

Evidence Helps Refine Melanoma Management

BY SUSAN LONDON

SEATTLE — Evidence from recent and ongoing trials is helping to clarify the best strategies for managing cutaneous melanoma.

A hurdle to better melanoma management has been the high variability of the disease, exemplified in part by its wide-ranging presentations, said Dr. William Dzwierzynski, professor of plastic and reconstructive surgery at the Medical College of Wisconsin in Milwaukee. In fact, accumulating evidence suggests that melanoma may encompass several different diseases with differing biology.

When initially evaluating a suspicious skin lesion, the type of biopsy is critical. "Excisional biopsy is probably the most key thing. You really try not to do an incisional or a shave biopsy," he said, unless the latter is deep and removes the whole lesion. Reassuringly, though, the type of biopsy does not affect survival (*Am. J. Surg.* 2005;190:913-7). "But we'll never know the depth of the lesion" with an incisional or shave biopsy, he pointed out, "so we'll never have the right prognosis."

Accurate diagnosis of melanoma requires permanent sections. "Melanoma is not accurately diagnosed on frozen sections. Don't do frozen sections on melanoma—you get a lot of false-negatives and a lot of false-positives," Dr. Dzwierzynski said at the annual meeting of the American Society of Plastic Surgeons.

Positron emission tomography (PET) imaging is unreliable for staging in patients with melanoma, yielding a false-negative rate of 79% when used preoperatively to identify occult nodal metastases (*Cancer* 2005;104:570-9). "There is not any conclusive data that

PET scan is any more accurate than a chest x-ray or lab tests," he added. On the flip side, patients should not be assumed to have metastases solely based on a positive PET scan.

"I send everybody who has a melanoma that is 1 mm or greater to an oncologist," he added. "I tell them that the oncologist probably won't have anything to offer you, and that's a good thing. But



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they are the ones who are going to know if there are any investigational studies or treatment trials."

Whenever possible, patients with advanced disease should be referred for clinical trials. "Investigational therapies—I think this is where the promise is," Dr. Dzwierzynski commented.

When it comes to resecting the tumor, contemporary margins are 1-3 cm for most invasive melanomas. Prospective studies have found no difference in survival between margins of 1-2 cm and larger margins of 3-5 cm, but methodologic limitations leave the issue unresolved, he said.

Mohs surgery for invasive melanoma remains controversial. "There is a lot of distortion when you do Mohs," he noted. "It's really easy to get false-negatives and false-positives." To date, controlled survival data and randomized trials are lacking.

Sentinel node biopsy (SNB) is recom-

mended for patients whose tumors have a Breslow thickness of greater than 1 mm and for those whose tumors are thinner but have adverse features, such as ulceration or a Clark level of IV or V. Currently, it is done to obtain prognostic information and identify the roughly 20% of patients who may benefit from a complete lymph node dissection, Dr. Dzwierzynski noted.

The results of the first Multicenter Selective Lymphadenectomy Trial (MSLT-1) raised the possibility that SNB also may be curing disease in some patients and improving survival (*N. Engl. J. Med.* 2006;355:1307-17). An ongoing follow-up trial, MSLT-2, is looking more closely at the issue and the possibility that patients with only microscopic disease in the sentinel node may be spared further surgery.

Importantly, there is a learning curve to the SNB procedure. In MSLT-1, the false-negative rate was 10% in a physician's first 25 cases, but fell to 5% thereafter (*Ann. Surg.* 2005;242:302-13). "So right now, the recommendation is that it does take probably 30 cases for that learning curve," he said.

For pathologic evaluation of sentinel nodes, the combination of step sectioning (at less than 1-mm intervals) and hematoxylin and eosin staining with HMB-45 and S-100 immunohistochemistry has sensitivity approaching 98%, according to Dr. Dzwierzynski. A triple stain used at his institution—the MCW melanoma cocktail (Melan-A, MART-1, and tyrosinase)—has high accuracy (*BMC Cancer* 2003;3:15), albeit at a fairly high cost. In contrast, polymerase chain reaction has proven to be of limited use because it can be falsely positive in patients with subcapsular nevi.

The National Comprehensive Cancer Network recommends complete lymph

node dissection for patients with a positive SNB, but a recent analysis of national data found that only half of such patients underwent the procedure (*Ann. Surg. Oncol.* 2008;15:1566-76).

"Complete lymph node dissection is a curative procedure," he commented. As such, it is extensive, more so than the lymph node sampling done for, say, breast cancer. "In most of my axillary dissections, I will remove 35-40 lymph nodes," Dr. Dzwierzynski said. "For a superficial inguinal dissection, you should have at least 10 nodes, and for a deep dissection, you have at least 5 nodes."

