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Management of Human Melanoma: What Has the Last Decade Wrought?

Advances in the prevention and treatment of human melanoma have been slow. Although the widespread adoption of effective methods of early detection has led to earlier diagnosis, the increased incidence of cutaneous melanoma and absence of effective postsurgical interventions have led to an increasing overall mortality from the disease. In the year 2002, over 7,400 people died from cutaneous melanoma in the U.S. [1].

The past decade has seen advances or contributions in seven major areas:

- Detailed understanding of the biology and immunology of the disease process
- Detailed characterization of the “epidemic”
- Adoption of interferon by some practitioners as adjuvant therapy after surgical resection of the primary lesion and/or drainage of lymph nodes
- Development of strategies for prevention
- Development of a revised staging system
- Widespread utilization of sentinel node evaluation and biopsy
- Widespread usage of biochemotherapy for the treatment of advanced disease

In this issue, major reviews of the first three topics are presented, and all seven areas are briefly discussed below.

There is vast literature available on the immunology and immunotherapeutics of melanoma [2]. To date, however, this knowledge has not been successfully translated into clinical benefit. Melanoma cells have been among the most commonly used of experimental models, and a great deal of data about biological, biochemical, and molecular pathways has been generated. Surprisingly, little of this information has been appreciated in a disease context, a

notable exception being the work of the group at the Wistar Institute. We also have recently contributed a new perspective and postulate that oxidation of melanin and the establishment of a pro-oxidant state in melanoma pathogenesis may be a key early step in transformation, and a possible therapeutic target, through an abnormally regulated apoptotic process in melanoma [3, 4]. In the next issue, *Perlis and Herlyn* will summarize recent advances in the establishment of new model systems for the human disease and review key insights that have evolved from these studies. Most notable of these include the demonstration of the critical role of local homeostatic mechanisms in regulating tumor progression, the direct demonstration of UV-B light in the initiation and transformation of melanocytes, and the presence of abnormal apoptotic mechanisms in melanoma cells. That review suggests that there are many neglected features of melanoma growth that can be exploited for clinical benefit.

Beddingfield reviews the state of the epidemiologic data regarding melanoma incidence and concludes that the “epidemic” reflects multiple underlying reasons: a true increase in melanomas of malignant behavior, a high increase in localized and in situ lesions, and an increase in the number of biopsies performed [5]. Despite this “epidemic,” early detection has led to an increase in overall survival from 60% in the 1960s to nearly 90% today.

Einspahr et al. reviewed strategies for the prevention of both nonmelanoma and melanoma skin cancers and presented a detailed approach to the development of chemopreventative agents [6]. Unfortunately, only one chemoprevention trial to date has been positive, and modestly so, in participants at high risk for skin cancer (25% fewer new cutaneous squamous cell carcinomas in patients taking vitamin A). A useful review of the possibilities for the chemoprevention of melanoma was published recently [7]. Many new drugs are being explored in preclinical and

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in phase I and II trials for prevention of both nonmelanoma and melanoma skin cancers, and results of definitive trials are anticipated in 5-10 years.

Sabel and *Sondak* review the pros and cons of adjuvant interferon in the treatment of melanoma [8]. This is perhaps the best review I have read on this controversial topic. Although interferon-alpha has been approved for adjuvant treatment of high-risk melanoma, its use has declined in the past few years as the result of many trials, the results of which have been decidedly mixed. Those authors review the data critically in a question-and-answer format that will be of great help to clinicians sorting out their thoughts (and feelings) about this subject.

The revision of the staging system for cutaneous melanoma has been long overdue. A comprehensive review was published recently [9, 10]. The essential features are: A) tumor thickness has replaced level as the only measure of depth; B) ulceration is recognized as a bad prognostic sign at all depths and nodal states; C) the number of positive lymph nodes is prognostic, and D) nonvisceral metastases portend a better survival than visceral metastases.

The biological relationships and underpinning of this new staging system need to be further explored, but the data certainly suggest that angiogenesis is an important prognostic feature, results recently confirmed by others [11]. Sentinel node biopsy has been widely adopted in the short 10 years since the procedure was originally described by *Morton* and colleagues [12]. As recently noted [13], we are confronted with the paradoxical situation in which there is widespread agreement about its usage and considerable controversy about its utility and validity. *McMasters et al.* present an excellent commentary on the state of the

field and cite four major reasons to perform sentinel lymph node biopsy [13]: A) staging and, therefore, prognostication are improved; B) those patients best served by early therapeutic node dissection are more accurately identified; C) patients who are candidates for further intervention are identified, and D) further refinement of risk factors is possible, and more homogeneous groups of patients are identifiable for trials. Despite these apparent benefits, definitive trials need to be done to determine whether this procedure affects long-term outcome or mortality.

What about biochemotherapy for advanced disease? Although high response rates have been seen and complete responses in the 10% range have been achieved [14], several large randomized trials have now demonstrated no response or survival benefit and considerable toxicity and cost. We would be pleased if a new combination finally outperformed decarbazine alone, but the history of randomized clinical trials in metastatic melanoma suggests that biochemotherapy is not the answer and new approaches are needed.

In summary, the last decade has produced some real advances in our biological understanding and clinical management of cutaneous malignant melanoma. To progress further, the biological findings that make melanocyte progression and transformation biologically unique need to be defined and exploited, as has been done from the immunological viewpoint. *Perlis* and *Herlyn*, in their upcoming review, suggest new biological molecules for therapeutic intervention. We also have recently outlined the unique redox changes and transcriptional factor activations that characterize human melanoma cells [3]; these pathways offer antiapoptotic and redox modulation as additional therapeutic targets.

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