

Melanoma: Promising New Discoveries and Treatment Modalities for Difficult Clinical Scenarios — Part II

Melanoma continues to increase in incidence, rising more than 600% in the United States in the last 50 years. Fortunately, more often than not, it is discovered in early stages and is easily treatable with good long-term survival rates. Patients with stage I melanoma have survival rates of more than 90% at 5 years. This statistic may even improve once the new American Joint Committee on Cancer (AJCC) staging system for melanoma (version 7) is released later this year.

One year ago, in the July 2008 issue of *Cancer Control*, we presented a series of papers discussing the various existing treatments for melanoma as well as some promising new discoveries and treatments on the horizon. Although there are many ongoing trials for the treatment of all stages of melanoma, there is still much room for improvement of response rates and overall survival rates, especially for those with late-stage disease.

This issue of *Cancer Control* builds on our presentation in the July 2008 issue by furthering the discussion and presentation of approaches to difficult clinical scenarios in melanoma as well as some promising new approaches on the treatment horizon for this mysterious disease.

Epigenetics in cancer refers to changes in phenotype or gene expression in cancer cells without changing the underlying DNA structure. Such epigenetic changes result in aberrant gene regulation through mechanisms such as DNA methylation (either hyper- or hypomethylation), histone deacetylation, resistance to apoptosis, and changes in microRNA function. These epigenetic changes and the resulting gene regulation disturbances have been a focus of some cancer researchers interested in using these mechanisms as targets of pharmacologic manipulation. Dr Riker and colleagues discuss the ongoing efforts, investigations, and results of epigenetic research in cancer and particularly melanoma. Furthermore, the authors discuss the promising ongoing studies focusing on the current clinical efforts and future implications of targeted therapy in epigenetics.

Specific tumor molecular biomarkers have a role in therapeutic intervention as well as diagnostic and prognostic information. As research progresses in the biomarker arena, researchers can focus on developing more targeted therapies specific for individual tumor profiles/biomarkers and also work toward improving better prognostic models using specific tumor antigen expression or serologic concentration of melanoma-specific biomarkers. Dr Ugurel and coworkers review

the role of biomarkers in melanoma, both tissue-based and serologic, as well as their prognostic and therapeutic properties. Since melanoma is a highly antigenic tumor, these specific biomarkers, both serologic and primary tumor-associated, may have great implications in both prognostic modeling and therapeutic interventions. It is likely that a combination of therapy targeted to specific biomarkers, therapy directed to epigenetic markers, and immunomodulation will all play a concurrent role in the treatment of advanced melanoma.

While melanoma is a rare diagnosis in the pediatric population, accounting for 1% to 4% of all melanomas and 1% to 3% of all pediatric cancers, its incidence in this age group is rising. Drs Mills and Messina conducted an extensive review of the literature and discuss the epidemiology, risk factors, diagnosis, and survival of this rare disease. What is apparent from their paper is that pediatric melanoma patients, despite having a higher incidence of positive sentinel node disease (stage III disease), have survival rates that are similar to adults. This interesting fact can potentially be tied in to the specific epigenetics and biomarkers in pediatric melanoma that may create a certain molecular signature pattern. This specific pattern can then be used to predict prognosis and response to treatment as well as specific targeted therapeutic options in this population. In their discussion of genetic mechanisms, the authors point out that previous studies have found that loss of heterozygosity of tumor DNA is higher in the pediatric population than in adults. Higher frequencies of 11q23 allelic loss are seen in the pediatric population with melanoma along with a high frequency of microsatellite instability, all potentially leading to a specific role in the pathogenesis of melanoma in pediatric patients.

The standard of care for staging the clinically negative regional nodal basin after a diagnosis of primary cutaneous melanoma is to perform a sentinel lymph node biopsy (SLNB) at the time of wide local excision of the primary tumor. Dr Phan and colleagues present a review that examines the role, rationale, and indications for an SLNB. They specifically address its role in thin melanomas (< 1.0 mm) and the findings of the pivotal Multicenter Selective Lymphadenectomy Trial I (MSLT-1). The authors also provide insight into some of the arguments against SLNB, and they include a discussion on the fact that an SLNB provides important prognostic and accurate staging data and can be performed with minimal morbidity, ultimately identifying node-negative

patients who would not benefit from a completion node dissection, thus are spared the addition of adjuvant interferon systemic therapy.

Melanoma has a propensity to metastasize to the draining regional nodal basin. These major nodal basins are the cervical, axillary, and inguinal nodal basins. While the majority of node dissections are well tolerated with limited morbidity, most long-term morbidity is caused by lymphedema occurring in the arm or leg after a complete node dissection of the axillary or inguinal nodal basins. The incidence of lymphedema is relatively low, but it can be disabling, especially if it develops in the leg or if it is severe. Other acute morbidity of node dissections includes infection, wound dehiscence, and seroma formation. Dr Sarnaik and coworkers review the etiology and incidence of lymphedema and discuss pre- and postoperative measures that can be used to limit the acute and chronic morbidity resulting from completion inguinal lymphadenectomies.

The development of brain metastases in melanoma carries a poor prognosis. Nearly 75% of patients who die of melanoma will harbor brain metastases. Dr Sloan and coauthors discuss the potential therapies available for this difficult clinical situation. Stereotactic radiosurgery, open surgical resection, whole brain radiation, combination chemotherapy, immunotherapy, and biochemotherapy have all been used in the treatment of brain metastases from melanoma. The authors describe the results of each modality and some combination treatments with respect to melanoma brain metastatic disease.

While few new treatments have been developed for melanoma and only a handful of new drugs have been approved for this disease by the US Food and Drug Administration over the last decade, significant improvements in the outcome for patients with melanoma will likely stem from an improved understanding and management of the disease, as evidenced in the six articles herein. Better tools and biomarkers to predict the outcome for patients with early-stage disease, enhanced imaging modalities, improved supportive care, and more aggressive management for pediatric patients and for patients with brain metastases, all described above, will likely affect the survival of patients with melanoma. Newer developments in the fields of targeted therapy and immunotherapy for melanoma are rapidly coalescing into phase I and II clinical trials that appear promising. The next time melanoma is reviewed as a topic of importance for *Cancer Control*, we hope to report on the results of early trials with up to a half-dozen promising agents that may for the first time have a significant impact on the clinical course of patients with stage IV melanoma.

Now to a different subject. There is widespread agreement that sociocultural values, beliefs, and attitudes markedly influence research and practice in cancer prevention. Unfortunately, the study of sociocultural con-

structs in cancer screening research among African Americans reported by Dr Deshpande and colleagues reveals that these constructs are seldom clearly defined, and the sources and psychometric properties of sociocultural measures are rarely included in the literature. Clearly, a common language and a standardized set of measures for sociocultural constructs need to be developed if different research studies are to be effectively compared. Sadly, this provocative article is the last of the series "Cancer Culture and Literacy," a journal feature since July 2006. We thank Dr Cathy Meade for her outstanding leadership in both conceiving and fostering this series that has stimulated interest in and, hopefully, action on many critically important but often-overlooked factors in effective cancer prevention, early diagnosis, and care.

We hope you will both enjoy and benefit from reading this issue of *Cancer Control*.

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