

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

In 2008, almost 70,000 new cases of invasive melanoma will be diagnosed in the United States, according to Surveillance, Epidemiology and End Results (SEER) database records. Over 7,500 people will die of the disease in the same year. The incidence of melanoma has risen so dramatically over the past 50 years (by almost 620%) that no other solid or blood malignancy comes close to it in increased incidence. Melanoma incidence is highest in white, elderly (over age 65) males, with white elderly females coming in as a close second when adjusted for age and race. The fortunate aspect of this dramatic increase in incidence is that more melanomas are being diagnosed at earlier stages where they are more treatable and curable. The systemic treatment modalities that are available today for melanoma are promising (immunomodulatory-targeted therapies, angiogenesis inhibitors). However, we still have a long way to go before we as clinicians and researchers make a dent in the overall treatment of this deadly disease.

It is increasingly clear that the activation of oncogenes drives the neoplastic process. Melanoma is no exception, and it has been shown that mutations in the BRAF and Ras genes occur in over two-thirds of melanoma tumors. One line of inquiry taken by Dr Messina and colleagues is to focus on the signal transducer and activator of transcription (Stat) proteins in melanoma. Their paper describes that while no Stat-3 activation was found in benign melanocytic lesions or in normal skin melanocytes, Stat-3 was activated in a large percentage of melanoma tumors. They also discuss the interferon receptor, which signals through this pathway and shows presence of the interferon receptor on melanoma metastasis, providing direct evidence that this may be a mechanism for interferon action in melanoma. The Stat pathway can be added to the growing list of therapeutic pathways in melanoma.

The availability and ease of profiling of thousands of genes and even entire genomes have opened up the previously mysterious process of melanoma progression to the sunlight. Dr Ren and associates review the voluminous data gathered by gene analysis, expressed RNA analysis, micro-RNA analysis, and epigenetic methods to present a fascinating glimpse into this. They show from their own studies that overexpression of many cell cycle and tumor-promoting genes and reduced levels of adhesion genes occur at a critical transition point where a melanoma changes from intermediate to thick. This paper is an interesting review of

current data in a field that is likely to transform how we treat melanoma in the future.

One particularly difficult clinical situation is the surgical treatment of melanoma in patients with heavily sun-damaged skin. The difficulty is two-fold in this situation. First, diagnosis in a background of severely sun-damaged skin can be difficult under the microscope, especially if seen on frozen section where a background of melanocytic hyperplasia may obscure the true borders. Lentigo maligna (LM) is a subtype of noninvasive pigmented dysplasia that may progress to melanoma in situ (MIS), and then to invasive melanoma (lentigo maligna melanoma, LMM), and it is sometimes difficult to pathologically differentiate between LM and MIS unless examined under the microscope by an expert dermatopathologist. Secondly, LM and LMM (as well as MIS) are typically found on chronically sun-damaged skin on the head and neck of elderly patients.

Half-centimeter margins are standard and part of the National Comprehensive Cancer Network (NCCN) guidelines for the surgical management of MIS. This presents a surgical challenge since most often these lesions are on the face where extensive surgery can be disfiguring and cosmetically displeasing. Dr Clark and coworkers discuss this difficult situation and present their experience using a staged contoured approach to assessing surgical margins and then excising the central pigmented lesion once the margins are cleared. With their modification of earlier-described procedures (the square procedure as described by Johnson et al¹ at the University of Michigan in the late 1990s) and the use of frozen sections and immunostains coupling with Mohs micrographic surgery, the authors present a rational, rapid, tissue-sparing approach to a difficult clinical scenario that is all too common in everyday practice.

Melanoma is such a heterogeneous disease with variable biology, it appears that no two cases are alike. This dictum can be directly applied to those patients with in-transit metastases. Why do some patients with intermediate-thickness melanomas have negative sentinel nodes while others matched for age, gender, and primary tumor pathologies have positive sentinel nodes? Why do these same patients have what seems to be random chances of developing in-transit metastases? The answer must lie in the biology of the disease. If there are 70,000 or so cases of melanoma expected in 2008, half of which will be on the extremities (35,000) and then anywhere from 3% to 10% of those cases

(based on the literature) have the propensity to develop in-transit metastases, we have a real clinical problem for 750 to 3,500 patients per year. In-transit metastases can be the harbinger of distant dissemination, and they can be painful, bothersome, and even limb-threatening if bulky, fungating, or juxtaposed to neurovascular bundles. The gold standard is surgical resection if the entire lesion or lesions can be resected. Other potential treatment modalities for those lesions that are too numerous or too widespread to be resected are systemic chemotherapy, radiation, local injections, hyperthermic isolated limb perfusion (HILP), or the minimally invasive counterpart to HILP, the isolated limb infusion (ILI). Dr Gimbel and colleagues present the various potential treatment modalities and discuss the published response rates as well as toxicities associated with these modalities. HILP and more recently ILI are staples in the management of in-transit metastases located on the extremities. As a minimally invasive and less morbid treatment modality than HILP, ILI has received a lot of interest in the United States since its description by Thompson et al² from the Sydney Melanoma Unit in the late 1990s. These two modalities are extensively discussed, and the most recent data on efficacy are provided.

