Immunotherapy And Cure in Metastatic Cancers: Benefits, Challenges and New Frontiers

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Historical perspective in Melanoma:

Most metastatic or stage IV solid tumours have been historically incurable as opposed to blood cancers, some of which have been cured with chemotherapy. The median survival from metastatic melanoma historically was 6-9 months as seen from the curves below (figure 1). Some patients with poor prognostic markers including spread of cancer to solid organs such as liver and abnormal levels of LDH on blood tests fared worse despite chemotherapy than those who had metastases to nodes, skin and a normal blood LDH level (1).

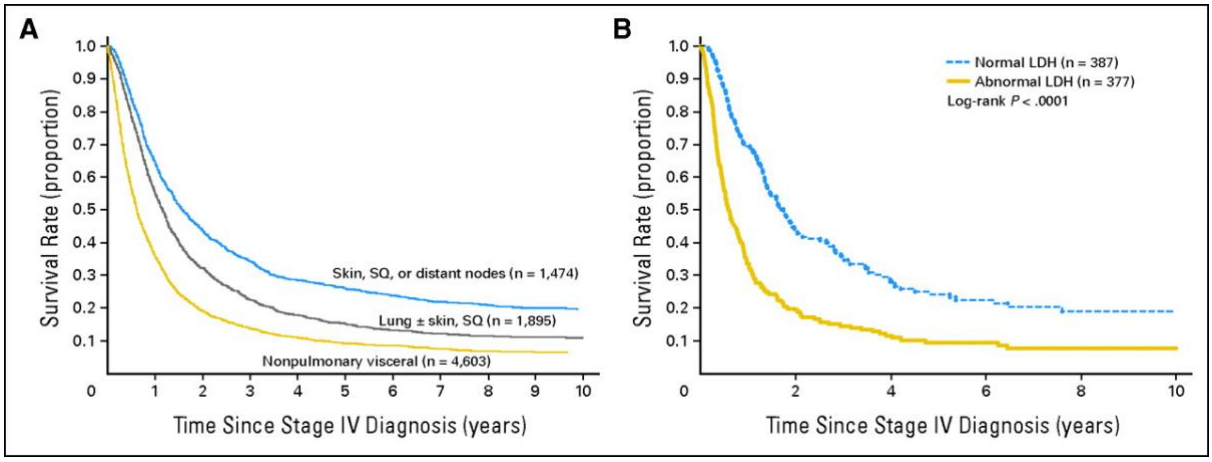

Figure 1. Historical survival from stage IV melanoma based on sites of disease (left) and blood LDH levels (right).

Melanoma was the first tumour type in which immunotherapy was approved and therefore has been a good model to study the trends in survival and long-term responses from evolution of therapies in the last decade.

Cancer and the Immune System

The immune system is a complex network of organs, proteins and white blood cells in the body, whose main role is to recognise ‘self’ vs ‘non-self’ and destroy invading foreign organisms like bacteria and viruses, or abnormal cells, including tumour cells. A failure to detect and eliminate these abnormal cells can result in uncontrolled growth, as seen in cancer.

When cancer cells are destroyed or broken down, they release proteins called antigens which are presented to a type of white blood cells called ‘T cells’ which can then specialise to become ‘memory’ T cells. The memory T cells remember the specific antigens and are able to amplify the responses generated by the immune system in attacking the antigens should there be future exposure to these specific antigens. This leads to immunity, a commonly known concept in infectious diseases – for example as seen with

Covid-19 immunity from previous infection. This is a complex pathway and there are several mechanisms that regulate T cell function and immune responses, including inhibition of T cell activation. This is one of the mechanisms in which tumour cells evade T cells and are able to grow uncontrolled.

Cancer Immunotherapy therefore uses this concept to turn the immune system against the tumour, rather than directly killing tumour cells as seen with tradition treatments such as chemotherapy or radiation therapy.

Controlling Immune Responses through T cells

T cells can be regulated through various complex mechanisms to either be stimulated or inhibited. Signalling molecules called Cytokines, which are released from detection of certain pathogens or abnormal cells in the body, can activate T cells in a non-specific way. Activation and expansion of T cells require 3 signals.

The first is through specific recognition of an antigen by receptors on T cells, from receptors on an 'antigen presenting cell'. The next signal is to provide "co- stimulation" through additional receptor attachments between the antigen presenting and T cells to reinforce the bond. The third signal is the release of cytokines to further strengthen and amplify the activation of T cells to generate an immune response.

