The Antitumor Immunity of Ipilimumab: (T-cell) Memories to Last a Lifetime?

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Ipilimumab has shown an overall survival benefit in 2 randomized phase III studies. A minority of patients achieve long-term disease control, highlighting the potential of this immunotherapeutic approach. In ongoing efforts, investigators are continuing to characterize these patients’ unique clinical courses and correlate their responses with underlying mechanisms of antitumor immunity. Clin Cancer Res; 18(7); 1821–3. ©2012 AACR.

In this issue of Clinical Cancer Research, Prieto and colleagues (1) report long-term follow-up data for 177 patients treated with ipilimumab in some of the earliest trials in its development. Their results underscore the remarkable, durable benefits a subset of patients with melanoma achieve from ipilimumab, hint at the promise of combining ipilimumab with interleukin 2 (IL-2), and raise the provocative question of whether, in some patients, metastatic melanoma can be cured.

Ipilimumab (Yervoy; Bristol-Myers Squibb) is a fully human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4 (CTLA-4). Following T-cell activation, CTLA-4 is recruited to the plasma membrane, where it functions in an autoregulatory role, attenuating T-cell activation and proliferation through several mechanisms (2). Although CTLA-4 plays an essential role in maintaining immunologic tolerance, in the setting of malignancy, CTLA-4 may restrain effective antitumor immunity. As shown in Fig. 1, antibodies that block CTLA-4, such as ipilimumab, release T cells from this immunologic checkpoint and may enable them to exert their full antitumor effect.

Ipilimumab was shown to confer an overall survival benefit in 2 phase III trials (3, 4). The objective response rate was modest [~10% (3)], but a portion of patients in these trials achieved durable disease control. Although ipilimumab is distinct in its mechanism of action and side-effect profile, the pattern of durable responses induced by this agent is similar to that described for a subset of patients who received IL-2 (5).

Prieto and colleagues have assembled findings from the largest reported long-term clinical experience with ipilimumab. They provide updated data from 3 previously published studies that examined ipilimumab with gp100 vaccination [protocol 1 (6)]; ipilimumab with concomitant IL-2 [protocol 2 (7)]; and ipilimumab via a strategy of intrapatient dose escalation (± gp100) until occurrence of response or intolerable side effects [protocol 3 (8)]. The authors evaluate a total of 177 patients treated with ipilimumab, with a median follow-up of 32, 84, and 71 months, respectively. The clinical and correlative implications of the data presented are profound and stress several important themes that have arisen during the development of ipilimumab, and especially highlight the exceptional durability of responses.

The authors offer robust data to support the finding that patients who achieve a response after treatment with ipilimumab are likely to be alive many years later. In their study population, a total of 15 patients ultimately achieved a complete response (CR). The durability of responses among patients who attained a CR is remarkable: All except one are ongoing, with the longest lasting 99+ months (median, 83 months). Although it is tempting to consider these patients “cured,” such a view should be approached with caution, because one patient did relapse after a CR lasting 42 months. The question of how this patient’s tumor escaped after induction of a seemingly effective antitumor immune response underscores the complex relationship between tumor and host immunity. Did the patient’s immune response select for tumor cells with reduced immunogenicity? Did the tumor microenvironment shift in favor of immune suppression? Do patients ever achieve tumor eradication, or is an ongoing memory response required to hold microscopic disease in check? Cases of durable partial response (PR) may support the notion that an ongoing active immune response continues to control disease for years. In long-term follow-up, 9 patients with PR are still alive years after initiation of treatment, with 3 patients maintaining a stable PR without further treatment and the remainder benefiting from subsequent treatments.

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Delayed response kinetics is a hallmark of ipilimumab, and Prieto and colleagues provide a more robust description of this phenomenon than was previously available. Among the 15 patients who ultimately achieved a CR, an average 30 months was required to reach this endpoint. In one case, a patient achieved a CR at 70 months, nearly 6 years after starting treatment. These observations emphasize the variability of response patterns and the wide window of time for ipilimumab to affect tumor burden. These responses may be best evaluated with the use of immune-related response criteria, an adaptation of the World Health Organization criteria, which were designed to accommodate the delayed kinetics and variability of responses to ipilimumab (9).

