Melanoma Newsletter

ALBERTA SOCIETY OF MELANOMA

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Mission Statement

- Provide support to people living with melanoma and their families
- Alleviate fear, misconceptions, and to encourage a positive attitude about living with cancer
- Foster and support melanoma research
- Disseminate information about melanoma

CUTTING EDGE

MANAGEMENT AND TREATMENT

Role for adjuvant therapy with interferon α-2b in melanoma patients

In the spring of 1996, the U.S. Food and Drug Administration (FDA) quickly approved the use of interferon α-2b (IFNα-2b) in patients with Stage III melanoma. At the time it was the only officially endorsed drug in the treatment of melanoma. The basis for this rapid approval was a seminal article by Dr. John Kirkwood, a medical oncologist at the University of Pittsburgh, who had reported for the first time in a randomized control study a significant benefit to high-risk melanoma patients who received IFNα-2b. Dr. Kirkwood and colleagues (of the Eastern Co-operative Oncology Group [ECOG-1684 study]) had noted an improvement in both time to recurrence and overall survival of about 40% in patients with documented lymph node recurrence (i.e., Stage III) who had received adjuvant immunotherapy using high-dose intravenous IFNα-2b daily for one month, followed by low-dose IFNα-2b by subcutaneous injection three times per week for 48 weeks. The overall survival had increased from a mean of 2.8 years in the control group to 3.8 years in the treatment group. Almost overnight, cancer centers throughout North America had accepted IFNα-2b as standard therapy in Stage III patients. Unfortunately, the modest gains in survival rates were offset by the considerable toxicity associated with treatment. Patient testimonies in previous ASM newsletters have described in detail the severity of side-effects associated with IFNα-2b, and therefore do not require any reiteration. Detractors of the ECOG-1684 study focus on these negative effects as justification for denying patients IFNα-2b. These critics also contend that it is unreasonable to propose that IFNα-2b be standard therapy in this setting on the basis of a single positive trial.

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For the past year the world has awaited the results of a repeat study from the same group. The basis of the second study (ECOG-1690) was not simply to validate the merit of high-dose IFNα-2b in high-risk melanoma patients, but to determine whether a similar benefit could

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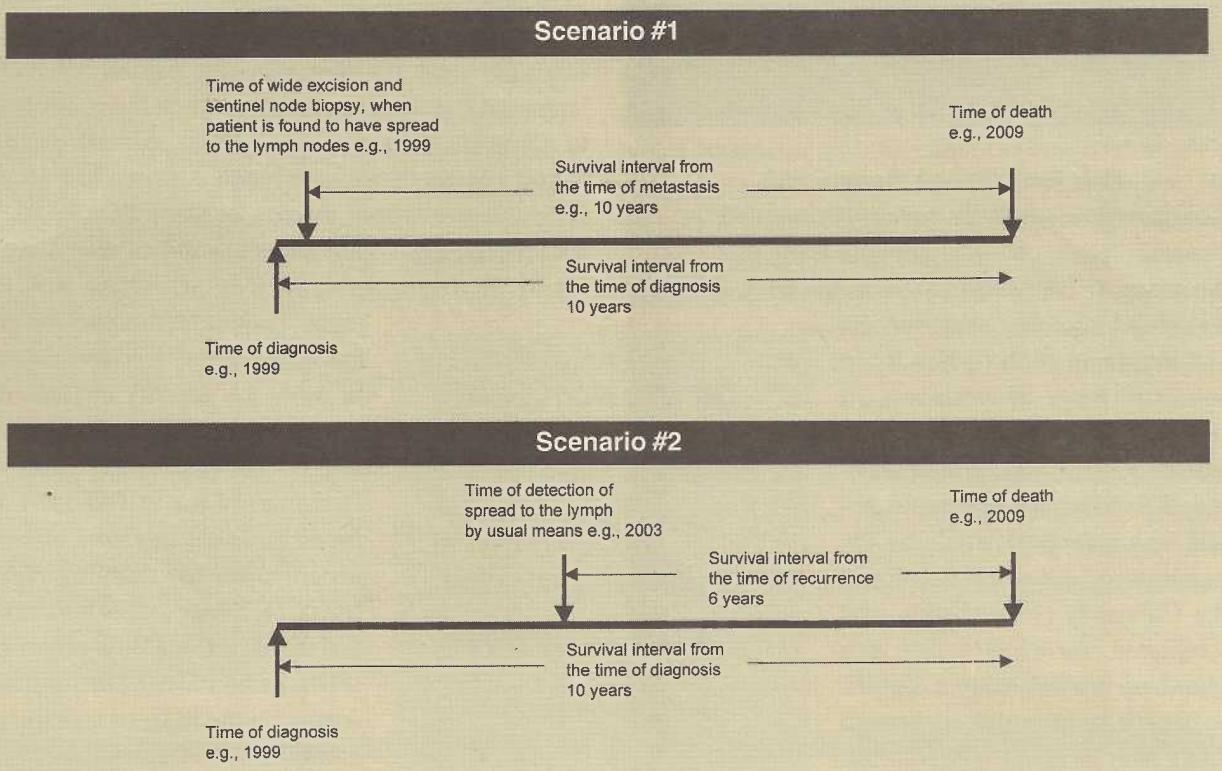
be achieved using a less toxic regimen. In this study, patients were assigned to one of three treatment arms: 1) no treatment (i.e., controls), 2) high-dose IFNα-2b as used in the ECOG-1684 study, and 3) low-dose IFNα-2b by subcutaneous injection three times per week for 104 weeks. Although the final analysis has yet to be published, preliminary data has been presented at several international meetings over the past year. There are considerable similarities between the two studies in terms of benefit to patients who received high-dose IFNα-2b; the overall survival rate in this group was slightly better than that reported in the ECOG-1684 study. However, when this rate was contrasted with the current untreated controls, there was no statistically significant improvement in overall survival. The reason for why the observation group in the ECOG-1690 study did so much better than those in the ECOG-1684 study is unknown, but has been the subject of considerable conjecture (see below). It is possible that the unexpected improvement in the control group in the repeat study has masked the potential benefits of IFNα-2b. Regrettably, the less toxic regimen using low-dose IFNα-2b did not result in any improvement in either time to recurrence or overall survival.