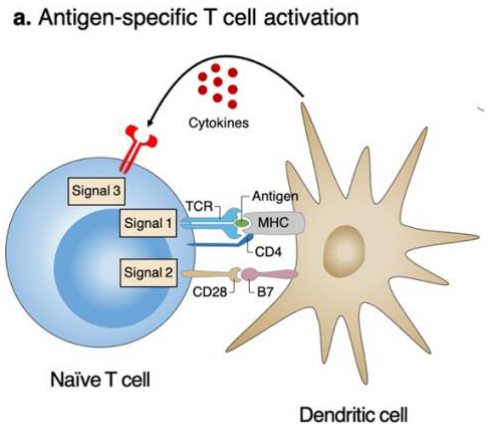

Figure 2: Activation of a naïve T cells by 'antigen presenting cells' such as dendritic cells require three signals ((2)

However, uncontrolled T cell stimulation and ongoing immune activation can lead to significant damage and a response to control this is required when the immune response is no longer needed. One of the feedback mechanisms this is achieved through are Immune Checkpoints which are part of the adaptive immune system. In simplistic terms, the Checkpoints work by dampening the "co-stimulation" signal 2, in the activation of T cells and function as brakes on the immune system.

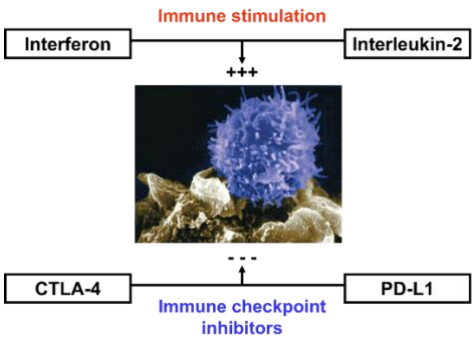

Figure 3. Immune responses are regulated through a balance of activation of T cells (blue) by cytokines such as Interferon or Interleukin-2 (denoted by +++) and inhibition of T cells by immune checkpoint inhibitors such as CTLA-4 or PD-L1 (---).

Cancer Immunotherapy is not new.

An eminent surgeon William Coley first noted the effect of immune activation in treating cancer in 1891 from the disappearance of a patient's tumour after infection from a bacteria known as Streptococcus pyogenes and began injecting bacteria into patients to treat their cancer.

Many different types of immunotherapies have since been studied and used in cancer treatment in the last 2-3 decades including vaccines, viral therapies, adoptive T cell therapies, cytokines and others as seen in the image below. Of these immune checkpoint inhibitors have been the most commonly used across several tumour types in the last decade.

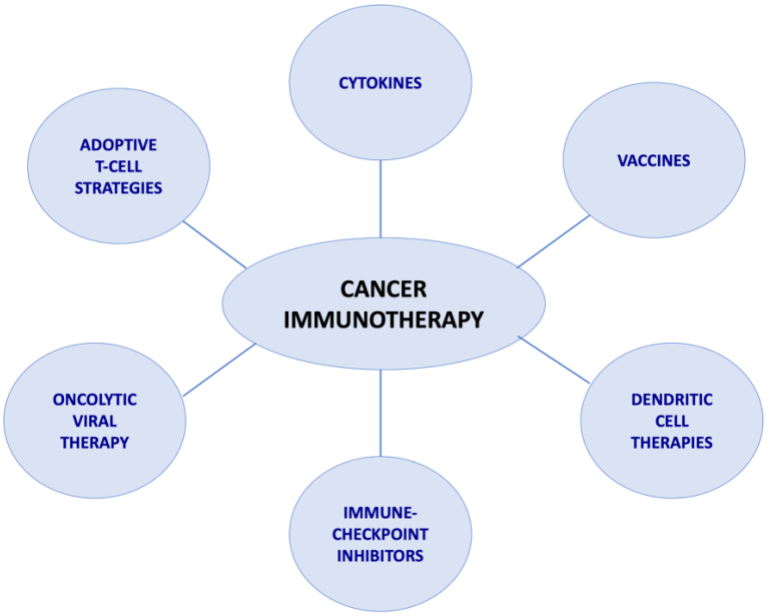

Figure 4. Types of cancer immunotherapy

Immune Checkpoint Inhibitors

James P Allison and Tasuku Honjo were awarded the Nobel Prize in Physiology and Medicine in 2018 for their work showing that inhibition of checkpoints resulted in amplified T cell activation, unleashing an immune attack on cancer cells. This discovery was the basis of development of immune checkpoint inhibitor drugs in cancer treatment.