An important consideration in interpreting these findings is the fact that many of the patients who achieved CR received >4 doses of ipilimumab (range, 3–11), the dosing currently approved by the U.S. Food and Drug Administration for commercial use. The influence of this additional ipilimumab on the accomplishment of a CR or the likelihood of a delayed response requires further study.

Unfortunately, only a subset of patients experience long-term disease control from ipilimumab, and identifying which patients are likely to benefit is an ongoing effort. The absolute lymphocyte count after the first ipilimumab dose was associated with response (1). HLA status did not seem to distinguish patients who benefited, because there was no difference in the rate of response to ipilimumab between HLA-A*201–positive and HLA-A*201–negative patients. This is consistent with our retrospective analysis and in line with ipilimumab’s proposed HLA-independent mechanism of action (11).

Although ipilimumab confers impressively durable disease control for those who respond, a majority of patients do not respond. Ongoing efforts to increase the number of patients who benefit from ipilimumab are focused on combining ipilimumab with chemotherapy, targeted therapy, or other immunotherapies. Prieto and colleagues report on a long-term follow-up of patients treated with ipilimumab in combination with IL-2. The high objective-response rate of 25% (CR, 17%) achieved with this combination approach is intriguing, but it may have been influenced by the selected patient population. Ultimately, the attempt to weigh the benefits of this combination against the toxicities of receiving both agents will require a randomized trial, as the authors suggest. Of note, the typical immune-related adverse events observed with ipilimumab do not seem to occur more commonly with this combination, although in this study many patients received lower doses of ipilimumab (<3 mg/kg). Groups of patients who had been treated in protocols 1 and 3 (without IL-2) and were previously treated with IL-2 showed rates of

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**Figure 1.** A, T-cell activation requires 2 signals (arrow). One signal involves the TCR recognizing a peptide antigen bound to an MHC on the surface of an APC. The second signal involves costimulation through the interaction of CD28 on T cells with B7 (B7-1/CD80, B7-2/CD86) molecules on APCs. B, upon T-cell activation, CTLA-4 is recruited to the plasma membrane and functions in an inhibitory role, binding with higher affinity than CD28 to B7. Through several mechanisms, this binding results in inhibition of T-cell activation and function. C, ipilimumab binds to CTLA-4 and blocks its inhibitory role. By disabling the inhibitory functions of CTLA-4, ipilimumab enhances T-cell activity. APC, antigen-presenting cell; TCR, T-cell receptor.
response to ipilimumab similar to those observed in populations that had not previously received IL-2. This implies that tumors that are resistant to IL-2 can retain sensitivity to ipilimumab, and may suggest a complementary mechanism of action.

Four patients who progressed on ipilimumab achieved CRs after undergoing adoptive cell transfer (12). The possible benefit these patients received from prior ipilimumab treatment, and whether such a benefit contributed to the subsequent success of the adoptive cell transfer, is unclear. Nonetheless, because the persistence of infused cells is important in adoptive cell transfer, and ipilimumab may have a role in potentiating the longevity of such cells, additional research will continue to evaluate this combination approach. One study is already underway (ClinicalTrials.gov Identifier: NCT00871481).

Finally, the authors observed no significant benefit from combining ipilimumab with a vaccine comprised of 2 gp100 peptides emulsified in Montanide ISA-51, in similarity to results from the separate large, randomized phase III trial (3).

Ipiilimumab has set a new standard of care for patients with melanoma. This important long-term analysis of patients treated in some of the earliest trials in ipilimumab's development shows the true promise of ipilimumab for engendering long-lasting antitumor responses. For a subset of patients, ipilimumab seems tantalizingly close to a cure. Understanding the immunologic features that identify patients who are most likely to benefit, and finding complementary therapies that can enhance the activity of ipilimumab, are important next steps in expanding the number of patients who will be able to benefit from this promising therapy.

Disclosure of Potential Conflicts of Interest
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