Complication rates of complete lymph node dissection are generally high, and they tend to be higher after inguinal procedures (48%-84%) than after axillary ones (47%-53%), he noted.

Several trials have shown that adjuvant high-dose interferon therapy modestly improves outcomes among patients with melanoma at high risk for recurrence, but with the tradeoff of substantial toxicity. The benefits are lost when the dose is reduced and therapy is shortened. "But there may be a subgroup in which interferon is useful," he added, so an individualized approach, with discussion of risks and benefits, is needed. It should not be given automatically "because it's the only thing that's available," he said.

The optimal approach to follow-up of patients with treated melanoma has not been established, but follow-up is typically lifelong and multidisciplinary, according to Dr. Dzwierzynski. Importantly, all patients must have lymph node palpation for detection of recurrences, and full-body skin checks for detection of second primaries.

Dr. Dzwierzynski reported that he had no conflicts of interest in association with his presentation. ■

Bevacizumab's Melanoma Results Are Less Than Significant

BY PATRICE WENDLING

BERLIN — The addition of bevacizumab to chemotherapy failed to significantly improve progression-free or overall survival in previously untreated advanced melanoma in the phase II BEAM trial.

Median progression-free survival was 5.6 months for bevacizumab (Avastin) plus carboplatin and paclitaxel-based chemotherapy, and 4.2 months for chemotherapy alone. Despite a hazard ratio of 0.78, the difference was not statistically significant ($P = .14$), Dr. Steven O'Day reported at a joint congress of the European Cancer Organization and the European Society for Medical Oncology.

Overall survival was widely reported before the congress as having been significantly increased by 4 months with bevacizumab, but an unplanned post hoc analysis performed just before the formal data presentation showed that the survival benefit had narrowed and had taken the statistical advantage with it.

Median overall survival went from 12.3 months in the bevacizumab arm and 8.6 months in the chemotherapy arm at a median follow-up of 13 months in the initial analysis (HR, 0.67; $P = .04$) to 12.3 months and 9.2 months, respectively, at a median follow-up of 18 months in the post hoc analysis (HR, 0.79; $P = .19$).

Response rates also favored bevacizumab over chemotherapy (25.5% vs. 16.4%), but were not significantly different ($P = .16$) in the Roche Pharmaceuticals-sponsored study.

Although the revised data sent stock analysts and journalists scrambling, the findings are still cause for optimism in a disease with few treatment options and a 5-year survival of less than 5%, according to Dr. O'Day, chief of research and director of the melanoma program at the Angeles Clinic and Research Institute in Santa Monica, Calif.

"I am optimistic because strong trends of improvement were seen across all efficacy parameters" (progression-free survival, overall survival, and response), he said in an interview. "This was a randomized, phase II with 2:1 randomization, so it wasn't powered for overall survival to be significantly different. I'm also optimistic because even the worse prognosis patients with M1c disease and elevated [lactate dehydrogenase] seemed to benefit from this treatment."

Based on the current data, Roche plans to go forward with a larger, randomized phase III trial that is adequately powered to detect a significant survival benefit, he said.

BEAM (A Study of Bevacizumab With Carboplatin and Paclitaxel Chemotherapy for the First-Line Treat-

ment of Patients With Metastatic Melanoma) included 214 patients (mean age, 60 years) with stage IV M1a/b, M1c disease, of which 73% was M1c disease and 54% of M1c patients had abnormal lactate dehydrogenase levels. Patients received chemotherapy with or without bevacizumab 15 mg/kg administered intravenously on day 1 every 3 weeks.

Bevacizumab, an anti-vascular endothelial growth factor (VEGF)-specific inhibitor, was evaluated because melanoma is a very vascular tumor, and elevated VEGF levels correlate with tumor progression and worse prognosis. The addition of bevacizumab to chemotherapy has improved outcomes in other cancers, including metastatic colorectal cancer and non-small cell lung cancer.

No new safety events were observed in the trial. Grade 3/4 treatment-related adverse events that occurred with 2% or more increased incidence in the bevacizumab arm included febrile neutropenia, neutropenia, peripheral neuropathy, pulmonary embolism, hypertension, anorexia, and musculoskeletal pain. There were two deaths in the bevacizumab arm and none in the chemotherapy arm, Dr. O'Day said.

He has served an advisory/consultant role and received research funds from Genentech Inc. and Roche for clinical trials. ■