A New Immunotherapy for Melanoma?

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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Review of: "Improved survival with ipilimumab in patients with metastatic melanoma," by Hodi et al. (2010). The New England Journal of Medicine, 363(8), 711–723. doi:10.1056/NEJMoa1003466. For a researcher's view of this paper, please see the article by Friese on page 287.

For over a decade, clinical trials for individuals with metastatic melanoma have failed to provide results leading to new agents to treat this malignancy. This recent report by Hodi et al. (2010) suggests that the prolonged wait for a new therapy may be ending.

Metastatic melanoma remains a devastating malignancy. Although incidence rates of most malignancies have stabilized, incidence rates of melanoma in the United States are continuing to rise. An estimated 68,130 new cases will be diagnosed in 2010, and deaths are predicted to exceed 8,700 (Jemal, Siegel, Xu, & Ward, 2010). Approximately 3% of patients will be diagnosed with metastatic disease at the time of diagnosis and many will ultimately develop metastatic disease following what is believed to be a curative resection (Jemal et al., 2010; Ries et al., 2008).

At present, only two agents are approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic disease: interleukin-2 (IL-2, Proleukin) and dacarbazine (DTIC). Interleukin-2 is an immunomodulatory agent with significant toxicities limiting its use to a very select patient population. Although response rates as high as 16% have been reported with IL-2, not all patients will have durable remissions (Atkins, 2006). Treatment with DTIC is associated with clinical benefit in the way of partial responses in approximately 10% of patients, with durations lasting only 4 to 6 months (Tarhini & Agarwala, 2006). No second-line therapies are currently approved for metastatic melanoma.

Study Design

The Hodi manuscript reports the results of a multicenter, double-blind, randomized, phase III study in which 676 patients, all with an HLA-A*0201-positive tissue type, were randomized to one of the following three study arms: ipilimumab plus glycoprotein 100 (gp100) vaccine, ipilimumab alone, or gp100 vaccine alone. The study was open to unresectable stage III or stage IV patients who had received previous therapy with DTIC, fotemustine, carboplatin, temozolomide (Temodar), or IL-2. Patients were stratified based on metastasis stage and previous exposure

to IL-2. Randomization was performed utilizing a 3:1:1 strategy (ipilimumab plus gp100 vaccine [n = 403], ipilimumab alone [n = 137], or gp100 vaccine alone [n = 136]). All agents were administered once every 3 weeks for up to four doses. Additional courses of treatment could be administered to patients who exhibited at least stable disease for 3 months following week 12 of treatment (induction period), as well as to those with a confirmed partial or complete response to treatment.

Background

The use of immune-modulating strategies continues to be of significant interest in exploring methods to treat melanoma. In a recent review, patients who had responded to treatment with high-dose IL-2 were found to be progression-free for more than 13 years (Atkins, 2006). This has led to the exploration of additional immune-mediating strategies such as ipilimumab. Ipilimumab is a fully humanized monoclonal antibody that targets the cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), which has been shown to inhibit T-cell activation once the T cell has been activated. The subsequent "turning off" of the immune response may be responsible for the development of immune tolerance (Hodi et al., 2010; O'Day, Hamid, & Urba, 2007). Blocking the activity of CTLA-4 is believed to enhance T-cell activation, as well as the endogenous immune response to immunogenic tumors (Esper, 2009).

Previous research has looked at many different vaccine strategies in treating melanoma. Cytotoxic T lymphocytes (CTLs) have been shown to kill melanoma cells expressing the gp100 peptide in vitro. Clinical trials using vaccine strategies in combination have been much more promising than when utilized as a single treatment modality. The use of gp100 in combination with ipilimumab in one of the study arms was designed to enhance CTL responses with resultant killing of tumor cells and subsequent tumor regression (Medarex, Inc.).

Study Findings

The primary endpoint in the study was initially intended to be the best overall response rate, but was ultimately changed to overall survival. The primary comparison was ipilimumab plus gp100 vs. gp100; a secondary comparison was ipilimumab vs. gp100. The median overall survival for the three treatment arms is seen in Table 1. Of note, 4 of 23 patients (17.5%) in the ipilimumab-plus-gp100 arm and 9 of 15 (60%) in the ipilimumab-alone arm maintained an objective response for at least 2 years.

Table 1. Median overall survival in a study of ipilimumab and gp100, alone and together, for the treatment of melanoma

Overall survival	gp100 + placebo (n = 136)	Ipilimumab + placebo (n = 137)	Ipilimumab + gp100 (n = 403)
Median OS, months	6.4	10.1	10.0

Note. OS = overall survival. Data from Hodi et al. (2010).

As expected, the most commonly seen side effects in this study were immune related. Of these, grade 3 and 4 occurrences were seen in 10% to 15% of patients treated with ipilimumab and in 3% of the gp100-alone group. These events typically involved the gastrointestinal tract and skin, with the most commonly reported adverse event being diarrhea. Diarrhea of any grade was reported in almost one third of the patients in the ipilimumab groups. A total of 7 out of 14 deaths believed to be related to the study agent were attributed to immune-related adverse events (IRAEs).

Conclusions

The FDA is anticipated to review the application for approval of ipilimumab for the treatment of metastatic melanoma later this year. Approval of an agent such as this will require considerable education of both clinicians and patients regarding its immunomodulatory mechanism of action and associated IRAEs. Prompt intervention, particularly related to side effects such as diarrhea, is imperative for patient safety.

DISCLOSURES

The author has no potential conflicts of interest to disclose.

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