Many immune checkpoint inhibitors have been discovered and some are commonly targeted in cancer treatment currently including **CTLA-4** and **PDL-1** which work mainly in the lymph nodes and **PD-1** which is more in the peripheral tissues (eg., the tumour site).

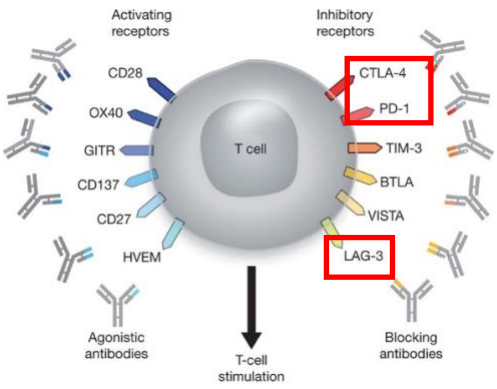

Figure 5. Several immune checkpoint inhibitors are being studied (right) and used in current practice (red boxes).

BENEFITS

Ipilimumab was a drug developed to recognise checkpoint CTLA-4 and was first used in trials over 15 years ago in metastatic melanoma. Intravenous Ipilimumab showed long term survival benefit with 20% patients who had responded to treatment and were alive 3 years out, remaining alive at 10 years of follow up (3). Although in a modest proportion of patients, this was a significant improvement compared to the historical survival from advanced melanoma of 6-9 months. It led to meaningful changes for patients who had maintained responses and were able to live normal healthy lives off treatment for many years.

Another checkpoint inhibitor **Nivolumab** targeting PD-1, has shown survival benefit alone and in combination with Ipilimumab in metastatic melanoma (4) (figure 6). When given together with Ipilimumab, at 7 years it led to an average long-term survival in up to 50% with flattening of the curve, showing maintained responses from around 3-4 years onwards. While overall survival could include death from any cause, melanoma specific survival, accounting for deaths only from melanoma, was found to be even higher at 57% in this population (5).

Similarly, this combination of checkpoint inhibitor drugs Nivolumab and Ipilimumab has also shown overall survival benefit in metastatic renal cell cancer patients over the previous standard of care, an anti-VEGF targeted therapy Sunitinib (6) and this benefit continues to persist at 8 years of follow-up. However, as seen from the curves of overall survival the tail appears to continue to decline (figure 7), as opposed to the plateau seen in longer term survival in metastatic melanoma patients. Unfortunately, the evidence for disease specific survival in metastatic renal cell cancer is not available and one could hypothesise that the drop in survival may be from causes unrelated to metastatic disease such as cardiovascular comorbidities which are more common in this patient population.

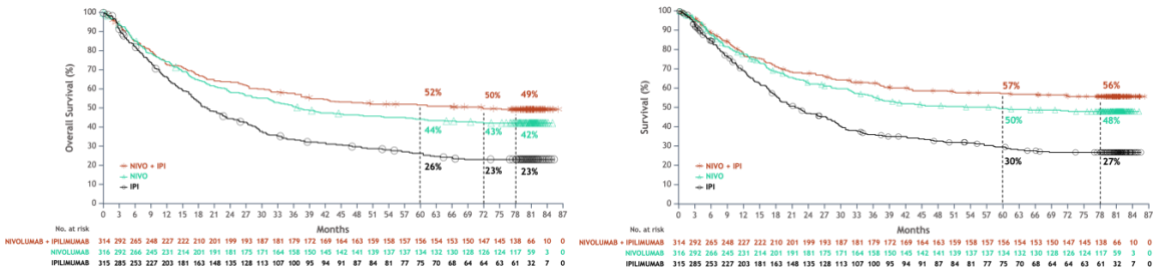

Figure 6. Overall survival (left) and melanoma specific survival (right) from combination Ipilimumab and Nivolumab (red) compared to Nivolumab alone (green) and Ipilimumab alone (black).

