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Metastatic melanoma can be cured: advances in immunotherapy and targeted approaches

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"There is no denying the importance of the identification of specific genetic alterations involved in the pathogenesis of melanoma and the therapeutic opportunities that have arisen therefrom"

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The therapeutic options for patients with metastatic melanoma have improved substantially in the last few years. The approvals of the checkpoint inhibitor, ipilimumab, and the BRAF inhibitor, vemurafenib, transformed melanoma treatment and have relegated chemotherapy to where it belongs – 'the dustbin of history' (attributed to Leon Trotsky, Petrograd Second Congress of Soviets, October 25, 1917). A recent article in *Clinical Investigation* described this 'Therapeutic Renaissance' with a focus on the 'emergence of novel targeted agents for metastatic melanoma' [1]. There is no denying the importance of the identification of specific genetic alterations involved in the pathogenesis of melanoma and the therapeutic opportunities that have arisen therefrom. The discovery of mutations in *BRAF*, *c-KIT*, *NRAS* and *GNAQ* have led to an improved understanding of melanoma cell biology, a molecular classification that now supersedes histologic classification, and the identification of the abnormally activated MAP kinase pathway as a target for effective therapy. The review described the specific inhibitors that have been developed for melanomas with *BRAF* mutations (the BRAF inhibitors vemurafenib and dabrafenib and the MEK inhibitor trametinib) and *c-KIT* alterations (imatinib). By targeting specific mutations these agents inhibit the altered cellular pathways, and vemurafenib and dabrafenib led to tumor regression in more than 50% of patients and improved survival in patients whose tumors had the *V600 BRAF* mutation [2]; trametinib also improved survival compared with chemotherapy [3]. However, responses were rarely complete and because tumors can reactivate pathways by alternate means or deploy alternate pathways to maintain their growth advantage, they universally recur and patients eventually die from progressive tumor growth. This is not just true for melanoma, but is the pattern that has emerged for targeted therapy of most solid tumors. Long-term results may improve as we better understand the pathways involved, develop agents that can target multiple steps in one pathway (i.e., BRAFi and MEKi) or use combination therapy to inhibit multiple pathways. These strategies are being tested and may ultimately lead to long-term disease control (cure); however, currently, complete remissions are rare, development of drug resistance is the rule and nobody is cured with targeted therapy. Thus, despite the excitement generated by the randomized Phase III studies showing enhanced survival in patients with metastatic melanoma who received targeted therapy [2,3], we believe results with targeted agents are inferior to the results obtained with a variety of immunotherapies because of the latter's ability to induce long-term disease control and cure of a small but significant fraction of patients [4–6].

Keywords: BRAF V600E • CTLA-4 • dabrafenib • IL-2 • ipilimumab • MEK • melanoma • T-cell immunotherapy • trametinib • vemurafenib

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We believe it is important to remember that curative therapy for patients with metastatic melanoma, that is, IL-2, has been 'around' since the 1980s and was approved by the US FDA in 1998 [4]. IL-2 induces response rates of 15–20% with complete-response rates of 5% or more. In total, 70% of complete responders remain alive and free of disease at 15 years, as do 15% of patients who achieved a partial response. There are patients who have remained disease-free for >25 years. Despite these excellent, durable results, it is estimated that only 10% of eligible patients in the USA receive IL-2 [7]. This is probably a consequence of the complexity and toxicity of therapy; however, when curative therapy is possible, surely both of these obstacles can be overcome?

Attempts to improve the antitumor effects of IL-2, to reduce its toxicity and to identify pretreatment characteristics or biomarkers that could identify patients most likely to benefit from IL-2 therapy generally have not been successful. We recently reported a pilot study in which the addition of stereotactic body radiotherapy to a limited number of metastatic sites combined with IL-2 led to a response rate of 67% in a limited number of patients with metastatic melanoma and renal cell cancer [8]. A greater frequency of $CD4^+$ effector-memory T cells was observed at baseline in responding patients, which if confirmed might be a useful biomarker for patient selection. The addition of a melanoma peptide vaccine to IL-2 was reported to increase the response rate and progression-free survival significantly [9], but since the peptide and adjuvant used in this study are not available for routine clinical use this result has not altered standard high-dose IL-2 therapy.

Immunotherapy has again attracted attention – this time because of the approval of the checkpoint inhibitor – ipilimumab (anti-CTLA-4) – which improved survival of patients with metastatic melanoma [5,6]. Although IL-2 has never been shown to improve survival, there are similarities between it and ipilimumab. Response rates are low (10–20%); complete responses are uncommon, but responses can be very durable [10]. One study reported that 11% of patients were alive 56–101 months after treatment with ipilimumab [11].

The presumed ultimate mechanism of action of high-dose IL-2 and ipilimumab is the activation of tumor-reactive T cells. Rosenberg and his colleagues have performed a series of studies that demonstrated the efficacy of adoptive transfer of tumor-reactive T cells. Cell transfer therapy with autologous T cells obtained directly from the tumor (tumor-infiltrating lymphocytes) can induce durable (>3 years) complete remissions in melanoma patients who have previously failed IL-2 therapy [12]. The Surgery Branch and others have attempted to improve adoptive immunotherapy using genetically modified T cells derived from the peripheral blood to express either a traditional tumor-reactive T-cell receptor or a chimeric antigen receptor, which contains genes encoding the variable regions of the heavy and light chains of antibodies with signaling molecules from T cells (e.g., CD3ζ, CD28, CD137) [7]. These approaches have shown early evidence of clinical efficacy.

When the clinical results of immunotherapy trials are considered together, a pattern emerges. The overall quantity of responses appears to be lower than the best results observed with targeted therapy; however, not all patients progress and the survival curves seem to plateau, indicating a superior quality of responses that result in a small percentage of patients with metastatic melanoma who are cured. A comparison of idealized survival curves for immunotherapy with those of targeted therapy shows an apparent early benefit to targeted therapy, which is eventually overtaken by the immunotherapy group because of the development of drug resistance to targeted therapy and the durability of remission following immunotherapy [13]. These observations led us to our algorithm for the management of patients with metastatic melanoma. Regardless of their tumor's *BRAF* mutation status, we recommend enrollment of patients on an IL-2-based clinical trial if eligible, or standard high-dose IL-2. If patients are not eligible for high-dose IL-2 we recommend ipilimumab-based therapy (on trial if possible), again regardless of their mutation status. Initial therapy with the BRAF inhibitor is generally reserved for patients whose tumors have V600 mutations and have progressive disease in need of a rapid response, are eligible for a clinical protocol or who express a preference for oral therapy. This is based on our reading of the literature and personal experience indicating that an immunotherapy-induced tumor regression has a significantly greater chance of leading to the cure of our patients. Of course, along with everyone else in the field, we are very excited about the potential efficacy of the combination of the most effective targeted and immunotherapy regimens. The next decade should be very exciting as we learn the optimal sequence and combination of agents, with the goal not just to induce tumor regression but to cure melanoma.

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