Improving the Therapeutic Benefits of Ipilimumab

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Currently there are only three FDA-approved drugs available for the treatment of metastatic melanoma: dacarbazine, interleukin-2, and the lesser-used hydroxyurea. None of these drugs has been shown to improve overall survival (OS). The review by Thumar and Kluger provides a well-balanced overview of ipilimumab, the first agent to demonstrate a survival benefit in patients with metastatic melanoma.[1] The response to ipilimumab is most notable for its durability, a feature rarely observed in patients with high tumor burden or in response to other systemic therapies. However, a minority of patients (10% to 15%) treated with ipilimumab meet standard criteria for radiographic response. In this commentary, we focus on the question of how we can build on the success of ipilimumab. We briefly review one area of active investigation: the combination of ipilimumab with targeted inhibitors of BRAF.

Ipilimumab is a humanized monoclonal antibody (mAb) that functions by blocking a key regulatory molecule of the immune system, CTLA-4 (cytotoxic T-lymphocyte antigen 4). The efficacy of ipilimumab as a second-line agent for the treatment of metastatic melanoma has been evaluated in a randomized, double-blind, phase III clinical trial. A total of 676 patients with unresectable stage III or IV melanoma were assigned, in a 3:1:1 ratio, to receive gp100 (peptide vaccine) plus ipilimumab at a dose of 3 mg/kg, ipilimumab alone, or gp100 alone. The median OS was 10.0 months in the patients who received gp100 plus ipilimumab, 10.1 months in those treated with ipilimumab alone, and 6.4 months in those given gp100 alone. There was no significant difference between the 2 groups of patients receiving ipilimumab. The highest rates of best overall response (complete response [CR] or partial response [PR])—10.9% (15 of 137 patients)—and disease control (CR, PR, or stable disease [SD])—28.5% (39 of 137 patients)—were seen in patients who received ipilimumab alone. Sixty percent (9 of 15) of the patients who achieved a CR or PR when treated with ipilimumab alone had durable objective responses of at least 2 years (26.5 to 44.2 months [ongoing]).[1] At present, we are awaiting results from a second randomized, double-blind phase III trial comparing the combination of ipilimumab (10 mg/kg) and dacarbazine to dacarbazine alone in the first-line setting.

Targeted inhibitors of BRAF are another promising, recent development in the treatment of melanoma. Approximately 67% of melanomas harbor mutations in the serine-threonine BRAF kinase, with the most common (80%) being a single amino acid missense nucleotide substitution (V600E) that constitutively activates BRAF and the downstream signal transduction of the MAP kinase pathway.[2] More recent studies have demonstrated that this mutation is predominantly found in the subtype of melanomas localized to skin that has not experienced chronic sun exposure.[3] Several potent BRAF inhibitors have been developed, including PLX4032 (Plexxikon; also known as RG7204, Roche), GSK2118436 (GlaxoSmithKline), and BMS908662 (Bristol Myers Squibb). PLX4032 has been shown in a phase I/II clinical trial to cause tumor regression in a majority of patients with metastatic melanoma that harbored the BRAFV600E mutation.[4] In the extension phase of the phase I trial, 32 patients with BRAF-mutant metastatic melanoma were treated with the maximum tolerated dose (960 mg twice daily) of PLX4032. A total of 26 of 32 patients (81%) demonstrated tumor regression...
based on the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0), with PRs in 24 patients and CRs in 2 patients. The median progression-free survival (PFS) was more than 7 months. A phase III study (BRAF Inhibitor in Melanoma [BRIM3]) currently underway has multiple goals: to compare PLX4032 to dacarbazine and to learn whether PLX4032 therapy will translate into an OS benefit. A notable liability of targeted inhibitors is the development, or selection, of mutations that confer resistance to the targeted agent and permit relapse of disease. Combining the impressive response rate of BRAF inhibitors with the notable durability of response of ipilimumab may be superior to treatment with either agent alone.

Genetic instability is a fundamental aspect of tumorigenesis that may contribute to resistance to targeted approaches but that is a potential gold mine of novel immune targets.[5,6] One study using genomic analysis of missense mutations in human cancer cell lines has estimated that approximately 10 novel antigens are generated as a consequence of the genetic instability of these cell lines.[7] A complementary study, which used a mathematical modeling approach, has predicted that there are tens to hundreds of unique, novel antigens in tumor cells that can be recognized by the immune system.[8] Treatment with targeted therapies, such as BRAF inhibitors, may result in tumor cell death, releasing tumor debris and liberating potential tumor antigens. Combining BRAF inhibitor therapy with ipilimumab may facilitate immune recognition of these novel tumor-specific antigens. Thus, the combination of targeted therapies and ipilimumab might enhance induction of immune responses to these novel antigens, effectively turning one drug into many. Furthermore, this combination could focus the immune system on tumor antigens, minimizing immune activation in normal tissues and consequently reducing the incidence of immune related adverse events.

There are a number of promising therapies for melanoma on the horizon, some of which were not mentioned in this commentary: KIT inhibitors, MEK inhibitors, anti-PD-1 monoclonal antibody, among others. Ipilimumab is the first drug to improve OS in patients with metastatic melanoma; however, only a subset of patients derived clinical benefit. In the future, treating patients with ipilimumab in combination with targeted inhibitors or other novel therapies may improve response rates, durability of tumor response, and survival. As we move forward in testing these combinations, additional factors, such as the immune-potentiating or immune-suppressive effects of targeted inhibitors, will have to be considered. Preclinical and clinical studies presently underway and in development will shed further light on the potential for combination therapies to build upon the foundation of successes of individual agents. The most exciting aspect of this strategy is that it is likely to be therapeutically applicable to other types of cancers.

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