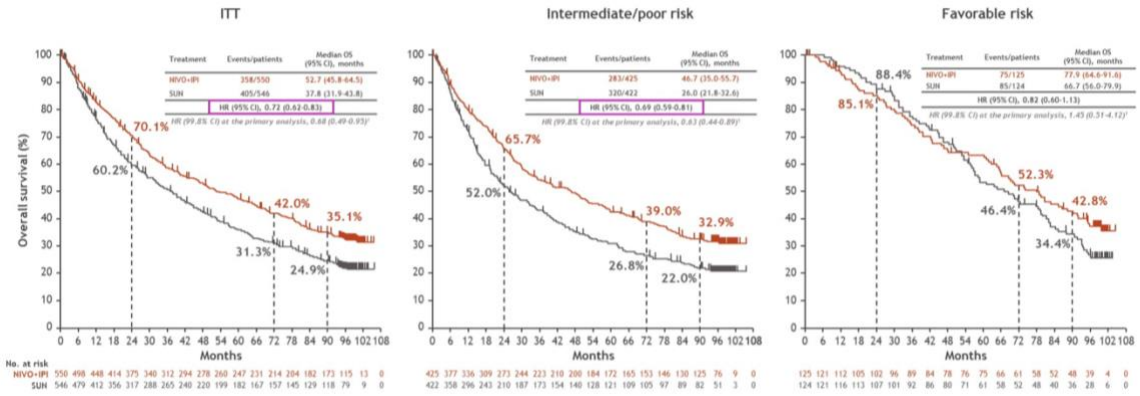

Figure 7. Overall survival in all metastatic RCC patients (left), metastatic RCC patients with intermediate-poor risk (middle) and favourable risk (right) with combination Ipilimumab and Nivolumab (red) compared to then standard of care Sunitinib (black).

Does longer term survival benefit equate to cure in metastatic disease?

Defining Cure

Cure in cancer may be defined as a return to normal life expectancy for age and health. As checkpoint inhibitors have not been around for more than 15 years and as there is a theoretical risk of relapse beyond this period, formally they may not be termed “curative”; however, very late relapses in long term survivors are extremely rare, rendering many patients functionally cured, which is an important consideration.

Not just Immune checkpoint inhibitors

Novel immunotherapies other than checkpoint inhibitors are now being investigated in various cancers. One such drug **Tebentafusp** is a T cell receptor modulator therapy which works by acting as a bridge between cancer cells and T cells through binding and linking T cells to a protein gp100 expressed heavily on uveal melanoma cells, bound to a specific marker HLA-A*02:01 as seen in the image below (figure 8). This leads to redirection and recognition of cancer cells by T cells, allowing them to target and destroy them.

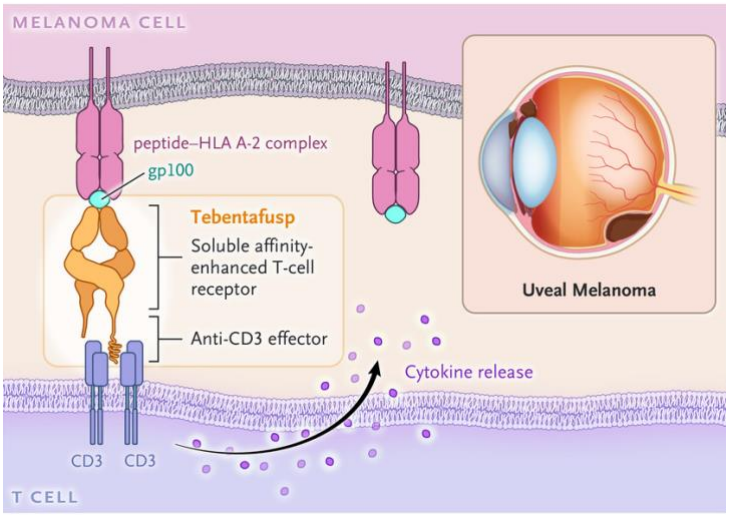

Figure 8. Mechanism of action of Tebentafusp

Tebentafusp is the first drug to demonstrate an overall survival benefit in patients with the rare uveal subtype of metastatic melanoma with a HLA-A*02:01 mutation(7). In a clinical trial of previously untreated patients with metastatic uveal melanoma, Tebentafusp showed significantly better survival compared to other routinely used treatments including anti-PD1 checkpoint inhibitors in about 80% of the patients. Recent data showed that this benefit was maintained with 27% treated with Tebentafusp still alive at 3 years, compared to the historical poor life expectancy of 6-12 months. This led to Tebentafusp gaining several regulatory approvals including Food and Drug Administration and is currently the favoured front-line therapy in these patients.

