The Future of Melanoma Immunotherapy

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Abstract

The resurgence of immunotherapy in melanoma has led to impressive gains in therapeutic outcome. Yet we remain limited in our ability to predict response, toxicity, and prognosis. In this brief review, we outline pressing questions for clinical investigation using the backbone of checkpoint inhibition in melanoma. Future trials must also evaluate strategies to improve the economics of melanoma therapy.

Keywords

Immunotherapy, melanoma, checkpoint inhibitors, PD-1, biomarkers, pharmacoeconomics

In no other cancer in recent times has the impact of immunotherapy been so profound as melanoma. An understanding of molecular underpinnings in this disease has led to the rational development of immunotherapy, leading to unprecedented tumor response and importantly an improvement in overall survival in metastatic melanoma. The identification and development of antibodies to block the immune checkpoint proteins cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) led to regulatory approvals of ipilimumab (anti-CTLA-4) and nivolumab and pembrolizumab (anti-PD-1), and most recently the combination of ipilimumab plus nivolumab in the US. The availability of these immunotherapies has prompted medical oncologists to become more optimistic about long term durable responses and even cure in advanced melanoma.

Anti-PD-1 therapy is now the standard front-line option for most patients with unresectable metastatic melanoma. For BRAF V600 mutated melanoma, targeting the mitogen-activated protein (MAP)-kinase pathway through combined BRAF and MEK inhibition is an alternative option, especially in the face of rapidly progressive or symptomatic disease. In ipilimumab-naïve patients, the objective response rate to single agent nivolumab or pembrolizumab ranges from 33–44%, with 1-year survival exceeding 70%.[1,2] Contrast this to the chemotherapy era, where the median survival for metastatic melanoma was typically well under one year.[3] The clinical investigation into dual inhibition of the PD-1 and CTLA-4 checkpoints was the natural sequel. In a series of well-conducted clinical trials, combination nivolumab plus ipilimumab has demonstrated a high objective response rate of approximately 50–60%.[4-6] However, more than half of the patients receiving the combination experienced grade 3 or 4 toxicity, and one-third needed to discontinue therapy secondary to adverse effects. But whether the very high response rate will translate into a meaningful improvement in survival compared to the far less toxic single agent anti-PD-1 therapy is yet to be determined. Hence, the applicability of the ipilimumab/nivolumab combination to all comers of metastatic melanoma is questionable. Rather, we believe the decision between single-agent and combination immunotherapy must be determined on a case-by-case basis, taking into account the burden of disease, need for rapid response, and existence of co-morbid conditions. Investigations into altered dose schedules of checkpoint inhibitor combinations are underway (NCT02714218, NCT02089685), and may help identify a more tolerable combination regimen without compromise of efficacy.

While the start of this decade could be defined as the 'watershed' era in melanoma therapeutics, we are far from declaring total victory over melanoma. Over 10,000 deaths are predicted to occur in the US in 2016,[7] a number that continues to rise over prior years despite our therapeutic advances. Moreover, projections estimate melanoma will double in incidence and become the fifth most common cancer in this country by 2030, certainly a sobering statistic.[8] Hence we must continue to build on recent successes in immunotherapy. We believe the following questions must form the premise of the current and next generation of clinical trials of immunotherapy in melanoma:

1. Can we identify predictive and prognostic biomarkers of efficacy and toxicity?
2. What is the optimal duration of immunotherapy?
3. Can we identify other critical pathways involved in 'tolerance of the cancer cell' and thus identify new targets for intervention?
4. How do we lower the cost of melanoma therapy, including costs associated with management of toxicities?

To date, the search for a sensitive and specific biomarker to predict response to checkpoint inhibition has been elusive. Programmed death receptor ligand-1 (PD-L1) expression on tumor cells measured by immunohistochemistry, which would seem to be a logical predictor of efficacy, has yielded inconsistent results in melanoma. But it may well have a predictive role to play. A potentially significant preliminary observation from a phase III randomized trial is the similar progression-free survival (PFS) of 14 months observed in melanoma patients with PD-L1 positive tumors whether treated with nivolumab as a single agent or in combination with ipilimumab, suggesting that the toxicity of the combination may be avoided in this cohort of patients.[6] Conversely, for PD-L1 negative tumors, the PFS was longer with the combination versus nivolumab alone (11.2 months versus 5.3 months). Many ongoing trials are using PD-L1 status as a stratification factor, and future results will determine the validity of this test as a reliable and reproducible biomarker. Tumors with high mutational loads (including those with microsatellite instability) appear to respond better to anti-PD-1 therapy, suggesting that testing for mismatch repair defects in tumors may serve as a genetic biomarker of response.[9,10] Elegant work on the pre-treatment tumor transcriptome have described signatures for response and resistance to anti-PD-1 therapy.[11] The potential for rational clinical translation is immense. These are just a few examples of biomarker discovery in immunotherapy that will likely undergo further refinement with ongoing investigations. Examination of the gut microbiome, tumor stroma, tumor-host interface, and blood-based biomarker testing are other avenues of special interest that may help shape our understanding of the complex host-tumor immunologic cross talk that occurs.

Immunotherapy is now poised to serve as the backbone to combination therapy in melanoma. Ongoing trials are examining other immune targets including TIM3, LAG3, OX40, CD137, and ICOS to name a few. Epigenetic modulation using histone deacetylase inhibitors in combination with checkpoint inhibition has sound preclinical rationale and is now being investigated in the clinic.[12] The importance of prospective tissue and blood biomarker investigation in these trials cannot be over-stated and must be a priority.

Finally, it is time to critically examine ways to lower the cost of immunotherapy. The optimal duration of immunotherapy should be evaluated in a prospective fashion. Do we really need to continue an anti-PD-1 agent for years when ipilimumab is only given four times over 9 weeks? Is there a role for periodic maintenance after a period of induction in the responding patient? Can lower doses of drug and better ways to recognize and manage toxicity lower the human and financial costs associated with immunotherapy? It is incumbent on us and our pharmaceutical and biotechnology industry partners to collaborate to answer these questions. We look forward to the day in the not too distant future when the phrase '*fiscally responsible personalized immunotherapy*' can become a reality. As providers of healthcare, we owe this to our patients and to society at large. ∎

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