The ROYAL MARSDEN

Advances in the treatment of melanoma

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The incidence of melanoma is rising faster than any other cancer in the UK, having nearly doubled in recent decades to around 16,000 new cases per year. Melanoma prognosis is highly dependent on disease stage. Although early detection can lead to successful treatment, metastatic melanoma has historically been regarded as 'untreatable' with very poor survival rates of around 6 to 9 months.

The average number of life years lost due to melanoma (around 20) is higher than for any other cancer as a consequence of about a third of patients being diagnosed under the age of 50. However, over the past 10 years, The Royal Marsden has led on key clinical studies that have transformed the treatment landscape of melanoma.

Background

Melanoma is a type of skin cancer that arises from pigment-producing cells called melanocytes. Because these cells originate from the neural crest and migrate to different parts of the body, molecularly distinct melanomas can form in the eyes and, rarely, on internal surfaces such as the mucosal linings of the gut, nose and genital regions.

Exposure to UV light is the main risk factor for cutaneous melanoma, which most often develops on sun-exposed areas of the face, back, chest and limbs. Importantly, skin examinations should involve checking for 'hidden', and often aggressive, melanomas on non-hairy acral surfaces such as the soles of the feet, palms and fingernail bed.

Targeted therapy

The first significant advances in the treatment of melanoma began with increased understanding of the mutational landscape and discovery of the BRAF gene mutation in around 50% of melanoma patients 15 years ago. This led to the development of the small-molecule BRAF inhibitors, vemurafenib, dabrafenib and encorafenib, which significantly increased survival compared with chemotherapy in BRAF-positive patients. However, most melanomas treated with BRAF inhibitors quickly recurred.

The mechanism of resistance to BRAF inhibition was found to be dominated by reactivation of the mitogen-activated protein kinase (MAPK) signalling pathway that regulates the proliferation and survival of melanoma cells. Cancer cells were able to reactivate the pathway by altering downstream kinase molecules, such as MEK.

Combined inhibition

Therefore, the next natural step was to target MEK with agents such as trametinib, cobimetinib and binimetinib, resulting in a new standard of care for BRAF-positive melanoma – combined BRAF and MEK inhibition.

Disappointingly, patients treated with combination therapy in the advanced setting still eventually relapse due to the plasticity of cancer cells, which allows them to adapt to overcome the inhibition of both BRAF and MEK in order to reactivate tumour survival.

This led to the realisation that targeted therapies were not curative treatments for advanced malignancies because resistance mechanisms pre-exist in a minority of tumour cells; under the pressure of effective therapies that destroy all the treatment-sensitive cells, resistant cells emerge and cause relapse.

Mutational burden

Because UV light is highly mutagenic, cutaneous melanomas are characterised by a very high mutational load, which means they are more likely to become resistant to targeted therapy. However, critically, when targeted BRAF/MEK inhibitor therapy was used in the adjuvant setting following surgery to remove stage III/IV disease, 12 months of treatment led to sustained survival benefit versus placebo.

This is probably due to the reduced disease burden of micro-metastatic disease in the adjuvant setting, which lessens the likelihood of resistant cells surviving compared with in widespread non-resected disease.

Therefore targeted BRAF/MEK inhibitor therapy represents a good adjuvant option for BRAF-positive patients, particularly those of childbearing age due a lack of endocrine side effects.

Achilles heel of cancer

A positive aspect of having high mutational load is that patients are much more likely to benefit from immunotherapy. Mutations are seen by the immune system as antigens therefore the more mutations there are, the more likely it is that one of them will cause the immune system to recognise the tumour as foreign and reject it.

Increasing use of immune checkpoint inhibitors, such as nivolumab and ipilimumab, across multiple cancer indications takes advantage of this. These therapies, used either alone or in combination with each other for around 2 years, are the mainstay treatment of patients with metastatic melanoma, and long-term survival data suggest that they may be curative in up to half of all patients.

Combination therapy with nivolumab and ipilimumab is now standard first-line therapy for patients with melanoma metastatic to the brain without symptoms, although symptomatic brain metastases remain a significant challenge and are more likely to benefit from multi-modal therapy that includes radiation techniques.

Adjuvant aperture

In the adjuvant immunotherapy setting, nivolumab is superior to ipilimumab and used interchangeably with pembrolizumab as the standard of care within 12 weeks of surgery. Notably, adjuvant nivolumab plus ipilimumab does not appear to outperform nivolumab alone.

Adjuvant treatment choice between single or combination immunotherapy, or targeted therapy (which has the benefit of oral administration, and interruption or continuation as needed), should be based around patient preference and convenience.

A key challenge to address with adjuvant therapy is that only 20% of all patients treated, and consequently put at risk of drug toxicity, actually derive benefit – 40% of melanomas will recur despite treatment and 40% don't actually require further treatment to prevent recurrence.

Presurgical (neoadjuvant) immune checkpoint blockade is currently being explored as a potential new treatment paradigm in melanoma, but randomised controlled studies are required to confirm observed high rates of complete pathological response and survival versus adjuvant therapy.

Adverse events

Unfortunately, immunotherapy for melanoma is associated with a wide spectrum of immune-related AEs that affect multiple organ systems and quality of life, sometimes irreversibly. These effects usually appear 6–12 weeks after treatment, but can take longer, and need to be recognised and treated early to avoid serious risk. AEs can be worse with combination therapy than with single agents, which is an important consideration for treatment choice.

As a guideline for primary care, immune checkpoint inhibitors should be withheld or discontinued in all patients with worse than mild AEs. Mild or moderate immune-related AEs can be treated in the outpatient setting with supportive measures or corticosteroids, respectively. Severe or life-threatening AEs (such as myocarditis and neurological effects) require hospital admission and immediate high-dose corticosteroids, along with additional immunomodulating agents.

Fortunately, use of immunosuppression to treat toxicities does not appear to impair the body's established antitumour immune responses.

The future

The Royal Marsden is championing exciting research into adoptive cell therapy, which involves isolating immune cells that have already identified and entered a tumour, expanding them outside the body and then reinfusing them. Promising neoantigen-directed peptide vaccines and bespoke RNA vaccines for melanoma are also under development.

Research is ongoing to address knowledge gaps around mechanisms of immunotherapy resistance and toxicity, biomarkers of benefit to therapy in any setting and practical challenges to implementation of novel therapies, such as successful tissue procurement and manufacturing timelines.

Pioneering Royal Marsden translational studies on post-mortem sampling to track metastases (PEACE), tracking disease through treatment (MELANOMA TRACERx), understanding immunotherapy toxicity (EXACT) and COVID-19 vaccine and infection response in cancer (CAPTURE) will no doubt contribute enormously to driving forward groundbreaking discoveries in modern melanoma medicine.