Available online at www.sciencedirect.com
ScienceDirect
EJSO
the Journal of Cancer Surgery
ELSEVIER
EJSO xx (2016) 1–10
www.ejso.com

Immunotherapy of melanoma

D. Kee [a,b,*], G. McArthur [a,b,c]

[a] Department of Cancer Medicine, Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne, Victoria 3002, Australia
[b] Department of Medicine, University of Melbourne, Parkville, Victoria 3010, Australia
[c] Sir Peter MacCallum, Department of Oncology, University of Melbourne, Parkville, Victoria 3010, Australia

Accepted 25 July 2016
Available online ■ ■ ■

Abstract

Immunotherapy for advanced melanoma has progressed dramatically in the last five years with the approval of immune checkpoint inhibitors targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Inhibition of these targets can break cancer-immune tolerance and result in durable objective responses with significantly improved tolerability over cytokine-based immunotherapy. Ipilimumab is an inhibitor of CTLA-4 and the first-in-class immune checkpoint inhibitor to demonstrate an improvement in overall survival in melanoma. Pembrolizumab and nivolumab target PD-1 and have improved single agent activity and tolerability in comparison to ipilimumab. The combination of nivolumab and ipilimumab results in even better response rates, reductions in tumor volume and progression free survival but at the expense of considerable autoimmune effects. Autoimmune side-effects and non-standard response kinetics represent a new challenge associated with cancer therapies that practitioners will have to become more familiar with as checkpoint inhibitors increasingly become part of mainstream oncological practice. Ongoing areas of investigation include drug development against novel immune targets; alternative treatment modalities, such as genetically modified oncolytic viruses; optimization of immunotherapy combination strategies; and the identification of reliable biomarkers to better guide treatment selection.

Keywords: Melanoma; Immunotherapy; Cytokines; Cancer vaccines; Antibodies; Monoclonal; Oncolytic virotherapy

Immunotherapy of melanoma

Introduction

Melanoma has long been at the forefront of cancer immunotherapy research. This has been both for practical reasons – that advanced melanoma is mostly refractory to chemotherapeutic treatment – but also due to observable clinical and pathological phenomenon suggesting a prominent role for the immune system in regulating its behavior. Unfortunately decades of trying to stimulate a more robust immune response with either cytokine therapy, therapeutic vaccines, or both, have yielded only sufficient efficacy to maintain researchers interest in the field – without having achieved sufficient improvements in patient survival for them to become widely adopted standards of care. However, this has recently changed. The development of antibodies directed against the immune checkpoints cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death-1 (PD-1) have achieved dramatic improvements in long-term survival that are likely to see them becoming the backbone of melanoma therapy for the foreseeable future. This review will focus on the currently available immunotherapeutics in melanoma with particular consideration given to the practical aspects of checkpoint inhibitor therapy.

Cytokine therapy in melanoma

The potential benefit of immunotherapy in melanoma was first realized in the 1990's with the cytokines interleukin-2 and interferon alpha (IFN-α).[1,2] In a series of phase II clinical trials, treatment with high-dose IL-2 induced durable remissions in 16% of patients with

* Corresponding author. Department of Cancer Medicine, Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne, Victoria 3002, Australia. Fax: +613 9656 1408.
E-mail address: damien.kee@petermac.org (D. Kee).

http://dx.doi.org/10.1016/j.ejso.2016.07.014

Please cite this article in press as: Kee D, McArthur G, Immunotherapy of melanoma, Eur J Surg Oncol (2016), http://dx.doi.org/10.1016/j.ejso.2016.07.014

advanced melanoma.[3] The median duration of response was 8.9 months but exceeded 59 months in the 6% of patients who were complete responders. Evidence of long-term disease control led the FDA to approve IL-2 therapy for metastatic melanoma in 1998, however, since then its used has remained highly restricted. Treatment expense and potentially severe side effects, including hemodynamic collapse, that often requires hospitalization and intensive care admission, have limited its use to specialist centers and to patients with healthy cardiovascular systems and excellent performance status. Furthermore, an overall survival benefit for the IL-2 has never been established through phase III clinical trial testing. For these reasons, IL-2 has not seen widespread adoption throughout the USA, and is rarely used in Europe, Canada or Australia.

