Ipilimumab for Advanced Melanoma: Let’s Not Throw Caution to the Winds

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The authors provide a timely and relevant review of the role that the immune system plays in regulating tumor growth and how immune modulation can alter tumor response. This review follows from the recently published phase III trial of ipilimumab,[1] a monoclonal antibody to cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the first therapy in several decades to produce prolonged overall survival (OS) in patients with metastatic melanoma. While this outcome underscores the importance of this therapy in treating metastatic melanoma, its clinical applicability, at least on a widespread level, necessitates further exploration.

Response Rates and Overall Survival

As Thumar and Kluger note, objective response rates (which include complete and partial responses) in patients treated with ipilimumab range from 5% to 20%. Hodi and colleagues showed a comparable objective response rate—11%—in patients who received ipilimumab monotherapy.[1] Median OS improved to 10.1 months compared with control groups who received only glycoprotein 100 (gp100) peptide vaccine (hazard ratio [HR], 0.66; \( P = .003 \)). While ipilimumab is the first therapeutic agent in decades that has shown prolonged OS in patients with metastatic melanoma, it is important to note that median survival in this patient population with the best-known therapy is generally accepted to be 6 to 9 months.

Adverse Events

The optimism engendered by this observed prolongation in OS must be carefully weighed against the frequent and sometimes life-threatening immune-related adverse events (irAEs) associated with ipilimumab. Since CTLA-4 is important for tolerance to self antigens, blockade of this pathway can result in autoimmune destruction of various organ systems. The resultant irAEs include, but are not limited to, enterocolitis, dermatitis, hypophysitis, hepatitis, pancreatitis, uveitis, nephritis, and arthritis.

The authors provide a thorough discussion of the incidence, diagnosis, and treatment of irAEs. Several important conclusions regarding treatment of irAEs should be emphasized. First, most adverse reactions are treated conservatively with supportive care and high-dose corticosteroids. However, more severe adverse reactions are associated with relatively high mortality rates (5% in one series[2]), necessitate cessation of ipilimumab therapy, and may require further immunosuppresion or surgery.[3] Second, corticosteroid therapy initiated to combat irAEs appears to have no effect on tumor growth or objective clinical responses.[4-6] Corticosteroids thus provide an effective treatment strategy for irAEs that does not compromise immune modulation—nonetheless, the side effects of high-dose corticosteroids are well known and threaten the patients’ already fragile health and quality of life. Third, there appears to be a correlation between the development of irAEs and objective response rates and survival.[2,4,7-9] This relationship is strongest when more severe (grade 3 and 4) irAEs occur, although this correlation has not been uniformly present.[10] The association between adverse events and tumor response suggests that a subset of patients produces a more robust response to treatment with CTLA-4 blocking agents. The identification of these
patients prior to treatment is of utmost importance, as is the development of strategies to maintain or improve response rates and survival while decreasing the severity of adverse events. Because severe adverse reactions to ipilimumab occur in a relatively small percentage of patients, and because they are reversible and readily managed in most cases, ipilimumab is certainly an attractive therapy for metastatic melanoma. However, it is important to keep in mind that adverse events can be life-threatening and that managing them with corticosteroids can also be harmful. When weighing the use of this novel agent in patients, clinicians should also recall that this scenario is similar to that seen with other agents used to treat melanoma: a small but significant survival benefit is accompanied by a substantial risk of adverse events. As indications for the use of ipilimumab expand, it is essential that patients be well-selected and have minimal comorbidities.

Education regarding the onset and treatment of adverse events is vital for patients and their families, and for medical personnel who will be treating these patients. We strongly recommend that ipilimumab, like interleukin-2, be used only in centers with complete nursing and medical teams familiar with its use.

Mechanism of Action

The most reliable way to maximize efficacy and reduce adverse events with ipilimumab therapy is to determine preemptively which patients will benefit most from this agent. An adequate understanding of its mechanism of action will help in achieving this goal. Several mechanistic theories have been postulated, including reversal of inhibition of memory cell proliferation by regulatory T cells, increased immunogenicity in the presence of melanoma-specific antigens such as NY-ESO-1, and upregulation of intratumoral CD8+ cytotoxic T cells with simultaneous decrease in intratumoral infiltration of regulatory T cells.[11] If these mechanistic speculations are confirmed, therapy with ipilimumab could be targeted to patients with more robust memory T-cell proliferation, higher density of melanoma-specific antigens on tumor cells, or a more favorable intratumoral T-cell microenvironment, respectively. Elucidating the exact mechanism of action would aid in predicting which patients would benefit most while avoiding subjecting other patients to the potential life-threatening adverse events associated with therapy.

Caveats From Experience With Another Anti-CTLA-4 Agent?

As mentioned earlier, ipilimumab is the first agent to demonstrate promise in the treatment of metastatic melanoma in decades. Thumar and Kluger's review points out some of the limitations of the trial demonstrating the efficacy of this agent; however, it is also important to note that another anti-CTLA-4 agent was previously studied and subsequently abandoned. Tremelimumab underwent phase II investigation in patients with metastatic melanoma and showed early promise.[8,12-14] Despite these early indications, a phase III trial failed to show a greater survival benefit than traditional chemotherapy.[15] It should be noted that the control groups in the phase III trials of ipilimumab and tremelimumab were not comparable and thus do not allow for anything more than reference between them. Additionally, despite these antibodies having identical therapeutic targets, mechanistic differences may exist between them, making anything more than casual comparisons challenging. Nonetheless, the failure of tremelimumab to demonstrate better efficacy than traditional chemotherapeutic agents in its phase III trial should give further pause to those anxiously hoping to embrace ipilimumab as a potentially effective agent in the fight against melanoma.

Conclusions

The recent phase III clinical trial of ipilimumab provides a promising future for immune modulation in the treatment of advanced melanoma. Despite its being the first therapeutic development in decades to show an OS benefit, we caution against its widespread use until more data become available regarding which patients would benefit most. In an era of personalized medicine, it is becoming essential to tailor treatment options to those patients most likely to benefit, especially if the treatments in question are associated with frequent and sometimes life-threatening adverse events. Immunotherapy, particularly blockade of the CTLA-4 pathway, has already proven essential in the battle against advanced melanoma. However, the inherent risks of immunotherapy necessitate judicious use in appropriately selected patient subsets by well-informed clinicians and patients.

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