 and PD-1 receptors are centrefold in the ligand-receptor interactions between the antigen presenting cells (APCs) and T-cells modulating the T-cell response to the antigen. CTLA-4 will control the state of activation of the effector T-cells and inhibits cytokine production therefore initiating tolerance. CTLA-4 also negatively modulates helper T-cell activity thus suppressing T regulatory cells activity. PD-1 induced on dendritic cells, macrophages, activated and T-regulatory cells, extensively modulates effector T-cell function within normal tissue and tumours.[6] PD-L1 is also expressed on the aforementioned cells including tumour cells to escape anti-tumour responses. It acts as a pro-tumorigenic factor by activating survival and proliferative signalling pathways when binding to its receptors.[7]

Monoclonal antibodies (mABs) can block the ligand receptor interactions of immune check points. CTLA-4 mAB Ipilimumab acts by blocking the binding of CTLA-4 on T-cells to ligands CD80/86 on tumour cells. Pembrolizumab and Nivolumab bind to the inhibitory receptor PD-1 consequently inhibiting PDL-1/ PDL-2 interactions and hindering T-cells cytotoxic mechanisms.[6] Atezolizumab, Avelumab and Durvalumab are PD-L1 inhibitors bind to PD-L1 disrupting the PD-1 axis reversing T-cell suppression enabling endogenous anti-tumour activity with long-term responses in a spectrum of cancers.[8]

Ir-AEs incidences and Our Cohort

ICI adverse events (AEs) are known as immune-related (IR) AEs which are graded in line with the 5th version of the Common Terminology Criteria for Adverse Events (CTCAE).[9] This study assesses patient demographics, therapeutic indications of immunotherapy, grade and emergence of ir-AEs in addition to the relationship between these and concurrent radiotherapy. Ir-AEs incidences were compared to those listed in the Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up (ESMO CPG 2022).

Immunotherapy was mostly used in the age groups whereby cancer areas were treated as per guidance which was prevalent in the male subgroup. This was also more prevalent in the metastatic setting.

A higher incidence rate of endocrinopathy namely thyroid dysfunction was seen, with hypothyroidism occurring in 14.8% (versus 9%, ESMO CPG 2022)and hyperthyroidism in 4% (versus 1-2%, ESMO CPG 2022) of patients in comparison to diabetes mellitus which occurred in <1% (versus 1-2%, ESMO CPG 2022) across ICI regimens, with similar rates of hypopituitarism of 1.8% (~1% with antiPD-1, 2-6% with anti-CTLA-4 and 9-10% incidence with combined therapy, ESMO CPG 2022) . In addition, ocular events such as anterior uveitis were more frequent in our cohort at 1.2% (versus <1%, ESMO CPG 2022). On the contrary, less commonly reported events were: skin toxicity, with 8% of individuals affected (versus >50% for all grades, ESMO CPG 2022), gastrointestinal mainly diarrhoea in 5.1% (versus ~35% with anti-CLTA-4 mAB, ~10% with antiPD-1 and ~32% with combination immunotherapy ipilimumab and nivolumab, ESMO CPG 2022) requiring colonoscopy in two patients with cessation of immunotherapy.[10] Similar incidences were observed for hepatitis 8% (5-10%, ESMO CPG 2022) with deranged liver function tests on a background of progression of metastatic liver disease whereby four patients were treated with steroid therapy for hepatitis. Furthermore, ir-pneumonitis with cough (2.9%) and CT related changes occurred in 1.7% of patients with CTCAE grade 2 and grade 3 toxicity were observed (in comparison to 2-4%, ESMO CPG 2022). A global lower incidence of IRAE's was observed in this cohort of patients, this could be a result of underreporting or underdiagnosing the individual organ dysfunction. However, our cohort numbers correlate with those reported by ESMO in terms of prevalence.

Ir-AEs were observed in 24.8% of individuals who had received chemotherapy prior to immunotherapy. Chemotherapy is known to potentiate the effects of immunotherapy as SACT may directly stimulate antitumour immunity.[12] As a result of this one can stipulate that this activity may also catalyse the adverse effects seen in patients treated with immunotherapeutic agents.

With respect to radiation exposure (in the form of external beam radiotherapy), a pooled analysis of trials by Ansher et al has not shown an increased risk of IRAE's in patients receiving an ICI within ninety days following radiotherapy versus those who had not received radiation.[11] An explanation for this is that adverse effects tend to occur in the organ that received radiation, rather than a systemic reaction to the combined effects of radiotherapy with concomitant ICI therapy. On the contrary, a statistically significant association between number of side effects and concurrent radiotherapy was observed in our cohort ($p = 0.028$). The number of side effects increases with concurrent radiotherapy. This could be related to the smaller number of individuals studied augmenting the correlation seen. In addition, patients receiving radiotherapy may still experience side effects from this independent of the systemic therapy received.

Limitations

Our study may be limited by the smaller number of patients observed retrospectively. In addition, the short observation period (from 2016 to 2020) may have not completely reflected the preponderance of ir-AEs in our local cohort of patients. Immunotherapy is now being used in various malignancies including the neo-adjuvant and adjuvant settings in sites such as melanoma, lung cancer and breast cancer, which could possibly result in an increased incidence in ir-AEs recorded locally to date.

CONCLUSION

The increasing use of immunotherapy for various cancer sites with immune checkpoint inhibitors has resulted in positive primary treatment outcomes. Secondarily, immune-related adverse events have been widely observed, as seen in the cohort assessed for all types of ir-AEs in this study.

The effective treatment of ir-AEs is dependent on their early recognition and prompt intervention with immune suppression and/or immunomodulatory strategies for the affected organ system and the grade of toxicity. Specialist physicians, nurses and pharmacists that manage ir-AEs should be involved early on, possibly requiring inpatient management in serious (≥ grade 4) or grade 3 ir-AEs that are refractory or unsatisfactorily responsive to outpatient therapy. Such an intervention can also hasten clinical work-up and therefore prevent complications from potentially life-threatening adverse effects. Setting up of a local immunotherapy service guided by the Clinical Oncologist and the Nurse Specialist may facilitate better management of patients on ICIs.[12]

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