Not just advanced cancer

Immune checkpoint inhibitors have been approved for use in a wide range of advanced tumour types including melanoma, lung, kidney, bladder, head & neck, colorectal, Hodgkin’s lymphoma etc. These drugs are now being used increasingly in earlier cancer stages with growing evidence in the adjuvant and neoadjuvant settings.

‘Adjuvant’ therapy is defined as treatment given after primary or curative therapy such as surgery in localised higher risk cancers, to prevent recurrence. Immune checkpoint inhibitors have been used in this setting to reduce the risk of relapse and have demonstrated reduced recurrence and improved survival in several cancers. For example, in melanoma patients with completely resected localised stage III disease, 1 year of treatment with anti-PD1 drug Pembrolizumab was shown to increase survival and reduce recurrence risk by almost 45% compared to placebo, with ongoing benefit at 3 years(8).

The benefit from this treatment is believed to be due to inhibition of the PD-1 checkpoint by immunotherapy, leading to generation of an anti-tumour response by activation of T cells, to target any residual microscopic metastatic cells following resection of the tumour. Most anti-tumour T cells are located

at the site of the tumour and therefore it is hypothesised in simple terms, that the bulkier the tumour, the stronger the immune response due to presence of more anti-tumour T cells.

This concept has been used to expand immunotherapy to the 'neo-adjuvant' setting which involves administering treatment prior to surgery, in order to activate and expand more anti-tumour T cells around the tumour leading to tumour shrinkage or in some cases disappearance. This is followed by surgery and further adjuvant treatment, based on the degree of response to neoadjuvant treatment measured microscopically by the proportion of viable cells remaining in the surgically resected tumour.

This approach was investigated in a recent early phase II trial of 345 patients with stage III-IV melanoma whose tumours were deemed operable. Half the patients underwent surgery upfront followed by adjuvant therapy with 18 cycles of Pembrolizumab for 1 year and the other half had 3 cycles of Pembrolizumab upfront, followed by surgery and a further 15 cycles of Pembrolizumab up to 1 year total. The results were very promising with 72% of the patients who underwent neoadjuvant + adjuvant immunotherapy being alive and relapse free at 2 years, compared to 49% of those who underwent adjuvant therapy alone (9). This additional benefit seen from an existing treatment, simply by changing the timing of treatment initiation is now being studied in a larger phase III trial and in various other tumour types.

CHALLENGES

While there have been remarkable advances in the last 2 decades from immunotherapies, even in immune responsive cancers such as melanoma, a significant proportion of patients do not derive benefit from these treatments and half the patients die from their disease. There is therefore an imminent and ongoing need to continue to understand and find ways to improve outcomes for our patients.

How do we improve immunotherapy to best serve our patients?

1. **Improve efficacy:** to increase duration of response and treatment free survival leading to longer term benefits and cure

    i. Understand factors of resistance to therapy: this is a challenging area of research due to the complex nature of resistance based on the interactions between cellular pathways, drug factors and patient genetic factors. For instance, there have been many studies investigating resistance to targeted therapies in patients with a BRAF mutated melanoma over the last 2 decades, however, despite identifying some of the cellular mechanisms, it has been difficult to translate this into clinically meaningful outcomes in practice due to heterogeneity between patients. There is growing work in understanding the biological changes that cancer cells undergo to adapt and evade the immune system and a particularly informative method is the post-mortem evaluation of the cancer environment, which is being undertaken in the UK through a clinical trial with the extreme generosity of our patients.

    ii. Identify and understand new targets for treatment: huge efforts have gone into this in the last 10-15 years and newer promising immunotherapy drugs, for eg., Relatlimab targeting checkpoint inhibitor LAG-3, are now coming into practice as additional options for treatment. However, the efficacy and challenges faced with any new immunotherapies remain similar.

    iii. Get more from existing targets of treatment: this is an interesting area of research with lots of activity. For instance, Botensilimab which is a 2nd generation checkpoint inhibitor targeting CTLA-4 has shown promising results in patients with checkpoint inhibitor refractory melanoma subtypes and other traditionally immunotherapy refractory cancers such as sarcoma and ovarian cancer in very early clinical trials. This is now under investigation in larger clinical trials.

    iv. Improve patient selection: currently there are very few identified biomarkers to identify patients that are likely to respond to immunotherapies. Some of the biomarkers whose expression has been correlated to increased response to immunotherapy include factors derived from tumour biopsies including measuring tumour mutation burden, expression of protein 'neoantigens', PDL-1 expression and other cytokines or white cells also known as tumour infiltrating lymphocytes (TILs) in the tumour microenvironment. Other biomarkers

being studied include those derived from non-tumour samples that are less invasive such as blood or gut microbiome; for instance, 'HLA' blood typing as used in uveal melanoma patients for Tebentafusp therapy. While these biomarkers are correlated to response, there are many patients with these markers who may still not respond to treatment and ongoing work in understanding these is underway to pave the way for precision Oncology.

