

Metastatic melanoma—challenges for the community oncologist

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The outlook for patients with advanced melanoma is bleak. Patients with stage IV melanoma have a median survival of 6–9 months,^{1–3} with 5-year survival rates of 1%–2%.^{1,4} An estimated 8,000 Americans will die of melanoma in 2008.^{1,5} Many of these patients are young, with a median age of ~50 years, and otherwise healthy.^{1,5} This loss of life represents a societal burden in excess of the actual numbers. Although melanoma is the ninth most common cancer in the United States,^{1,6} it ranks second among solid tumors in terms of years of productive life lost.

Common treatment approaches have included cytotoxic chemotherapy; interleukin-2 (IL-2)-based immunotherapy; and combinations of chemotherapy and immunotherapy (so-called biochemotherapy). Although some treatment approaches, most notably, high-dose IL-2 immunotherapy, have been shown to produce extremely durable tumor responses in a small percentage of patients,^{4,7,8} no treatment approach has shown a reproducible survival advantage in phase III trials.⁷ There is a critical need for new treatment approaches for patients with advanced melanoma.

Recent advances in the understanding of melanoma biology, immune regulation, and tumor-induced immune suppression are the foundation for new opportunities to improve therapeutic outcomes for patients with advanced melanoma. Studies of melanoma biology have uncovered critical factors that are important for melanoma cell survival, including activating mutations in *BRAF*, which occur in > 50% of melanomas; mutations in *KIT*, the gene encoding the c-Kit receptor, which are common in acral lentiginous and mucosal primary melanomas; overexpression of vascular endothelial growth factor, which drives tumor angiogenesis; and an assortment of factors that limit the apoptotic effects of various cytotoxic chemotherapy agents. The simultaneous development of therapeutic agents that

selectively target these pathways, including inhibitors of raf signaling, such as sorafenib (Nexavar); c-Kit signaling, such as imatinib (Gleevec) and dasatinib (Sprycel); angiogenesis, such as bevacizumab (Avastin); and agents that restore apoptosis, such as the Bcl-2 binder oblimersen (Genasense, G3139) and the heat shock protein 70-inducer elesclomol (STA-4783), has enabled clinical testing of targeted treatment strategies in patients with melanoma.

Studies of immune regulation and mechanisms of tumor-induced immune suppression have identified specific obstacles to effective immunotherapy for melanoma. They include the physiologic downmodulation of the immune response through the upregulation of the expression of molecules such as CTLA4 on the surface of activated T cells. Mechanisms identified for tumor-induced immune suppression have included stimulation of CD4⁺ CD25⁺ T-regulatory cell production, which limits inhibition of T-cell receptor signaling, and melanoma-cell expression of B7H1 (PDL1), which serves to restrict the cytolytic function of tumor-infiltrating T lymphocytes.

These biologic discoveries are clinically relevant because they underlie the identification and/or creation of therapeutic agents that directly or indirectly target these immunomodulatory pathways and potentially enable restoration of effective, tumor-specific immune destruction. Agents under study include antibodies directed against CTLA4 (ipilimumab [MDX-010] and tremilimumab) and those that block the effects of tumor-induced B7H1 expression (anti-PD1 antibody). In addition, novel cytokines, such as IL-15, and antibodies that selec-

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tively augment cytotoxic T cells, such as CD137, are promising.

Other efforts have attempted to selectively deplete T-regulatory cells through lymphodepletion with non-myeloablative chemotherapy coupled with tumor-specific adoptive immunotherapy or the administration of pharmacologic agents that selectively poison CD25^{high}-expressing T-regulatory cells, such as denileukin diftitox (Ontak). There also is a focus on strategies that will eliminate the immunosuppressive effects of T-regulatory cells through administration of antibodies that block the immunosuppressive cytokines, such as transforming growth factor-beta (TGF- β) or IL-10, that are typically released by these cells or the use of Toll-like receptor agonists that directly regulate the suppressive activity of T-regulatory cells.

The articles in this *Community Oncology* supplement highlight current and future opportunities for melanoma therapy. In the first article, Dr. Michael K. K. Wong describes current advances in the understanding of melanoma biology and tumor immunology that underpin current therapeutic strategies. In the second article, Dr. Mario Sznol describes preliminary results of the application of novel immunotherapeutic strategies in the treatment of advanced melanoma. Finally, Dr. Keith T. Flaherty describes the use of various targeted therapies in this patient population.

Although many of the clinical results are preliminary, and at best partially effective, they highlight strategic approaches and residual obstacles that will be critically important to the development of successful therapies for patients with metastatic melano-

ma. True benefit most likely will require the use of combination therapy. For tumor-targeted therapy, such combinations conceivably would involve agents that inhibit critical pathways within a specific tumor cell and resultant compensatory pro-survival pathways. For immunotherapy, such combinations could involve agents that block immune downregulation and inhibit various forms of tumor-induced immune suppression. In addition, vaccines could be added to focus the induced immune response against the tumor rather than against various host organs.

Melanoma represents more than a single disease. For the full potential of these novel treatment approaches to be realized, the tumors and patients best suited to respond to certain therapies must be identified. For targeted therapies, it will be important to restrict treatment to tumors that express or are dependent on the particular therapeutic target and, in the context of drug development, to ensure that the treatment effectively blocks the desired target through the use of on-treatment tumor biopsies or the assessment of surrogate markers. Only in this way can it be determined whether a negative result is the consequence of an inadequate choice of target or an ineffective delivery of the targeted therapy. For immunotherapy, it will be crucial to identify the tumor types most responsive, perhaps by analysis of tumor gene or protein expression, and the patients with potentially immune-responsive phenotypes (eg, those with a propensity to develop autoimmunity or a diminished immune-regulatory function). Finally, studies of these new treatment approaches and how best to apply them

are necessary for true therapeutic advances to become available to patients with this devastating disease.

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