# Ulcerated Melanomas May Respond to Interferon

BY NEIL OSTERWEIL

ORLANDO — Although ulcerated primary melanomas are notorious for having a poor prognosis, the presence of ulceration may be a signal that the tumor is one of a small proportion of melanomas that are sensitive to adjuvant interferon, European researchers suggested at the annual meeting of the American Society of Clinical Oncology.

A meta-analysis of two large published studies of adjuvant interferon therapy indicates that interferon treatment of ulcerated primary melanoma is associated with about a 25% reduction in the risk for distant metastases and about a 40% decrease in the risk of death, compared with interferon treatment of nonulcerated primary melanomas.

"After 20 years of adjuvant interferon trials, it took a [previous] meta-analysis in over 10,000 patients to demonstrate a 3% overall survival benefit," said Dr. Alexander M.M. Eggermont, professor of surgical oncology at Erasmus University, Rotterdam, the Netherlands. Most trials showed a significant impact on relapse-free survival, he said, but not on overall survival—leading to the suspicion that a fraction of patients are sensitive to interferon.

By identifying those patients who respond to interferon, clinicians can protect the majority of patients from "unjustified" exposure to interferon. Ulcerated primary tumors may be the sign that everyone's looking for, said Dr. Eggermont, speaking on behalf of colleagues in the European Organisation for Research and Treatment of Cancer (EORTC) Melanoma Group.

Ulcerated melanoma is a distinct biological entity with much worse prognosis, he said, pointing to an analysis by Dr. Charles M. Balch and colleagues of prognostic factors among 17,600 melanoma patients, which showed that for tumors of the same thickness, overall survival was much worse if the primary was ulcerated (J. Clin. Oncol. 2001; 19:3622-34).

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Earlier analyses of data from the EORTC 18952 and 18991 studies in the new meta-analysis suggested that tumor burden and ulcerated primaries were both likely determinants of interferon sensitivity, whereas autoimmune antibodies were not, Dr. Eggermont said.

The 18991 study involved 1,256 patients with resected stage III melanoma who were randomly assigned to long-term therapy with pegylated interferon alfa-2b or observation. The study included an 8-week induction period, followed by weekly maintenance for 5 years or until distant metastases were detected.

The 18952 study involved 1,388 patients with resected stage IIb or III melanoma who were randomized to observation or to intermediate doses of peginterferon alfa-2b (induction with 10 million IU daily for 4 weeks, followed by maintenance with either 10 million IU thrice weekly for 12 months or 5 million IU thrice weekly for 24 months).

Analysis of the 18991 study, which used peginterferon, showed that ulcerated primary melanoma was associated with a 23% reduction in risk for distant metastasis vs. observation, and the difference was even greater in patients with ulceration and one involved node. They had a 41% reduction vs. patients with ulcerated N1 tumors who underwent observation.

"For nonulcerated primaries, all primary end points were nonsignificant. The exposure of adjuvant interferon did not translate into a benefit," Dr. Eggermont said. "But if the primary was ulcerated, relapse-free survival, distant metastasis-free survival, and overall survival" were all significantly impacted.

This finding prompted the investigators to conduct the meta-analysis including all 2,624 patients in the combined trials. Looking at relapse-free survival by treatment group according to ulceration status, they found that, among all patients with primary tumors, there was no significant difference between the patients who were treated with interferon or those randomized to observation only.

But when they compared relapse-free survival among patients with ulcerated primaries, they saw that interferon-treated patients had a hazard ratio for relapse of 0.75, compared with similar patients who underwent observation only. There was also a significant benefit for interferon therapy of ulcerated stage IIB and III-N1 tumors, compared with observation, but not for patients with stage IIB or II N1 nonulcerated primaries.

In the combined studies, there was no overall survival advantage for interferon therapy over observation alone in patients with nonulcerated tumors. In contrast, interferon treatment significantly benefitted patients with ulcerations.

Ulceration also held up as a significant determinant of overall survival when the two studies were considered separately. Interferon conferred a survival advantage compared with observation in each study. "In these studies, with interferon given these ways, ulceration did seem to be a very powerful indicator of outcome," said Dr. Thomas F. Gajewski of the cancer research center at the University of Chicago, who was the invited discussant.

"Ulceration may be trying to tell us something about the biology of melanoma," he said.

