Anti-CTLA-4 Therapy, cont. from page 4

assessments are made at week 12 after beginning therapy. However, the biologic processes leading to tumor regression by T cell activation are complex and heterogeneous between patients; some on ipilimumab have delayed responses, which may occur after long periods (>6 months) of stable disease, while others manifest overt progression of disease at week 12 before eventually having clinical benefit with no additional therapy.

Even more intriguing is the description of new lesions occurring in the context of response in baseline tumors. Such patients would be categorized as having progression of disease by standard response criteria. However, at least a subset of such patients will have eventual regression of the new lesions, albeit later than the target lesions.

To date, the best hypothesis for these varying delayed responses is that the immune system may require time to sculpt responses to different tumors with potentially different antigens. There is also inherent biologic variation in the threshold for induction of an immune response.

Responses to ipilimumab have been generally durable, with some patients from the initial trials surviving >5 years.

How To Gauge Benefits

These novel patterns of clinical response have led to much discourse about how to quantify the clinical benefit of anti-CTLA-4 therapy. Investigators have proposed a series of immune-related response criteria, which take into consideration the appearance of new lesions.3,4 These criteria are currently being evaluated in several clinical trials of ipilimumab. From initial studies, it seems that patients who are identified as having clinical benefit by the various immune-related response criteria have similar overall survival to patients categorized as responders using standard criteria. Until the immune-related response criteria can be prospectively validated, overall survival will obviously remain the gold standard for judging clinical benefit of these and other novel biotherapies.

In the Wings

As of September, 2008, a phase III trial of ipilimumab for first-line therapy of melanoma is ongoing but closed to accrual. We in the field eagerly await the overall survival data from this randomized comparison of dacarbazine +/- ipilimumab. In the interim, other ongoing studies are focusing on the use of ipilimumab in patients with brain metastases, as some anecdotal reports of activity in brain lesions have been noted. A phase III trial of tremelimumab versus dacarbazine/temozolomide was reported at ASCO in 2008, with no survival advantage detectable. It is unknown at this time whether further trials of tremelimumab in melanoma are planned.

Conclusion

The development of anti-CTLA-4 antibodies is of great interest to those engaged in the treatment of melanoma patients. The observation of durable responses in refractory disease using a simple intravenous infusion to administer outpatient therapy is of obvious importance. We need to focus on how to categorize the responses to this therapy more accurately and to emphasize the need for close communication between patient and clinician to diagnose immune-related adverse events early, when they can be easily treated. Researchers have high hopes that the coming year will bring us closer to approval of a new immunotherapy for metastatic melanoma. Further hope can be gained from the early clinical trials of other immunomodulatory antibodies, such as anti-CD137, anti-CD40 and anti-PD1.

References

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Effective Immunotherapy for Patients with Metastatic Melanoma

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Immunotherapy has emerged as the most effective treatment for patients with metastatic melanoma. Much of the information concerning the immune response to melanoma has come from the study of tumor-infiltrating lymphocytes (TIL), immune cells that infiltrate into the stroma of the growing tumor and can be grown in vitro in the cytokine IL-2. TIL have been used to identify dozens of antigens that are presented on melanomas. Some antigens such as MART-1 and gp100 are shared by both melanomas and normal melanocytes, whereas others, such as NY-ESO-1, can be expressed on melanomas, but on no other adult tissue except the testes.

Most studies of immunotherapy for melanoma patients have been directed at those with metastatic disease. Although multiple trials of cancer vaccines have been performed in patients with resected lymph nodes at high risk of recurrence, none of these clinical trials have convincingly demonstrated prolonged survival. Some controversy exists surrounding the use of interferon alpha for the treatment of stage 3 melanoma; prolonged follow-up of patients in prospective randomized trials has yielded ambiguous results, and many oncologists are concluding that the toxicities of high-dose interferon are not warranted given the lack of conclusive evidence of effectiveness in this setting.

Substantial progress has been made, however, in the treatment of patients with metastatic melanoma. It is now possible to cause complete regressions of widely metastatic melanoma at multiple sites in the body utilizing immunotherapy approaches.

Immunotherapy Approaches To Metastatic Melanoma

Approaches to the treatment of patients with metastatic melanoma fall into three major categories, which are summarized in Table 1.

