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Latest Advances in Chemotherapeutic, Targeted, and Immune Approaches in the Treatment of Metastatic Melanoma

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Abstract

Melanoma is the most dangerous form of skin cancer owing to its metastatic potential and is an important public health concern. The melanoma incidence has been increasing worldwide. Although potentially curable when diagnosed early, metastatic melanoma carries a poor prognosis. Until recently, systemic therapy for metastatic melanoma was ineffective, but the recent successes in the development of new therapies for metastatic melanoma, such as mitogen-activated protein kinase (MAPK) pathway inhibitors, anti–cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), and programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway blocking antibodies, as well as combination strategies of cytotoxic chemotherapy and inhibitors of angiogenesis, have all yielded promising results, changing the continually evolving landscape of therapeutic options for patients with this disease. The aim of this review was to summarize the evolution of and recent advances in the treatment of metastatic melanoma. Therefore, we conducted a comprehensive PubMed search between January 1, 1960, and February 1, 2014, using the search term *melanoma* or *metastatic melanoma* combined with terms such as *chemotherapy, immunotherapy, CTLA-4, PD-1, PD-L1, adoptive T cell, targeted therapy, MAPK, molecular biology,* and *survival*.

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The incidence rates of melanoma have been rising for the past 30 years, and the malignancy currently ranks as the fifth and sixth most common cancer in men and women, respectively, in the United States.[1] In 2014, approximately 76,100 new cases of melanoma (43,890 in men and 32,210 in women) will be diagnosed, and an estimated 9,710 deaths will occur from this disease.[1] As such, the lifetime probability of developing melanoma in the United States is now estimated to be 1 in 37 for men and 1 in 56 for women, considerably higher than just a few decades ago (1 in 600 for both sexes combined in 1960).[1] Given the high incidence rates in young adults and the large number of deaths, melanoma results in significant years of potential life lost and lost productivity.[2] Although a few patients present with distant metastases at diagnosis, approximately one-quarter to one-third of all patients with melanoma will eventually experience recurrence and development of more advanced-stage disease. It is currently estimated that there are nearly 1 million melanoma survivors living in the United States.[3-5] Although melanoma accounts for only 4% of all dermatologic cancers, it is responsible for 80% of skin cancer deaths.[6] Melanoma is potentially curable when diagnosed early, but, historically, the prognosis of patients with metastatic disease has been poor, with median survival of less than 1 year and overall 5-year mortality close to 90%.[7] For almost 40 years before the approval of ipilimumab in 2011, no single drug or combination of drugs demonstrated a significant effect on the overall survival (OS) of patients with metastatic melanoma.[8] However, recent research in the fields of tumor biology and immunology has led to the development of new targeted and immunotherapeutic agents that prolong progression-free survival (PFS) and OS in patients with advanced melanoma. This review provides an overview of the latest advances in understanding the biology of melanoma and the treatment options for patients with advanced/metastatic disease. The present review is based on a comprehensive PubMed search between January 1, 1960, and February 1, 2014, using the search term *melanoma* or *metastatic melanoma* combined with terms such as

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chemotherapy, immunotherapy, CTLA-4, PD-1, PD-L1, adoptive T cell, targeted therapy, MAPK, *molecular biology,* and *survival.*

ARTICLE HIGHLIGHTS

- The incidence of melanoma has been rising for the past 3 decades.
- Historically, metastatic melanoma has had a dismal long-term survival rate due to an absence of effective treatment.
- Substantial recent research in the melanoma field has changed the treatment landscape, with 4 new drugs being Food and Drug Administration approved for advanced melanoma in the past 2 years.
- Immunotherapy is shown to induce durable responses in select patients with metastatic melanoma. A striking feature of immune checkpoint inhibitors is the impressive duration of response in select patients, noted initially with ipilimumab and now with the newest programmed cell death protein 1 blocking agents.
- Targeted agents are effective in inducing responses in select patients with metastatic melanoma carrying specific genetic mutations; however, resistance develops in almost all patients.
- Combination treatment strategies that include chemotherapy, targeted agents, and immunotherapy will transform the clinical approach to this disease and promise to improve patient survival in the coming years.

ROLE OF IMMUNOTHERAPY

The interplay between tumors and their immunologic microenvironments is complex, dynamic, and difficult to decipher; it is, however, of pivotal importance for understanding the functionality and efficacy of immunotherapeutic drugs. The recent molecular characterization of various mechanisms mediated by cancer cells to evade immune detection has sharpened the focus of cancer immunotherapy to develop targeted molecules capable of manipulating the tumor microenvironment in favor of an antitumor immune response. The increased immune specificity of such agents has resulted in better tolerability and a more favorable adverse effect (AE) profile than that of high-dose interleukin (IL)-2, the first nonspecific immunomodulator approved for the treatment of advanced/metastatic melanoma.

Individual human tumors harbor a multitude of gene mutations, the products of which are potentially recognizable as foreign antigens.[9] Many, however, are mistakenly identified as "self" by the host immune system, thus aiding cancer cell escape from immune detection and allowing tumors to survive and grow. Indeed, escape from immune control is now viewed as one of the hallmarks of cancer.[10]

There is increasing evidence indicating that some patients with cancer mount an adaptive immune response specifically directed against antigenic proteins expressed in their tumors. T cells secrete cytokines, which, in turn, generate acute inflammation that results in expansion of cytotoxic T cells, tissue destruction, and the potential control or even elimination of malignancy.[11] Unfortunately, T-cell functionality is impeded in cancers because the tumor milieu contains suppressive elements, including regulatory T cells and myeloid-derived suppressor cells; soluble factors such as IL-6, IL-10, vascular endothelial growth factor (VEGF), and transforming growth factor β; and ligands for co-inhibitory receptors that down-regulate cytotoxic T cell activity.[12] Signaling via co-inhibitory receptors, or "checkpoint molecules," such as cytotoxic T-lymphocyte—associated antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1), contribute to the down-modulation of $CD8^+$ and $CD4^+$ effector T-cell function, making these receptors logical targets for drugs such as ipilimumab (anti—CTLA-4 monoclonal antibody) and nivolumab and lambrolizumab (anti—PD-1 monoclonal antibodies). Melanoma cells have been found to express high levels of programmed cell death ligand 1 (PD-L1) (B7-H1) protein, a ligand for PD-1 receptor.[13]

ROLE OF TARGETED THERAPY

It is becoming increasingly clear that melanoma, similar to other cancers, arises from complex molecular aberrations in genes that alter critical signaling pathways that control cell proliferation, differentiation, and death. Approximately 50% of melanomas contain mutations that activate the RAS/RAF/MEK/ERK (mitogen-activated protein kinase) pathway, making it a prime therapeutic target (Figure 1).[14-16] The most common *BRAF* somatic mutation in cutaneous melanoma, particularly those without chronic sun damage, results from substitution of glutamic acid for valine at amino acid 600 in the gene encoding the serine-threonine protein kinase *BRAF V600E*.[14] The second most common *BRAF* mutation *is BRAF V600K* substituting lysine for valine,