Melanoma: More Answers, More Questions

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Treatment for patients with metastatic melanoma has changed dramatically in the past few years. Long held to be incurable, the first indication that immunotherapy with interleukin-2 (IL-2) could lead to durable complete remissions (CR) in patients with melanoma was reported in 1985 [1]. Subsequently, IL-2 combined with the adoptive transfer of in vitro cultured tumor-infiltrating lymphocytes to patients following myeloablative chemotherapy was shown to increase durable CR rates considerably, up to 20% [2]; however, adoptive immunotherapy is available at only a few centers. Despite its curative potential for a subset of patients with good performance status, it is estimated that <10% of eligible patients receive high-dose IL-2 [3]. Underutilization is undoubtedly related to the severe toxicity profile of IL-2 and the requirement for prolonged hospitalization in an ICU-like environment. Another contributing factor is the approval of two new effective agents—one a novel immunotherapy (ipilimumab) and another a targeted BRAF inhibitor (vemurafenib).

Luke and Hodi [4] provide an excellent review of the development of ipilimumab, an anti-CTLA-4 antibody that is presumed to enhance T-cell immunity by blocking inhibitory signals delivered when CTLA-4 on T cells engages the B7-1 and B7-2 ligands on antigen-presenting cells. Administration of ipilimumab to either untreated or previously treated patients with metastatic melanoma improved survival compared with controls, which led to FDA approval in 2010 [5, 6]. Despite low response rates (a CR rate under 2%), overall survival was improved, and landmark analysis demonstrated improvement in one- and two-year survival rates. Ipilimumab-induced remissions have proven to be durable; in one study, 14 of 15 CRs continued in remission for 54+ to 99+ months [7]. The pattern of tumor regression after ipilimumab was so different from that typically observed after chemotherapy that new response criteria—immune-related response

criteria—were proposed to recognize the uncommon ($\leq 10\%$) but important instances in which tumor progression (defined by traditional criteria) was followed by delayed, occasionally dramatic, and sometimes complete regression of metastatic disease [8]. The clinical value of these new criteria remains to be determined; however, recognition of this pattern of response has changed the way we manage patients receiving immunotherapy. It is now advisable, in the absence of symptoms or a decline in performance status, to continue the planned 12-week course of ipilimumab despite progression of disease, to ensure that therapy is not discontinued prematurely in a patient who might benefit from a delayed response.

Ipilimumab-related side effects were also different from those observed with traditional chemotherapy. Infusion reactions were rare, but a wide range of inflammatory toxicities were observed. Although the underlying mechanism of these toxicities has not been determined, the suspicion, based on clinical manifestations and the uniform presence of lymphocytic infiltrates in biopsies of affected organs, is that many of the side effects are manifestations of an autoimmune response. Ipilimumab toxicity can affect almost any organ system; the most common targets are the skin and GI tract [9]. The incidence of severe diarrhea and colitis and the 2% death rate in the initial randomized trial [5] were perceived as potential obstacles to the approval and subsequent use of ipilimumab in the community. Fecher et al. [9] summarized the opinions of a panel of melanoma specialists convened by Bristol-Myers Squibb months before the drug was approved to discuss the proper evaluation and management of ipilimumab toxicity. Their manuscript provides an excellent summary of the toxicities and serves as a practical guide to their recognition, diagnosis, and management. The authors emphasize the importance of education (of patient, patient's family, and staff) to identify problems early and the need to engage the support of a multi-

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disciplinary team. Because nearly every organ system can be involved and toxicity varies from patient to patient, this team may have different members for different patients. Replete with algorithms for management of toxicities of the skin, GI tract, liver, and endocrine system, the manuscript is a useful “handbook” for the conservative management of patients receiving ipilimumab. The proper role for steroids to suppress inflammation is described. Our patients will be served well if we heed the unassailable advice of the authors: “Vigilance and a high level of suspicion for possible immune-related adverse events (irAEs) on the part of the treating oncologist are essential to the use of ipilimumab” [9]. Patients should always carry the wallet card identifying themselves as patients receiving ipilimumab; they may become ill even after all planned ipilimumab infusions are completed and have to visit an emergency department or clinic where health care providers have no experience managing potentially life-threatening side effects.

There are still a number of unresolved issues in regard to ipilimumab therapy. For example, we do not know the optimal dose, the role of maintenance therapy, the value of retreatment for patients who progress after an ipilimumab-induced remission, efficacy in special populations (e.g., mucosal and ocular primaries), and importantly, the optimal sequencing of ipilimumab and vemurafenib in patients with a *BRAF* mutation has not been defined. The currently approved dose for ipilimumab is 3 mg/kg, but there is one study that suggests 10 mg/kg may be more effective [10]. The question of dose will be answered once the data from the recently completed randomized trial of 3 versus 10 mg/kg of ipilimumab have matured. Retreatment of patients who experienced clinical benefit from initial therapy with ipilimumab appears warranted based on clinical experience with the drug and the data from the original randomized trial in which 21 of 31 patients given reinduction therapy achieved a partial remission, CR, or had stable disease [5].