Melanoma is a disease that, like all cancers, should be approached via a true multimodality approach by a multidisciplinary team. The role for adjuvant radiation for regionally metastatic melanoma has not been clearly defined, and its use based on disease status may differ between medical centers. The addition of radiation after surgery to regional nodal basins can have devastating long-term side effects such as lymphedema. Additionally, radiation therapy after a node dissection is tolerated differently when given to the cervical nodal basins vs the axillas or the groin nodal basins. In a thorough review of evidence-based publications and clinical trials, Dr Berk outlines the role and use of radiation in the management of melanoma as well as its use in the management of unresectable primary cutaneous and mucosal melanomas.

Unfortunately, once classified as stage IV disease, the treatment for melanoma is largely unsuccessful. The gold standard is surgical extirpation if the lesions can be safely and entirely resected; this offers the best chances for overall survival. Systemic chemotherapy is not very efficacious in most cases, with response rates of up to 20% in most published series. Radiation therapy has a role in the treatment of bony and brain metastases, especially for palliation of symptoms. Dr McLoughlin and coworkers provide a thorough description on the management and available treatment modalities for limited and symptomatic stage IV melanoma. Covering surgical, radiation, and chemotherapy treatment options, they detail the published reports on successful management and palliation of stage IV melanoma. The authors con-

clude that with multidisciplinary planning and team approaches to stage IV melanoma, along with evaluations including physical examinations coupled with staging scans such as PET/CT scans and brain MRIs, there can be long-term survivors who will benefit from aggressive surgical intervention and complete resection of isolated and limited metastatic melanoma.

While melanoma is more common among Caucasians than Hispanics or African Americans, it does indeed occur in both these populations. Because of the low index of suspicion in the medical community and these minorities, diagnosis is often delayed, resulting in advanced disease at the time of presentation. Dr Rouhani and associates develop these points and also make a case for self-examinations and skin checks among all populations, including minority populations.

While melanoma has a well-deserved notoriety for being treatment resistant and aggressive, we are beginning to see possibilities for new advances in genetics and molecular biology to help us make better prognostic judgments and open up some novel targets for drug therapy. The use of Src-Stat pathway inhibitors is being explored in clinical trials based in part on the data described by Dr Messina and colleagues. The use of large-scale genetic analysis on melanoma has identified a crucial interval in the progression of melanoma, at a point where the depth of the melanoma transitions from intermediate to deep (1 mm to 4 mm vs > 4 mm) where many genetic changes that are typical of metastatic melanoma occur. Some of the clinical management challenges resulting from advanced disease are the focus of the other papers including the emerging field of ILI. The challenges of dealing with this difficult malignancy remain, and one area where we need to do more is increasing awareness of melanoma among Hispanics and African Americans.

Following directly on this note, our *Cancer, Culture and Literacy* section includes two related articles that describe research in progress for another special group — American Indians in the Northern Plains — who experience some of the highest cancer mortality in the nation. Dr Petereit and colleagues are involved in a broad range of investigations to attempt to improve this difficult development of trust between caregivers and the public, and a trusting partnership has been developed between a community hospital and multiple tribal organizations in South Dakota. The first of these two articles describes the effectiveness of having someone to guide individuals — a “patient navigator” — through recommended cancer treatment. Those assisted by such a navigator had three fewer daily interruptions of radiation treatment than their cohorts who had no such assistance, thus improving compliance and presumably the effectiveness of treatment. The second article describes excellent accrual to a clinical study evaluating whether abnormalities in the ataxia telan-

giectasia (AT) gene explain the apparent increased sensitivity to radiation effects among American Indians.

Accrual of patients to clinical trials in the United States is becoming increasingly difficult for a number of reasons. I call your attention to a plan now being put into action in the United Kingdom. There, the government is setting up a national network of 19 experimental cancer clinics that can investigate, manage, and report on patients who wish to participate in clinical trials. An interesting experiment!

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

Jonathan S. Zager, MD

Assistant Professor of Surgery
Cutaneous Oncology Program
H. Lee Moffitt Cancer Center & Research Institute
Tampa, Florida
E-mail: jonathan.zager@moffitt.org

Adil I. Daud, MD

Associate Professor
Medical Director of Affiliate Research
Cutaneous Oncology Program
H. Lee Moffitt Cancer Center & Research Institute
Tampa, Florida

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