Ulcerated primaries tend to express at higher levels genes linked to cell cycle, DNA repair, and epigenetics, and may also be linked to a vascular invasion phenotype that makes them more sensitive than nonulcerated tumors to interferon, he said.

Dr. Eggermont had no conflict of interest disclosures. Dr. Gajewski disclosed receiving honoraria and/or research funding from Bristol-Myers Squibb Co., Genentech Inc., GlaxoSmithKline, and Pfizer Inc. ■

# Radiation Reduces Lymph Node Field Relapse in Melanoma

BY DAMIAN McNAMARA

ORLANDO — Adjuvant radiotherapy following lymphadenectomy improved lymph node field control for patients with melanoma who were at an increased risk of relapse in an ongoing, multicenter trial.

Dr. Michael A. Henderson and his colleagues did not observe a significant difference in relapse-free or overall survival benefit between 109 patients randomized to adjuvant radiotherapy after surgery and 108 controls assigned to observation only.

The study was positive in terms of the primary end point, however. At a mean follow-up of 39 months, "radiotherapy patients were significantly less likely to develop a lymph node field relapse," Dr. Henderson said at the annual meeting of the American Society of Clinical Oncology. The hazard ratio was 0.56 vs. observation ($P = .041$).

An intent-to-treat analysis of an initial 248 patients "demonstrates an even larger and more significant advantage in lymph node field control" in the radiotherapy vs. observation patients (HR, 0.47; $P = .005$), said Dr. Henderson, a surgical oncologist at Peter MacCallum Cancer Centre in Melbourne. He had no disclosures.

In all, relapses in all-local, in-transit, or distant sites occurred in 161 patients during follow-up. This total included 62 patients with a first relapse in a lymph node field. There were 120 deaths (all but 2 due to melanoma), and about 40 patients have active disease.

This intergroup study from ANZMTG (Australia and New Zealand Melanoma Trials Group) and TROG (Trans-Tasman Radiation Oncology Group) included patients from 22 centers. Median age was 58 years in the radiotherapy group and 57 years in the observation arm. Men accounted for about 75% of each arm.

After 31 patients were excluded for "major eligibility infractions," the 217 remaining participants received 48 Gy of adjuvant radiotherapy in 20 fractions over 4 weeks or observation following complete resection of their palpable lymph nodes. Radiotherapy was delivered to axillae, groin, or parotid and neck lymph node fields.

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"This is the first multicenter, randomized, controlled trial of adjuvant radiotherapy after resection of node metastases," said study discussant Dr. Antoni Ribas, before outlining several concerns.

"Is local control a reasonable goal in the treatment of stage III melanoma?" he asked rhetorically. "Yes, if it's well tolerated. We know the really important event is systemic metastasis, which is what kills patients, and that will have to be balanced along with possible toxicities."

Quality of life measures and long-term effects of radiation are pending in the trial, and may ultimately guide how patients are counseled about an adjuvant radiotherapy option, said Dr. Ribas of the medicine and surgery faculties at the University of California, Los Angeles. He is a consultant and/or adviser to Pfizer Inc., MannKind Corp., and Sanofi-Pasteur Inc., and receives honoraria from these companies and Amgen Inc., as well as research funding from Pfizer.

The "early radiotherapy toxicity appears acceptable," Dr. Henderson said. At 2 weeks after radiotherapy, grade 3 toxicities included 18 cases of radiation dermatitis and two reports of pain. At 6 weeks post radiotherapy, five cases of radiation dermatitis, two reports of pain, and one case of fatigue were reported. There were no early grade 4 toxicities.

"Similarly, late radiotherapy toxicities were also uncommon," he continued. Grade 3 or 4 late toxicities in the radiotherapy arm included four reports of pain, four cases of skin toxicity, three reports of subcutaneous tissue toxicity, and one report each of bone, joint, and nerve damage toxicity.

The intent-to-treat analysis also showed no difference in relapse-free survival ($P = .53$) or overall survival ($P = .14$). Overall survival at 5 years was 38% in the radiotherapy group vs. 44% in the observation group, Dr. Henderson said.

A meeting attendee noted that the radiotherapy group's survival curve was below the observation group's curve and said, "At this immature stage of the trial, I don't think radiotherapy can be recommended." Dr. Henderson had no comment. ■