Interferon alpha also has measurable activity in melanoma. In small phase I/II trials conducted in the 1970's and 80's its modest response rate in metastatic melanoma was predominantly confined to those patients with a low disease burden.[2] Subsequent studies choose to focus on its use in the adjuvant setting. The pivotal ECOG 1684 trial, published in 1996, compared 12 months of high-dose IFN-a with observation in patients with high-risk resected melanoma.[4] It demonstrated a significant improvement in both relapse-free and overall survival. The estimated 5-year overall survival of the IFN-treated arm was 46% exceeding that of those that remained untreated at 37%. Based on these findings, IFN-α was approved for the adjuvant treatment of melanoma by the FDA in 1996 and the EMA in 2004. However, in trials subsequent to ECOG 1684 an overall survival benefit for HD-IFN has been less consistently demonstrated, with a recent meta-analysis of over 14 IFN studies suggesting an absolute overall survival benefit closer to 3% based on a calculated hazard ratio of 0.91.[5,6] Similar to treatment with IL-2, the toxicity experienced with interferon therapy can be substantial, and given the prolonged treatment course, can impact significantly on patients' quality of life.[7] Patients often experience flu-like symptoms, chronic fatigue, and biochemical and mood disorders. Given these toxicities and its more marginal effectiveness, the acceptance of IFN-α by clinicians and uptake from patients is far from universal. Notably, neither IL-2 nor IFN-α have established themselves as accepted comparator arms in subsequent phase III trials evaluating novel therapies in melanoma.

Vaccines and adoptive cell therapy

The broad range of toxicities experience by patients treated with cytokine therapies relates to the non-specific up regulation of the immune system inherent in these approaches. Strategies to generate a more tumor-specific T cell response include the use of cancer vaccines and adoptive cell therapy (ACT).

At its simplest level, therapeutic cancer vaccines involves immunization with tumor antigens in order to generate a tumor specific T-cell response.[8] Ideally, the antigens selected would be unique to the patient's tumor, however, the current difficulty in processing autologous tumor antigens has meant that most cancer vaccines strategies have focus on a handful of shared tumor antigens common to most melanomas. These have included melanocyte differentiation antigens, such as MART-1/melan-A, tyrosinase and gp100; the cancer-testis antigens, NY-ESO-1 and members of the MAGE families; and whole cell vaccines, most commonly derived from pooled melanoma cell lines. These antigens are then combined with an adjuvant medium designed to stimulate antigen uptake, and may be delivered in combination with various cytokines or autologous antigen presenting cells (APC's) that have been optimized ex vivo.

To date, despite some promising results in a number of phase II trials, there have been no cancer vaccines demonstrated to improve survival in patients with melanoma. Some of the more notable attempts include the combination of a gp100-vaccine with IL-2 that in a phase 2 study achieved objective responses in 13 of 31 (42%) patients with advanced melanoma.[9] In the subsequent phase III trial a statistically significant improvement in response rate (16% versus 6%) and PFS (2.2 versus 1.6 months) was seen with the addition of the vaccine to an IL-2 therapy backbone.[10] However, there was no improvement in overall survival and commenters noted that the response rate found was similar to prior studies of IL-2 monotherapy.[3,11] Other factors suggesting a lack of activity for the vaccine were that only a minority of gp100 vaccine treated patients actually developed a gp100 specific T cell response with there being no correlation between their presence of gp100 reactive T-cells and survival, and a lack of benefit in combination with ipilimumab in a subsequent phase III study.[12] MAGE-A3 was the target of the DERMA study, one of the largest immunotherapy studies undertaken to date. In this study, 1345 patients with stage IIIb or IIIc melanoma were randomized (2:1) between an adjuvant MAGE-A3 vaccine and placebo. Unfortunately, after a median follow-up of 28.0 months, almost no treatment effect has been identified with essentially identical DFS and OS between the treatment arms. Moreover no benefit was observed in a subset of patients with a gene expression signature that appeared top be predictive of benefit in a phase 2 study.[13] Finally, two adjuvant phase III studies involving Canvaxin™ (an allogenic whole cell vaccine comprised of 3 melanoma cell lines) and GM2-KLH/QS-21 (a ganglioside vaccine) are notable for being terminated early following interim analyses identifying a likely deleterious effect on survival in the vaccine treated groups.[14,15]

The clinical failures of therapeutic vaccines occurred despite evidence, in some studies, of being able to induce up to 30% of circulating T-cells to be antigen specific. This would suggest that generate T-cells were either of low avidity and/or subject to local inhibition within the

Please cite this article in press as: Kee D, McArthur G, Immunotherapy of melanoma, Eur J Surg Oncol (2016), http://dx.doi.org/10.1016/j.ejso.2016.07.014