2. **Improve safety and Quality of Life:** to better identify and manage toxicities from treatments.

   i. Rationalise combinations of immunotherapy: Immunotherapy toxicities occur from over stimulation of the immune system resulting in inflammation or auto-immunity potentially across any organ in the body. These can range widely with the commonest being irreversible endocrinopathies needing lifelong hormone replacement, colitis which could be debilitating or rarer toxicities such as myocarditis which may be fatal. While most toxicities are treatable when detected early, many toxicities require treatment with steroids or immunosuppression which can additionally adversely impact quality of life. It is known that combination or doublet immunotherapy such as with Ipilimumab and Nivolumab has over twice the risk of toxicity compared to single agent immunotherapy treatment, however, combination treatments are also more effective. Therefore, it is prudent to balance risk and benefit to select appropriate regimens for patients to maximise responses and minimize toxicity.

   ii. Optimise patient selection: While the risk of toxicities can range from 10-60% with various immunotherapy combinations, there is no biological way to identify those patients who may develop these toxicities. Certain clinical factors are currently used to broadly identify patients who may be at higher risk such as pre-existing autoimmune conditions at risk of flaring or frail patients who may not tolerate complications from therapy. These are however generalised and research is ongoing to identify robust predictive biomarkers to specifically identify patients at high risk.

   iii. Optimise duration of treatment: current practice is to administer adjuvant immunotherapy for a year post surgery or two years in the case of metastatic melanoma, or indefinitely if effective and tolerable in other metastatic cancers. These are based purely on clinical studies that established the evidence for efficacy and are arbitrary. While we know that early cessation of immunotherapy due to significant toxicity does not adversely impact on treatment response, it is unknown whether a shorter duration of treatment in all patients could result in similar benefits with reduced complications of treatment. Once again, biomarkers that could potentially indicate response to treatment such as measuring ctDNA, which is genetic material released from breakdown of tumour cells correlated with tumour burden in the body, may be useful in rationalising duration and amount to reduce overtreatment. Several clinical trials investigating this in melanoma, bowel and other cancers are underway to guide therapy.

   iv. Understand impact of steroid use and rationalise use of immunosuppression: moderate to severe immune related toxicities require dampening of the immune system with either steroids or other immunosuppressive drugs, occasionally in the long term, which carry an inherent risk of side effects such as increased infection risk and metabolic syndrome affecting diabetes, bone health, cardiovascular, gastrointestinal system etc, to name a few. There is growing research into the impact of these drugs on the anti-cancer effects of immunotherapy due to their biologically counteractive nature. While some retrospective evidence indicates that steroid use may reduce the impact of immunotherapy response and survival benefit, this remains controversial across cancer types in the absence of prospective large trials to establish the evidence definitively. In view of side effects, potential adverse impacts on therapy and preserving quality of life, judicious use of steroids and immunosuppression are needed to manage immune related toxicities.

v. Understand longer term toxicities: while life expectancy has increased significantly from immune checkpoint inhibitors in various cancers, due to the relative recency of these drugs, little is known about the longer-term toxicities from them. From surveys of long-term survivors from historically curable cancers such as testicular and lymphoma, it is known that patients experience a wide range of toxicities in the longer term, not just medically (eg., cardiovascular or fertility issues) but financially and psychologically. This data is lacking in survivors of immunotherapy treatments and is a vital growing area of research and unmet need globally to improve patient wellbeing post cancer immunotherapy.

