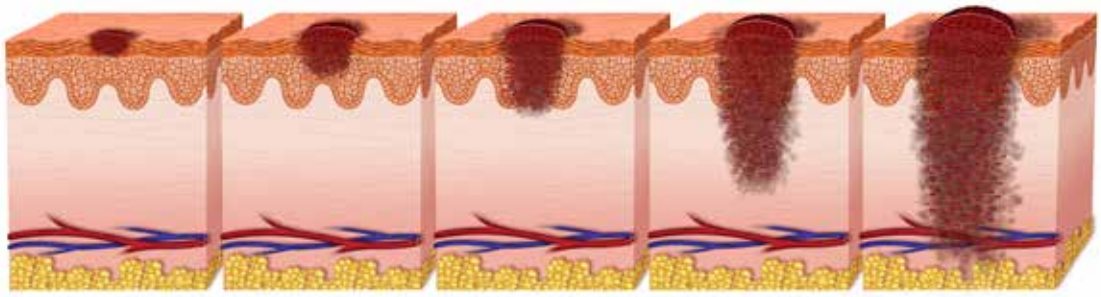
METASTATIC MELANOMA:

HOW DO LOCAL TREATMENT OPTIONS COMPARE WITH CURRENT STANDARDS OF CARE?



INTERVIEW WITH
DR NICHOLAS REFALO

Of all skin cancers, metastatic melanoma is the deadliest form. Early diagnosis allows it to be cured with surgery alone; later presentations considerably limit successful treatment options. Dr Nicholas Refalo, Consultant Oncologist at Mater Dei Hospital, explains to Dr Gabriel Ellul the toll which metastatic melanoma has on the Maltese population, and the current treatment options available.

TS: WHAT IS METASTATIC MELANOMA?

Melanoma is the malignant proliferation of melanocytes. As in all malignant growths, it is classified into stages depending on its degree of spread. Metastatic melanoma relates to stage IV of the disease, with metastatic spread to multiple organs, most notably lungs, liver, brain and bone. Spread occurs primarily via the lymphatic system, with haematogenous spread either arising secondary to the lymphatic dissemination of the tumour, or else once the tumour directly invades the vascular system.

A distinguishing and morbid aspect of stage IV melanoma is its poor survival rate with the 10-year survival rate being, at best, less than 10%. At this advanced stage of disease, the role of surgery and radiation is limited, and the only viable options are systemic treatment modalities.

TS: WHAT CAUSES THE DISEASE?

The aetiology of melanoma is a widely studied subject, with the principal causative factors being exposure to UV light and a genetic predisposition, amongst others. Additionally, there are a multitude of risk factors which decrease the overall survival rate, including older age, poor performance status at time of diagnosis, male gender, multiple metastatic sites, shorter disease-free intervals, leukocytosis, and neutrophilia prior to initiation of treatment.

Melanoma, in its aetiology, may arise from a number of different sites, with this forming the basis in the genetic variability of melanoma. Four distinct genetic types have in fact been identified: melanoma arising from normal skin without any preceding sun exposure; that arising from skin which had undergone chronic exposure to UV irradiation; melanoma arising from the soles of feet or the palms of the hands; and melanoma derived from mucosal surfaces.

This distinction has served to direct certain gene-based treatment modalities.

TS: HOW DOES ADVANCED MELANOMA MANIFEST ITSELF AND HOW COMMON IS IT?

These patients usually present with multi-organ involvement, mostly with metastases to the lungs, liver, brain and bone. Locally, metastatic melanoma accounts for up to 10 new cases a year. They are usually referred with curative intent, but current treatment options provided by the public health care system allow only palliation at the very best.

TS: HOW SO? WHICH TREATMENTS ARE AVAILABLE LOCALLY?

Locally we make use of dacarbazine, an alkylating agent approved by the FDA in 1975 - more than 4 decades ago. Patients on this drug only have a one-in-eight chance of tumour shrinkage.[1] In fact, an analysis of a total of 23 RCTs concluded that the objective response rate for monotherapy with dacarbazine hovers around 15%.[2]

Furthermore, responses are rarely sustained, with fewer than 2% of patients with metastatic melanoma, treated with dacarbazine, surviving for more than 6 years.[3] Consequently, the primary purpose of dacarbazine is palliation, not treatment, of metastatic melanoma.

Despite these shortcomings, dacarbazine remains the only form of chemotherapy funded by our healthcare system here in Malta. All other options, available abroad, require private funding.

TS: HOW DOES THIS COMPARE TO CURRENT STANDARDS OF CARE?