In regard to special populations, a retrospective analysis of 33 patients with mucosal melanoma demonstrated that, despite differences in molecular phenotype and clinical behavior, mucosal melanomas can respond to ipilimumab with durable remissions perhaps comparable to those of similarly treated patients with cutaneous melanomas [11]. Mucosal melanomas uncommonly have *BRAF* mutations (<10%) but do harbor recurrent mutations and/or amplifications of the receptor tyrosine kinase KIT. The latter appear to be more common in vulvar than anorectal or nasal cavity melanomas, and some patients with KIT alterations benefit from therapy with imatinib [12]. The authors describe 33 patients with mucosal melanoma who had been treated with ipilimumab on clinical trial or in the ipilimumab expanded access program. The majority (75%) of patients were previously treated and received either 3 or 10 mg/kg of ipilimumab every 3 weeks for 4 doses. Responses were observed in 2 of 30 patients; 1 patient had a CR lasting 22+ weeks. These response rates are consistent with what has been observed with ipilimumab for cutaneous melanoma. The durability of responses and overall survival of these patients, which were the key benefits of ipilimumab therapy in the phase III trials, cannot be evaluated adequately because of the small number of patients and short follow-up. However, ipilimumab has activity in mucosal melanomas and is a reasonable option for initial therapy.

Currently, our team offers immunotherapy to all suitable patients who present with *BRAF* wild-type tumors. Whenever possible, patients are enrolled in a clinical trial. If that is not possible, we choose high-dose IL-2 or ipilimumab based on performance status, tumor burden, presence of comorbidities, or patient preference. As discussed by Luke and Hodi [4], patients whose tumors harbor *BRAF*^{V600E} mutations have a broader range of choices. The clinical benefits after therapy with the *BRAF* inhibitors vemurafenib and dabrafenib were compared and contrasted, and data after treatment with single-agent MEK inhibition (trametinib) were also discussed. Each of these agents improves progression-free and overall survival compared with chemotherapy; however, responses are not durable. The promising early results of combined therapy with dabrafenib/trametinib compared with dabrafenib alone also were noted. Designed to overcome a major mechanism of resistance to *BRAF* inhibition, namely reactivation of MEK, combined therapy led to higher response rates and significantly enhanced progression-free survival compared with *BRAF* inhibitor alone [13]. The combination appears to be an improvement over *BRAF* inhibition alone. Phase III trials comparing single agent *BRAF* and *MEK* inhibition to combined therapy will determine which regimen is superior. However, combined therapy appears to suffer the same limitations as single-agent targeted therapy: the inevitable development of resistance. This is manifest by disease recurrence in our patients and visible as a failure to observe a plateau in the survival curve. Thus, at present, the major difference between immunotherapy and targeted therapy is the ability of the former, albeit in a minority of patients, to produce durable remissions.

The promising clinical results with these two new agents generated great interest in testing them in combination. Vemurafenib has a high response rate. Tumor cell death presumably generates antigen for presentation to generate additional tumor-specific T cells that can be stimulated by ipilimumab; therefore, combining targeted therapy with immunotherapy could lead to higher rates of durable tumor regression. Unfortunately, the first attempt to combine the two drugs at their full approved doses resulted in excessive elevation of aminotransferase levels [14], so it is back to the drawing board to figure out a safe dose and schedule for the drug combination.

For the patient with melanoma and a *BRAF* mutation who walks into the office today, participation in one of many clinical trial opportunities is still the best option. Otherwise, the choice is between immunotherapy (interleukin-2 or ipilimumab) and one of the FDA-approved *BRAF* inhibitors, vemurafenib or dabrafenib. At the Earle A. Chiles Research Institute, we generally recommend first-line immunotherapy and use vemurafenib after a failure of immunotherapy. We use vemurafenib initially for patients with bulky or progressive disease who need a rapid response or who express a strong preference for oral therapy. This algorithm is primarily based on the durability of remissions following immunotherapy; however, there are recent data that indicate that just under half of patients initially treated with a *BRAF* inhibitor had rapid disease progression resulting in death and were unable to complete ipilimumab treatment [15]. This is a rapidly evolving field, and there are many strategies by which patients can

receive both agents without administering them together. No doubt we will read much more about these strategies in the near future.

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EDITOR'S NOTE: Please see the accompanying articles on pages 717, 726, and 733 of this issue.