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Durable benefit and the potential for long-term survival with immunotherapy in advanced melanoma

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ABSTRACT

Historically, the median overall survival for patients with stage IV melanoma was less than 1 year and the 5-year survival rate was ~10%. Recent advances in therapy have raised 5-year survival expectations to ~20%. Notably, a subset of melanoma patients who receive immunotherapy with high-dose interleukin-2, and now ipilimumab, can achieve long-term survival of at least 5 years. A major goal in melanoma research is to increase the number of patients who experience this overall survival benefit. In this review, we discuss the attributes of immunotherapy and newer targeted agents, and consider how combination strategies might improve the chances of achieving durable benefit and long-term survival. We also discuss three areas that we believe will be critical to making further advances in melanoma treatment. To better understand the clinical profile of patients who achieve long-term survival with immunotherapy, we first present data from ipilimumab clinical trials in which a subset of patients experienced durable responses. Second, we discuss the limitations of traditional metrics used to evaluate the benefits of immunotherapies. Third, we consider emerging issues that clinicians are currently facing when making treatment decisions regarding immunotherapy. A better understanding of these novel treatments may improve survival outcomes in melanoma, increase the number of patients who experience this overall survival benefit, and inform the future use of these agents in the treatment of other cancer types.

Introduction

Survival outcomes for patients with stage IV melanoma have traditionally been poor. With standard therapies such as dacarbazine (DTIC), median overall survival (OS) is 6–10 months and the 5-year survival rate is ~10% [1,2]. The recent availability of ipilimumab and BRAF pathway targeted agents has raised survival expectations and shifted the treatment paradigm for melanoma. An important challenge for the melanoma community is how to incorporate these new treatments into day-to-day clinical decision making to maximize the chances that a patient will experience long-term benefit. In this review, we discuss the clinical attributes of immunotherapy and BRAF pathway targeted agents when used as monotherapy and their potential to be used in combination regimens. We also discuss the following issues that will be critical to making further advances in melanoma treatment: (1) characteristics of patients who achieve long-term survival with immunotherapy, (2) the need for improved clinical trial endpoints that fully capture the clinical benefits of immunotherapy, and (3) emerging questions in need of answers to

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ensure that appropriate treatment decisions are made about immunotherapy.

New treatments: immunotherapy and targeted therapy

Immunotherapy

Initial attempts to improve outcomes in patients with advanced melanoma focused on the use of high-dose interleukin-2 (HD IL-2), a cytokine that induces T-cell activation and proliferation [3]. The rationale for using HD IL-2 to treat advanced melanoma was based in part on two observations that suggest involvement of the immune system in the natural history of melanoma. First, a small proportion of patients experience spontaneous tumor regression in primary, but not metastatic, tumors in the absence of systemic intervention, suggesting that melanoma may be an immunologically modulated malignancy [4]. Second, HD IL-2 demonstrated promising antitumor activity in murine models [5].

HD IL-2 was evaluated in a series of phase II melanoma trials. In a US National Cancer Institute study, while only 7% of melanoma patients treated with HD IL-2 achieved complete regression, responses were maintained for up to 91+ months [6]. In eight phase II melanoma trials of HD IL-2, the objective response rate was 16% with response durations ranging from 1.5 to more than 122 months [7,8]. In a randomized, phase III study, the objective response rate was 6% among 93 patients treated with HD IL-2 [9]. Although HD IL-2 may provide durable responses of over 10 years in some patients, its use is limited by severe toxicity that can affect multiple organ systems (e.g., cardiovascular, respiratory, nervous, renal, digestive, and skin) [10]. For this reason, HD IL-2 is generally reserved for selected patients who are treated as inpatients at specialty centers. The toxicities associated with HD IL-2 have prompted investigations of low-dose IL-2 (LD IL-2) regimens. Although LD IL-2 is less toxic than HD IL-2 [10], it has failed to produce complete and durable response in melanoma clinical trials [11,12]. Despite these limitations, the experience with HD IL-2 provides proof-of-concept that modulation of the immune system might offer durable clinical benefit in melanoma. In the era of more tolerable immunotherapies, the role of single-agent HD IL-2 remains to be determined, but T-cell agonist strategies with more limited toxicities will likely play a role in future combination regimens.

Improvements in our understanding of tumor immunology have led to the development of targeted immunotherapies aimed at specific immune-checkpoints. Immune-checkpoints that are currently being targeted in melanoma include cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1). CTLA-4 and PD-1 are inhibitory receptors with nonoverlapping roles in modulating the adaptive immune response. CTLA-4 acts primarily early in the immune response to regulate T-cell proliferation and migration to the tumor, whereas PD-1 and its ligand PD-L1 regulate T-cell activation and proliferation at the tumor site [13].