In view of the poor survival rates with the available chemotherapeutic modalities, as evidenced by data supporting dacarbazine, there has been a shift towards immune-mediated therapies and targeted therapies in Europe.

Over the past decade, with an enriched understanding of the pathogenesis of melanoma, novel therapies have been adopted in a multitude of European countries, which have had a profound impact on the survival rates of patients with metastatic melanoma.

These most notably include a drug called ipilimumab, an immunomodulator targeting the function of cytotoxic T-lymphocyte associated antigen-4 (CTLA-4).

Activated T-lymphocytes express this antigen, which in turn hinders positive stimulatory signals directed towards them. Thus, CTLA-4 acts negatively, to inhibit T-cell activation in the healthy individual.

Ipilimumab acts against CTLA-4. As a monoclonal antibody, it inhibits it and thus obtunds its inhibitory effect on T-cell activation, thereby indirectly prompting the T-cell mediated immune system to counter cancer more effectively.

Response rates to ipilimumab are encouraging. A phase III trial on previously treated, unresectable advanced melanoma showed an overall rate of survival of 45.6% after 12 months of therapy, and 23.5% after 24 months of ipilimumab monotherapy. Such trials also compared the efficacy of this monoclonal antibody when given in combination with vaccination strategies, producing even more favourable results.[4]

These results have prompted the FDA to expedite its approval of ipilimumab as a treatment modality for metastatic melanoma in March 2011, after more than a decade without any pharmaceutical innovation in the field.

The response rates to dacarbazine pale in comparison to the results achieved through this novel treatment.

And while these results are encouraging, the same can be said to another treatment strategy which is currently being given much attention through research and clinical trials. As outlined previously, melanoma has been classified into four distinct genetic subtypes. Of those melanomas developing from normal skin, like the thighs and trunk, which has not been exposed to chronic insolation, around 60% have a mutation in the B-RAF gene.

The B-RAF gene acts as a proto-oncogene, with gain-of-function mutations allowing it to promote cell growth and division unchecked. The rationale behind targeted therapies is to shut down these genes, thereby annulling their positive effect on tumour growth.

The results obtained with such an approach are astounding: major shrinkage of advanced melanoma tumours was obtained through the use of a drug called PLX4032, with positive response rate in over 80% of treated patients.[5] And while most of these patients eventually suffered from melanoma recurrences, prompting the need for future studies of possible combination therapies making use of this novel drug, the results speak for themselves.

Similar approaches are also being adopted for the different genetic subtypes, with ongoing research on potential inhibitors of the KIT proto-oncogene, which also plays a significant role in the aetiology of advanced melanoma.

TS: WHAT ARE YOUR VIEWS ABOUT THE DIFFERENCE IN RESPONSE AND SURVIVAL RATES BETWEEN THESE NOVEL THERAPIES AND THE ONES ON THE GOVERNMENT FORMULARY?

To this day, dacarbazine remains the only systemic therapy available for advanced melanoma patients on the government formulary. And as discussed previously, the response rates for dacarbazine do not, in any way, match those obtained through the novel treatments available today.

As things stand, I feel confronted with the difficult situation of informing my patients that the only available "cure" afforded to them through the public health system is one which has nowadays been all but superseded by drugs which are not part of the formulary. The best I can offer them, presently, is dacarbazine, a drug which is palliative and not curative.

The price for immunotherapy or targeted therapy ranges in the tens of thousands of euro a month, with an estimated yearly cost of more than €120,000 for 12 months of therapy, despite discounts by the local pharmaceutical companies.

We are currently in a situation where advanced melanoma patients in Malta, who have a modest level of income, cannot afford basic curative treatment, which is otherwise available in other European countries.

Oncological centres across Europe, from well-established centres in Western Europe to less developed countries such as Albania, have made the necessary shift: they are treating their patients with these novel drugs for advanced melanoma, thus affording them a better chance of recovery.

TS: WHAT ARE YOUR CONCLUDING REMARKS?

The situation is in a dire need for change.

In the present state of affairs, all Maltese patients diagnosed with advanced melanoma have only two options: either buy this costly medication or else ask for help from local charitable institutions.

The former is a viable alternative only to those who are insured or else have the necessary financial means. With regards to the latter option, we cannot constantly rely on charity to provide for the needs of these patients. If these two options fail, the chances of successful recovery from advanced melanoma remain very, very slim.

The annual incidence rates of advanced melanoma may not be as high as in other, more well-known forms of cancer. However, we have a duty to each of our patients.

I believe that this situation warrants more public exposure; there is a need for greater public advocacy on the issue. That is why I have decided to speak up.

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