Been There, Not Done That — Melanoma in the Age of Molecular Therapy
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In 1976, the detection of estrogen-receptor expression in melanomas ushered in the era of targeted therapy in melanoma, although we did not use that term back then. In 1992, Cocconi et al. found that dacarbazine plus tamoxifen provided a higher response rate and longer survival than dacarbazine, but only in women. Subsequently, whether melanoma cells express estrogen receptors was questioned, and the efficacy of tamoxifen could not be confirmed. Since then, the drug has not been used to treat melanoma. However, molecular analysis of tumors has revealed specific growth-promoting pathways in human cancers that have become targets for therapy.

BRAF is a member of the Raf kinase family, which signals from growth factor receptors on the cell surface to the nucleus. The most common mutation in BRAF (BRAF V600E) is found in 30 to 60% of melanomas. BRAF V600E constitutively activates the MAPK–ERK signal-transduction pathway, which enhances the proliferative and metastatic potential of tumor cells. Sorafenib, the first BRAF-targeted agent that has been studied in metastatic melanoma, has not shown major clinical effects in this disease and is now recognized as a weak BRAF kinase inhibitor.

In a phase 1 study, the use of the selective BRAF V600E kinase inhibitor vemurafenib (PLX4032) was associated with a response rate of 69% in patients with melanoma with tumors that harbored the BRAF V600E mutation. In this issue of the Journal, Chapman and colleagues report the results of a phase 3 study, called BRAF Inhibitor in Melanoma 3 (BRIM-3), in which patients with metastatic melanoma with the BRAF V600E mutation were randomly assigned to receive vemurafenib or dacarbazine. The treatment response was determined by the investigators. During the trial, an independent data and safety monitoring board determined that survival end points had been met, and patients who were treated with dacarbazine were permitted to cross over to receive vemurafenib. At the time of the reported analysis, the hazard ratio for death in the vemurafenib group was 0.37 (95% confidence interval [CI], 0.26 to 0.55; P<0.001), and the hazard ratio for progression-free survival was 0.26 (95% CI, 0.20 to 0.33; P<0.001). Although the adverse-events profile for vemurafenib was generally mild, dose interruption and modification were required in 38% of patients.

Melanoma, like other cancers, is a collection of heterogeneous tumors that are differentiated by means of molecular markers, and each molecularly defined subgroup will probably have a different treatment algorithm. The results of the BRIM-3 study represent a major shift in the way we think about and treat melanoma.

For this preliminary report in the BRIM-3 study, follow-up was short, and the final estimate of survival outcomes is still to be determined. Furthermore, the study used investigator-reported response, not the findings of an independent response-review board, which could bias the rates of response and progression-free survival, though not the rates of overall survival. The latter rates will be influenced by the decision of the data and safety monitoring board to allow patients to cross over to receive vemurafenib. Whether the reportedly low rate of complete response to vemurafenib (0.9%) is the true rate and whether such a response would remain durable after the discontinuation of vemurafenib is not yet known.

To put the BRIM-3 study into perspective, interleukin-2 and ipilimumab have been approved by the Food and Drug Administration as immunotherapies for metastatic melanoma. The 2-week administration of high-dose interleukin-2 produces an objective response in 16% of a highly selected group of patients and complete remission in 6% of patients, with a median duration of complete response of more than 10 years. Four doses of ipilimumab produce a median survival of 10 months (a 4-month advantage over a vaccine control group), a median progression-free survival of 11 weeks, and an objective response rate of 7% (with a rate of complete remission of 0.5%).

There are several potential long-term health consequences of BRAF V600E inhibition, which can cause paradoxical stimulation of MAP-kinase-mediated events in wild-type BRAF cells and has been suggested as a mechanism for susceptibility to nonmelanoma skin cancers in patients receiving vemurafenib. Thus, careful surveillance of pa-
tients for other cancers is warranted. Although little is known about the use of targeted adjuvant agents in patients undergoing surgery, it is now reasonable to consider testing of adjuvant vemurafenib in patients with high-risk stage II or III melanoma with the BRAF V600E mutation on the basis of the findings in the BRIM-3 study.

Mechanisms of resistance to BRAF V600E kinase inhibitors include upstream and downstream events and activation of alternative pathways that are therapeutic targets. Experience with other tumor types has shown that the use of a combination of agents that block multiple pathways has a substantial effect on both efficacy and toxic effects. Thus, the choice of the components of drug combinations must be scientifically based and tested in clinical studies.

The inhibition of BRAF V600E in mutated melanoma cells blocked phosphorylated ERK, upregulated melanocyte-differentiation antigens with resultant improved recognition by antigen-specific T cells, and did not impair T-cell function, which set the stage for combining immune therapy with BRAF V600E targeted therapy. MAPK has been implicated in the control of cell-cycle checkpoints, and MEK inhibition has been shown to enhance the effects of chemotherapy in vitro, providing a platform for combination cytotoxic chemotherapy and BRAF blockade. The benefit of vemurafenib does not seem to be adversely affected by previous treatment with other agents. Until further information is available, careful consideration of the use of immune therapy before the initiation of vemurafenib may be warranted.

The new understanding of molecular pathways changes the way we classify melanomas and influences therapy. The development of vemurafenib is an example of the translation of these concepts into clinical practice. For patients with metastatic melanoma with the BRAF V600E mutation, the availability of vemurafenib is a major defining moment that will have an important effect on survival and quality of life. Vemurafenib will be part of our therapeutic armamentarium for patients with melanoma and potentially for those with other cancers harboring BRAF V600E mutations, as well as a valuable tool for exploring new approaches to melanoma treatment.

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