Ipilimumab, which targets CTLA-4, was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency in 2011 for the treatment of unresectable or metastatic melanoma. A survival benefit with ipilimumab was demonstrated in two randomized, controlled phase III trials (MDX010-20 and CA184-024) [14,15]. In study MDX010-20, previously treated melanoma patients received ipilimumab 3 mg/kg plus the melanoma peptide vaccine gp100, ipilimumab 3 mg/kg alone, or gp100 alone [14]. The median OS for these treatment groups was 10.0, 10.1, and 6.4 months, respectively. The hazard ratio (HR) for death compared with gp100 alone was 0.68 ($p < 0.001$) for the ipilimumab plus gp100 group and 0.66 ($p = 0.003$) for the ipilimumab-alone group. In study CA184-024, previously untreated patients received ipilimumab 10 mg/kg plus DTIC or DTIC plus placebo [15]. The median OS for these treatment groups was 11.2 and 9.1 months, respectively (HR, 0.72; $p < 0.001$).

Data from these and other clinical trials suggest that a proportion of patients treated with ipilimumab can achieve survival of at least 5 years. In study CA184-025, a companion study of extended ipilimumab treatment in patients who received ipilimumab in previous phase II trials, 5-year survival was 16.5% to 17.0% for ipilimumab 3 mg/kg and 17.6% to >49% for ipilimumab 10 mg/kg [16]. In study CA184-024, 5-year survival was 18.2% for ipilimumab plus DTIC versus 8.8% for DTIC plus placebo [17]. A meta-analysis of pooled OS data from ipilimumab trials, which included data from 1861 melanoma patients, reported a 3-year OS rate of 22% (95% CI, 20–24%); furthermore, a plateau in the pooled Kaplan–Meier curve began at approximately 3 years after initiation of therapy, and extended through follow-up of as long as 10 years [18]. Importantly, some patients included in the pooled analysis were no longer receiving treatment, suggesting that treatment-free survival is possible with ipilimumab.

The success of ipilimumab was closely followed by the development of additional immune-checkpoint inhibitors, including nivolumab and pembrolizumab (MK-3475), which target PD-1. These agents have demonstrated clinical activity in early clinical trials and are being explored in ongoing phase III studies (Table 1). In a phase 1 study of nivolumab, 28% (26 of 94) of patients with melanoma showed an objective response that lasted from 1.9 to 24.9 months [19]. A phase Ib study of pembrolizumab reported an objective response rate of 38% among 117 evaluable patients [20]. Whether responses to nivolumab and pembrolizumab will be similarly durable to responses to ipilimumab remains to be determined, but preliminary evidence suggests that this may be the case [21,22].

Preliminary data from phase I clinical trials suggest that antibody-mediated targeting of PD-L1 may also be an effective melanoma treatment strategy (Table 1). Among 52 evaluable patients treated with BMS-936559 (MDX 1105), 9 (17%) achieved an objective response and 14 (27%) had stable disease (SD) lasting 24 weeks or more [23] (NCT00729664). Antibody-mediated blockade of PD-L1 with MPDL3280A, another PD-L1 inhibitor, was associated with objective responses in 9 of 35 evaluable patients, with all responses ongoing or improving at the time of tumor assessment [24] (NCT01375842). A phase I clinical trial is also underway to evaluate the PD-L1 inhibitor MEDI4736 in several advanced tumor types including melanoma (NCT01693562).

Targeted therapy

Concurrently with the development of the newer immunotherapies, a better understanding of the biology of melanoma has led to the development of molecular targeted therapies. The mitogen-activated protein kinase (MAPK) pathway is one of the major signaling networks involved in melanoma tumorigenesis [25]. A major driver of this pathway is BRAF, which can initiate a cascade of events including phosphorylation and activation of MEK. BRAF mutations are found in ~50% of melanomas, with most (70–95%) consisting of a V600E substitution, while a smaller proportion (5–30%) are V600K substitutions [26]. Along with ipilimumab, agents that target BRAF and MEK have now emerged as key treatments for advanced melanoma.

Vemurafenib, an inhibitor of mutant BRAF, was approved by the FDA in 2011 for the treatment of melanoma patients harboring the BRAF V600E mutation based on improved OS versus DTIC in the BRIM-3 phase III study [27]. At a median follow-up of 10.5 months for vemurafenib and 8.4 months for DTIC, median OS was 13.2 and 9.6 months, respectively (HR, 0.62) [28]. One-year OS rates were 55% and 43% in patients treated with vemurafenib