NEW FRONTIERS

The success of immune checkpoint inhibitors has led to interest and investigation into other novel immune modulating therapies.

mRNA Vaccine Therapy:

This is an immune modulating therapy that has been under investigation for the last 3 decades, with abundant use in infectious diseases, particularly with the recent Covid-19 pandemic. It has been studied in anti-cancer immunotherapy trials since 2009, gaining recent significance from promising results in early phase melanoma trials. This technology works by collecting tumour and blood samples from patients to identify mutations in specific protein 'neoantigens' in collected samples. These patient tumour specific neoantigen mutations are then used to manufacture specific genetic material mRNA that is injected back into the patient. The injected mRNA is translated in the body to proteins which target T cells and produce amplified anti-tumour immune reactions and memory T cells, potentially leading to long term responses.

A phase II study in melanoma patients with surgically resectable high-risk stage III and IV melanoma using personalised mRNA vaccine with Pembrolizumab given adjuvantly following curative surgery in 100 patients demonstrated slowing of cancer recurrence and about a 44% improvement of recurrence risk at 18 months, compared to 50 patients who received standard of care Pembrolizumab alone (10). These exciting results show potential for a novel adjuvant therapy that may be better than immune checkpoint inhibitor therapy alone and is now being investigated in larger phase III trials. While toxicity profiles were not dissimilar between groups, there was a slight increase in renal impairment which would need to also be confirmed and considered.

Cellular Therapy

Cell based therapy in solid cancer is not new and was pioneered by Dr Rosenberg and colleagues in the 1990s with several early studies showing efficacy in metastatic melanoma since. Cell therapy is an umbrella term for many immune modulatory therapies including Tumour Infiltrating Lymphocyte (TIL), T cell Receptor (TCR) or Chimeric Antigen Receptor Therapies (CAR T).

Of these, Tumour Infiltrating Lymphocyte (TIL) therapy has gained prominence in melanoma recently and involves surgical procurement of tumour tissue from the patient, isolation of white cell subtypes or TILs in the tumour microenviroment and amplification of these in a lab to manufacture a product with enhanced anti-tumour response within 3-4 weeks. In the interim, the patient receives white cell depleting chemotherapy following which the TIL product is then infused back into the patient as a one-off treatment. A cytokine called Interleukin-2 is then administered to further boost the function of infused T cells.

A phase III trial of patients who received prior anti-PD1 therapy for metastatic melanoma investigated TIL therapy versus anti-CTLA4 Ipilimumab and demonstrated more durable responses with TIL therapy of 7 months compared to 3 months with Ipilimumab. 53% had ongoing responses at 6 months with TIL therapy compared to 27% with Ipilimumab (11).

The main limitations of TIL therapy are logistical and infrastructural issues arising from needing inpatient admission for the treatment period, for monitoring and managing toxicities and the manufacturing process requiring access to a licenced facility that limits the treatment access to specialist centres at this stage.

In recent years, Lifileucel, the first commercially manufactured TIL therapy by Iovance has been

investigated in several melanoma trials with promising results.

- **Refractory melanoma:** a recent phase II study of 153 patients with metastatic melanoma who had been heavily pre-treated and progressed on several lines of therapy including immune checkpoint inhibitors, demonstrated early and durable responses from Lifileucel, with 47% alive at 4 years(12). Complete remission was observed in 8 patients and partial responses in over 40 patients. The median survival in this cohort was up to 14 months. While toxicities from TIL therapy itself are minimal, toxicities occurred in >30% patients related to the chemotherapy and IL-2 infusions within the first 2 weeks – these were predictable and manageable with inpatient monitoring. This is very encouraging in a cohort of patients with extremely limited treatment options and poor prognosis.
- **Cell therapy in other cancer types:** Lifileucel has more recently also demonstrated anti-tumour activity in combination with anti-PD1 Pembrolizumab in a phase II trial in patients previously not treated with anti-PD1 therapy, including traditionally non-immunogenic cervical, head and neck cancers as well as melanoma. Excellent responses were observed with 100% of the melanoma patients, 87.5% head and neck and 86% of the cervical cancer patients showing tumour shrinkage (13). These results are very promising and further trials investigating these in larger populations for confirmation are underway.

In view of the promising responses observed with Lifileucel an application for regulatory approval by the FDA was made in the USA for treating advanced melanoma and is currently undergoing priority review with expected approval in the coming weeks.

SUMMARY

- Historically almost all metastatic solid tumours were incurable.
- Checkpoint inhibitors are probably curative in some patients with advanced melanoma.
- Nevertheless, half of patients still die from metastatic melanoma.
- Exciting therefore to see cellular therapy and vaccine data.
- The success of immune checkpoint inhibitors has revitalised cancer immunotherapy and significant further progress is expected in the next 5 years.

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