The age of cancer immunotherapy

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Since William Coley's initial experiments in the 1890's, the promise of utilising the bodies own targeted weapons of mass destruction, the immune system, had promised without delivering. The attraction of using the immune system, was that it had the potential to unleash the immune system onto cancers in the same way that viruses are eliminated in a targeted and relatively non-toxic manner as "foreign" material. The challenge was that cancers are actually not "foreign" although they have acquired properties that remove many of the normal cellular processes that enable them to survive and evade regulatory signals.

Over the next 100 years, researchers developed tools to better understand and characterise the immune system culminating in the discovery of immune checkpoints in the 1980s. The acceptance of immunotherapy as a cancer therapy however would still take another two decades when the CTLA-4 inhibitor ipilimumab changed treatment paradigms in melanoma. For the first time, immunotherapy was not only shown to result in responses but indeed durable long-term remissions for patients with advanced melanoma.

Since these pivotal data were presented in 2010, the field has increased exponentially with trials in most tumour types and moving from advanced stage to earlier. The investigation of novel immunological targets and stories of not only durable remissions, but also cures for patients with advanced cancer have buoyed the field to better understand not only tumour characteristics that predict for better responses to these therapies, but also the immune phenotype and indeed the microbiome. As immunotherapies are increasingly being used, it is now also clearer that their toxicities are unique and can also be life threatening.

In this issue of *Cancer Forum* we focus on immunotherapy, what it is, how it works, the cancers it is most useful in and the main toxicities. The aim was to provide a practical guide for clinicians, acknowledging that much of the data are being superseded by an ever-increasing number of trials.

Overview of immunotherapy

It is important to return to basic immunology to understand how immunotherapies work, Dr's Brown and Mislang explain the cancer immunity cycle, why immune checkpoints are critical and how their manipulation by tumours results in suppression of T-Cell activation signals.[1]

Tumours responsive to immunotherapy

Next we review the pivotal data in tumours responsive to immunotherapy including melanoma,[2] lung cancer,[3] urological cancers,[4] haematological malignancies[5] and other rarer subtypes.[6] The pivotal studies are presented as well as their relevance to clinical practice. The field is rapidly evolving to include more tumour types, but also more combination therapies.

Toxicity

Drs Sandhu and Guo provide an excellent guide to the frequencies and management of toxicities that occur with either single agent or combination immunotherapy.[7] The most important lesson is to be aware of even the very uncommon adverse events, as failing to recognise and monitor for these can have catastrophic consequences if not managed immediately.

Biomarkers

Having agents that are effective results in the need to better identify patients most likely to benefit. Towards this, Dr Cooper discusses the emerging biomarkers for immunotherapy, their predictive capability and pitfalls.[8]

Conclusion

Immunotherapy has now entered treatment paradigms in a number of tumour types. Some are already funded through the Australian Pharmaceutical Benefits Scheme, while others are likely to be funded in the near future. However, not all patients benefit, resulting in increasing efforts to better understand the immune microenvironment and more importantly methods to manipulate it in order to effect improved clinical outcomes. Undoubtedly we are entering a new age in which cancer immunotherapy threatens to supersede traditional cytotoxic therapies and perhaps even targeted therapies with the ultimate goal of long term remissions with minimal toxicities.

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