Nonspecific stimulation of immune reactions

Because natural immune responses to melanoma exist, attempts at nonspecific immunomodulation have shown some continued on page 2

Three Main Approaches To Cancer Immunotherapy

1 Nonspecific stimulation of immune reactions
   a. Stimulate effector cells (interleukin-2)
   b. Inhibit suppressive factors (anti-CTLA-4)

2 Active immunization to enhance antitumor reactions (cancer vaccines)

3 Passively transfer activated immune cells with antitumor activity (adoptive immunotherapy)

Table 1.
**Effective Immunotherapy, from page 1 effectiveness.** Administration of a hormone involved in T cell growth, called interleukin-2 (IL-2), can activate naturally occurring anti-melanoma immune cells. Of 305 consecutive metastatic melanoma patients treated in the Surgery Branch at NCI, 13 percent achieved objective responses by standard RECIST (Response Evaluation Criteria in Solid Tumors) criteria; four percent had complete regressions.

Patients who experience complete regression rarely recur. It was the durability of the regressions induced by IL-2 that led to its approval by the US Food and Drug Administration in 1998 for the treatment of patients with metastatic melanoma (Figure 1). IL-2 administration is the only FDA-approved treatment capable of curing patients with metastatic melanoma. The capillary leak syndrome associated with the administration of IL-2 has limited its widespread use, but this side effect can be readily managed, and treatment-related mortalities add up to less than one percent of patients seen in experienced centers.

Another experimental approach to nonspecific immunomodulation, not FDA-approved, is the administration of an antibody that reacts with (inhibits) a cell surface inhibitory molecule, cytotoxic T lymphocyte-associated 4 (CTLA-4). Of 139 patients with metastatic melanoma treated with anti-CTLA-4 in the Surgery Branch at NCI, 17.7 percent have achieved objective clinical responses, including some complete responses ongoing beyond 5 years. Approximately 15 percent of patients who receive anti-CTLA-4 will develop severe enterocolitis, and 5-10 percent of patients will develop hypophysitis requiring steroid replacement.

**Active immunization to enhance antitumor reactions**

A second major approach to the immunotherapy of metastatic disease involves active immunization with cancer vaccines. Despite much work in this field, only rare and highly sporadic objective regressions of metastatic melanoma are seen using this approach. Though it is possible to generate large numbers of antitumor lymphocytes in patients utilizing active immunization, many of these lymphocytes are of very low avidity for melanoma recognition and have little clinical impact.

**Adoptive cell transfer (ACT) immunotherapy**

The third and most effective treatment for patients with metastatic melanoma is adoptive cell transfer (ACT). This approach involves the ex vivo identification of autologous lymphocytes with antitumor activity that can be stimulated in the laboratory, grown to large numbers, and then infused into cancer patients along with appropriate growth factors to keep these transferred cells alive and functional in the patient.

ACT has several advantages compared to other forms of immunotherapy. It is necessary to identify only a small number of highly reactive antitumor lymphocytes, which can then be further stimulated and expanded in vitro to large numbers for patient administration. In vitro tests can be used to identify the cellular characteristics required to mediate tumor regression.

An important factor for the success of ACT is the ability to deplete the host of inhibitory
be generated from only half of patients with melanoma. We have thus developed techniques to genetically alter the normal circulating lymphocytes of a patient to endow these cells with antitumor activity. TIL express T cell receptors that can recognize melanoma antigens. The genes encoding these T cell receptors have been cloned into retroviruses that can be used to convert normal peripheral lymphocytes into cells capable of recognizing the melanoma.

The first applications of this gene therapy approach were recently published. Two patients, one with metastatic melanoma to the liver and another to the lung hilum, experienced objective regressions when treated with these genetically modified cells.

Factors that can negatively influence the transferred cells. Utilizing lymphodepletion with cyclophosphamide and fludarabine and adoptive cell transfer of autologous TIL, an objective response rate of 49 percent was seen in 43 consecutive patients with metastatic melanoma (Table 2). Increasing the prior lymphodepletion by adding total-body irradiation increased the objective response rate to 72 percent in 25 consecutive patients. Durable responses have been seen in multiple metastatic sites including lung, liver, brain, lymph nodes and subcutaneous sites (Figure 2A,B). Following lymphodepletion, the transferred cells expand in vivo and persist in the peripheral blood, sometimes adding up to 75 percent of all circulating CD8+ lymphocytes.

