

## The Promise of New Technologies and Therapies

Over the last 40 years, the troops in the war on cancer have advanced much closer toward their goal of a cure. New developments in the field of cancer research and treatment hold the potential to make quantum leaps in our understanding of the malignant process. Some of these new technologies and treatment approaches for patients with melanoma are reviewed in this issue of *Cancer Control*.

It is an exciting time to be involved in the care of patients with melanoma. After years of frustration, we can now offer some new therapies. A new standard of surgical care for the melanoma patient has been established with the lymphatic mapping and sentinel lymph node (SLN) biopsy procedure. With this technique, nodal staging has become less morbid for the patient as well as more accurate — a win-win situation!

The new staging system for melanoma has been recently adopted by the American Joint Committee on Cancer and will be established next year at the level of the nation's tumor registries. This new staging system, reviewed by Christina J. Kim, MD, Charles M. Balch, MD, and the AJCC Melanoma Staging Committee, is based on a powerful 17,000-patient database established from the major melanoma programs throughout

the world. This tool provides the basis for the recommendation from the Committee that all patients with melanomas greater than 0.76 mm in thickness undergo a nodal staging procedure, particularly for clinical trial work or for determining the patients who should be offered adjuvant therapy. To obtain the nodal staging information, the SLN procedure is recommended as this is the least morbid procedure for the patient. It is also recommended that nodal staging with a microscopic examination of the SLN be included in the initial staging of the tumor.

In December 1995, the US Food and Drug Administration approved the first effective adjuvant therapy for "high risk for recurrence" melanoma patients: interferon alfa-2b based on a trial from the Eastern Cooperative Oncology Group (ECOG). Patient groups identified as high risk for recurrence are those with nodal metastasis (stage III) and those with stage T4 N0 M0. Patients with in-transit, local recurrence, or resected stage IV disease are also at high risk for recurrence. Although the ECOG trial did not specifically address these groups, adjuvant therapy should be considered for these patients. The three ECOG trials are cited in the "Best Readings" section of this issue and provide a body of literature of compelling evidence for the effectiveness of

this adjuvant therapy. A number of medical oncologists are concerned that one of the trials (ECOG 1690) showed a disease-free benefit but no overall survival benefit in favor of high-dose interferon alfa. They wonder how this fairly toxic therapy can be justified if there is no survival benefit. Probabilities come into play when making a final argument as to the appropriate adjuvant therapy or control arm for any study for stage III melanoma. If three trials are performed investigating a therapy for a disease and the trials are powered at the 0.8 level and have a significance level of 0.05, the chance of obtaining one negative result with an effective therapy is  $3 \times 0.8^2 \times 0.2 = 38\%$ . (ECOG 1684 and 1694 show an overall survival benefit, but ECOG 1690 does not.) If three prospective, randomized studies are each powered at the 0.8 level with a significance of 0.05 and two of the trials show a significant overall survival benefit while the third does not, the probability of such a result if the therapy is truly not effective is  $0.05 \times 0.05 \times 0.8 \times 3 = 0.006$ . Thus, with the ECOG data from the three trials, there is compelling evidence that interferon alfa-2b should be the standard of adjuvant care for the stage III melanoma population.

Also in this issue, Steven O'Day, MD, and colleagues review the biochemotherapy protocols that

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seem to give the highest response rates for patients with systemic disease. These results are better than those from single-agent therapy and are compared to what was possible 10 years ago, but the article also identifies the limitations of this approach.

Manuscripts on immunotherapy, gene therapy, and microarray analysis attempt to highlight the future of melanoma therapy. Melanoma is probably the best studied solid tumor from an immunologic standpoint. Microarray techniques have the potential of identifying more reliable prognostic factors for melanoma and making a blueprint (geneprint) of the tumor to perhaps custom-design therapy. Dendritic cells are the current "hot" topic for immunotherapy approaches, and advances in this field are reviewed. Melanoma vaccines are finally being evaluated in NIH-funded phase III national prospective, randomized trials.

An exciting new trial was recently initiated among 15 insti-

tutions in the state of Florida. Florida has the third highest incidence of melanoma in the United States, and yet only 3% to 5% of this population are placed on clinical trials. A regional cooperative group titled "Florida Melanoma Investigator Group" has been organized to engage in clinical trial work. The Florida Melanoma Trial I, which evaluated the combination of adjuvant radiation therapy and interferon alfa-2b in patients with resected gross nodal disease, has been completed. The second trial from the group, the Florida Melanoma Trial II, will randomize patients with a positive SLN to either complete lymph node dissection (CLND) and adjuvant interferon alfa-2b or the adjuvant therapy alone. This trial will define the role of CLND in patients with melanoma. It differs in design from previous trials examining the efficacy of ELND since only those patients with documented nodal metastases, ie, those with a positive SLN, will be randomized on the study to either CLND or no further surgery.

Over the last 40 years, the 5-year survival for patients with melanoma in the United States has increased from 60% to 85%. Perhaps some of this improvement is due to better therapies, but most of the apparent survival increase is thought to be due to a heightened awareness to the diagnosis of "early" curable melanomas. In the Cutaneous Oncology Clinic at our institute, the mean tumor thickness at diagnosis has steadily decreased from a value of 2.5 mm in 1987 when the clinic was established to 1.5 mm in 2001. No one will argue that as a group, the people diagnosed with melanoma in 2001 will do better than those diagnosed 40 years ago. With the new technologies and therapies available today, patients and clinicians will hopefully not have to wait another 40 years to see a similar survival increment.

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## EDITORIAL NOTICE:

Several of the articles in this issue of *Cancer Control* refer to the use of interferon alfa-2b in treating patients with melanoma. The Schering Sales Corporation recently circulated an announcement alerting physicians to changes in the safety information regarding therapy with interferon alfa-2b (INTRON A). The new label includes the following boxed warning:

Alpha interferons, including INTRON® A, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping INTRON A therapy. See **WARNINGS**, and **ADVERSE REACTIONS**.