Recent Advances in the Treatment of Melanoma

In 2013, more than 70,000 new cases of cutaneous melanoma will be diagnosed.1 Fortunately, most of these cases will be early-stage disease, which is associated with excellent survival rates. Patients with stage I melanoma have 5- and 10-year survival rates of 97% and 93%, respectively.2 The diagnosis of advanced stage (IIIB, IIIC, and IV) disease, although representing a minority of patients with melanoma, continues to be associated with a relatively poor prognosis. However, the last 3 years have been remarkable in terms of new therapies and FDA-approved treatments for patients with advanced disease. Targeted therapies such as vemurafenib, a potent selective BRAF inhibitor, as well as immunotherapies like ipilimumab, an anti-CTLA-4 antibody, have revolutionized melanoma management and provided hope for patients with advanced disease. With the approval of four new therapies (ipilimumab, vemurafenib, dabrafenib, and trametinib) for stage IV disease, we have seen more FDA-approved therapies for metastatic melanoma in the last 3 years than we saw in the previous 2 to 3 decades combined. It truly is an exciting time in melanoma management, with effective new therapies currently available and possibly even more efficacious therapies in late-stage clinical trial development. We are now in an era where determining the appropriate control arm of a clinical trial is difficult as new therapies are quickly replacing the old standard of chemotherapy. Given all of the advancements, patients are surviving longer. Therefore, defining survivorship issues and developing accurate follow-up guidelines will be needed.

This issue of Cancer Control details the research behind these promising new discoveries that continue to advance the treatment of this challenging but now more manageable malignancy.

At the start of the issue, Dr Etzkorn and colleagues discuss the “Mole Patrol,” a free skin cancer screening program initially developed in 1994 by the faculty at Moffitt Cancer Center in Tampa, Florida. Screeners at these events primarily consisted of volunteer physicians (dermatologists, surgical oncologists, and dermatopathologists) but also included nurse practitioners and physician assistants who worked in dermatology or cutaneous oncology practices. The “Mole Patrol” screened over 5,000 individuals between 2007 and 2010, quite a feat for a community-based screening program. The authors report on the presumptive diagnoses made at these events, as well as the associated demographic and risk factors. Nonmelanoma skin cancer is associated with male sex, age ≥ 50 years, personal history of skin cancer, lower skin phototype, and increased chronic sun exposure based on screening physical examination characteristics. The yield of presumptive atypical pigmented lesions was increased in participants < 50 years, supporting that this population may benefit from skin cancer screening with their dermatologists or primary care physicians.

In the next article, Dr Delman and coauthors discuss an important new advance in the surgical management of stage III melanoma metastatic to the inguinal region. Their description of the technique and results of videoscopic inguinal lymphadenectomy (VIL) groin dissection is inspiring. The notion that surgeons can reduce wound complications, decrease hospital length of stay, and still potentially achieve a similar oncological outcome with a minimally invasive approach to groin disease may revolutionize how patients and surgeons alike approach sentinel node-positive disease in the groin. We eagerly await the results from a larger series as well as an update on the intermediate and long-term oncological outcomes from this revolutionary minimally invasive surgical approach to groin nodal disease.

The biology behind melanoma mutagenesis has directly led to the new drugs for metastatic melanoma. Dr Bello and colleagues provide a thorough review of several signaling pathways in melanoma as well as the mechanism of aberrant signaling and malignant transformation with the acquisition of BRAF, NRAS, KIT, GNAQ, and GNA11 gene mutations. They methodically describe how the newer FDA-approved agents, as well as agents in clinical trial development, are used to target these various signaling pathways in patients with melanoma. Specifically, the authors review the MAPK and PI3K pathways as well as the numerous targeted compounds in clinical use, and they describe the impressive clinical responses seen with these agents, which have helped to revolutionize melanoma treatment.

Dr Kudchadkar and coauthors then expand upon the Bello article by reviewing the agents that are available and in trial for the treatment of metastatic melanoma. They focus on the FDA-approved agents, while also discussing the therapeutic potential of programmed death-1 (anti-PD-1) antibodies and combination signal transduction inhibitors. The pivotal trials leading to the approval of vemurafenib and
ipilimumab are discussed. In addition, the authors highlight the recent advancements in newer anti-PD-1 and anti-PD-L1 immunotherapies.

Building on the concept of immunotherapy, Dr Phan and coworkers discuss the role of adoptive cell T-cell transfer (ACT) with autologous tumor-infiltrating lymphocytes (TILs) and the encouraging results from clinical trials using TIL harvest and transfer as therapy for patients with metastatic melanoma. Impressive results have been seen with ACT therapy; objective responses have been seen in 40% to 72% of patients with metastatic melanoma, with up to 40% of those patients experiencing complete responses that are long-lasting. The authors discuss the emerging techniques to engineer T-cell receptors or chimeric antigen receptors using lymphocytes from peripheral blood, and they report how that therapeutic alternative may increase the already impressive results seen with the current ACT therapies. Ongoing clinical trials are also combining the targeted therapy (vemurafenib) or immunotherapy (ipilimumab) with ACT to capitalize on the high response rates seen with each individual therapy and hopefully achieve a synergistic effect from the combination.

The development of brain metastases from melanoma is usually associated with a poor prognosis and poses a major therapeutic challenge to clinicians. Two current approaches are associated with the best control rates: stereotactic radiosurgery or resection of isolated brain metastases. These therapies offer the best chance for prolonged disease-free survival. Dr Kenchappa and colleagues discuss the biology behind the development of brain metastases from melanoma, the current limitations in treating these metastases with systemic therapies, and some promising ongoing research that is dedicated to the treatment of melanoma metastases in the brain. Much of this research also capitalizes on the effective systemic therapeutic strategies that have emerged, including targeted agents, immunotherapy, and ACT therapy.

Lastly, an article by Dr Deneve and coauthors strays from the melanoma theme but discusses a presentation of a rare sarcoma – cutaneous leiomyosarcoma (LMS). As a single-institution series of 38 patients with cutaneous LMS, the authors discuss their experience in treating this uncommon malignancy via a multidisciplinary approach at a high-volume cutaneous and sarcoma program. Although LMS is usually a low-grade tumor that does not often metastasize, the authors describe their workup and treatment algorithm, as well as their patient outcomes.

Together, these articles provide a comprehensive overview of the latest surgical and medical advancements in metastatic melanoma and in leiomyosarcoma, and they also provide a glimpse into what advancements are on the horizon.

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