Prolonged survival of patients is seen using the ACT approach (Figure 3). The Surgery Branch at NCI is now seeing patients with metastatic melanoma from around the world, and other centers are beginning to study the application of cell transfer therapy for the treatment of patients with metastatic disease. (To refer a patient to the Surgery Branch, call 301-451-1929.)

ACT Approaches and Gene Therapy

The success of ACT approaches has led to the development of gene therapy for the treatment of patients with metastatic melanoma. TIL with antitumor activity can

Figure 2A Complete response of multiple liver metastases in a patient with metastatic melanoma treated with cell transfer therapy. This patient remains disease-free over 4 years later.

Figure 2B Regression of metastases in the heart (upper panel), the adrenal gland (middle panel), and intraperitoneum (lower panel) in a patient with melanoma treated with cell transfer therapy.

Survival of Patients with Metastatic Melanoma Treated with Autologous Tumor-Infiltrating Lymphocytes and IL-2

Figure 3 Survival curves of patients treated with cell transfer therapy using autologous TIL, either with no lymphodepleting chemotherapy, with a non-myeloblastic chemotherapy, or with the non-myeloblastic chemotherapy plus the addition of total body irradiation (TBI).
Anti-CTLA-4 Therapy for Melanoma

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It is now generally accepted that immunotherapy has a role in the treatment of advanced melanoma. This is based on the durable clinical activity of interleukin-2 (IL-2) in a subset of metastatic melanoma patients and the ability of interferon alfa to prolong the disease-free survival of patients in the adjuvant setting.1,2 Enthusiasm for both of these therapies is limited by the relatively small number of patients who derive lasting clinical benefits and by a well-characterized panel of toxicities.

Paths to Improved Immunotherapies

Research has therefore been focused on the development of immunotherapies that may benefit a larger number of patients. The accompanying article by Dr. Steven A. Rosenberg describes the efforts of his group at NCI to develop adoptive T cell therapy for melanoma. Another area of recent research interest is immunologic checkpoint blockade; the best-known therapeutics in this new field are antibodies that block CTLA-4.

Anti-CTLA-4 Therapy

CTLA-4 is best characterized as a ‘brake’ that binds to costimulatory molecules on antigen-presenting cells, preventing their interaction with CD28 on T cells and also generating an overly inhibitory signal constraining further T cell activation. Teleologically, CTLA-4 is necessary to prevent hyperstimulation of T cells that could lead to harmful autoimmunity or activation-induced cell death of T cells. The functional role of CTLA-4 is best demonstrated by the lethal autoimmune observed in CTLA-4 knockout mice. However, temporary inhibition of CTLA-4 has been hypothesized to allow for more robust T cell activation. The first anti-CTLA-4 antibody was made by Dr. Jim Allison in an attempt to provide a limited release of this immunologic braking mechanism, in the hope of permitting the immune system to recognize targets on tumor cells more effectively.

Initial laboratory experiments demonstrated that anti-CTLA-4 antibodies used as monotherapies could indeed mediate rejection of some mouse tumors. For the well-known B16 mouse melanoma, anti-CTLA-4 therapy could provide long-term protection from tumor challenge, but only when combined with a GM-CSF-secreting tumor cell vaccine.

Ipilimumab and Tremelimumab

To date, two human monoclonal antibodies designed to block CTLA-4 have been used in clinical trials in melanoma. Ipilimumab is an IgG1 antibody being jointly developed for use in melanoma by Medarex and Bristol-Myers Squibb. Tremelimumab is an IgG2a antibody developed by Pfizer. Both products have shown clinical activity as single agents in patients with advanced refractory metastatic melanoma. Clinical trials for ipilimumab and tremelimumab have also revealed a unique panel of mechanism-based immune-related adverse events. The vast majority of the immune-related adverse events are low-grade pruritus and diarrhea, while some cases of more serious colitis, hepatitis and hypophysitis also have been described. These side effects are medically manageable, usually with corticosteroids, assisted by simple algorithms.

In phase II trials reported at ASCO this year, ~270 patients were treated with the optimal dose (10 mg/kg) of ipilimumab in the second-line setting. At week 12 after starting, 6-11% of patients had an objective response, ranging from six to 15 percent when tumor}

References