One possible explanation for the substantial improvement in overall survival in the control group may be due to a phenomenon known as lead-time bias. It is pos-



Legend

A hypothetical case of a patient who is diagnosed with melanoma in 1999. After biopsy of a suspicious looking pigmented lesion of his left leg, he is found to have a high-risk melanoma, 4 mm in tumor thickness, indicating that he is at considerable risk for spread to the lymph nodes. To assess for this possibility the patient undergoes sentinel lymph node biopsy at the time of his local, wide-excision and is found to have microscopic metastasis to the lymph nodes, and therefore has Stage III disease. Despite treatment of various types over the years, the patient ultimately succumbs to his disease 10 years later (i.e., 2009). Now imagine the same patient who declines sentinel node biopsy at the time of his definitive excision for his melanoma. Four years later, he presents to his doctor with an enlarged lymph of the left groin, which after biopsy proves to be due to spread of his melanoma (Stage III). The patient receives a lymph node dissection, and various treatments over the years, but still dies from his disease in 2009. Although the natural course of the disease in terms of when the patient dies is the same for both scenarios, in the first situation the patient lives with Stage III disease for 10 years, whereas in the second situation he appears to have Stage III disease for only 6 years. The first scenario gives the false impression that the patient is living longer due to lead-time bias in which the "clock" is reset to time zero when the patient is first found to have more advanced disease (i.e., Stage III).

sible that a significant number of patients enrolled into the repeat study were found to have lymph node metastasis after a sentinel biopsy was performed which has become almost routine at most cancer centers since 1993. As has been previously discussed (Spring 1998 ASM newsletter), this recent advance in the surgical management of melanoma permits the early detection of spread of the cancer to the lymph nodes, when it is still at the microscopic level. Early detection of spread by this method may have no bearing on the natural course of the disease, but may result in the impression that patients are surviving longer (see Figure). If there were a disproportionate number of patients that were recruited into the observation group after sentinel node biopsy rather than by clinical evidence of lymph metastasis, these patients would be perceived as doing better because of the lead-time bias associated with early detection of metastasis. This presumed improvement in the control group could have easily negated any possible beneficial effects of IFNα-2b in the treatment group.

Another potential confounding factor is that patients who relapsed were offered salvage therapy with IFNα-2b. Patients who had developed a recurrence of their disease were offered either a course with high-dose IFNα-2b (i.e., observation group), or a second course with IFNα-2b (patients previously treated). Review of the data has revealed that a greater proportion of patients in the control group received salvage therapy with IFNα-2b as compared to previously treated patients (31% vs. approximately 15-19%, respectively). Despite this crossover to the treatment arm, patients from the control group who were given salvage therapy would still be considered part of the observation group when the final analysis was performed. Interestingly, patients who received salvage therapy lived significantly longer than those who did not receive this treatment (mean 2.2 years vs. 0.8 years), suggesting that there is some beneficial effect to IFNα-2b. This improvement in overall survival associated with salvage therapy was more likely to influence the survival statistics of the observation group (because a disproportionate percentage of this group received this treatment), and thus could have diminished any differences between the controls and the treatment group.

In addition, the results of the ECOG-1690 study raise the question of whether starting too soon with IFNα-2b may mask any potential benefits. Until there is demonstrable recurrence most cancers like melanoma remain in a state of dormancy and therefore are relatively resistant to the toxic effects of anti-cancer drugs. Once they become more metabolically active they become more susceptible to these agents. Although IFNα-2b was primarily intended to trigger an immunological attack against any residual tumor cells, it also exhibits considerable cytotoxic effects on cancer cells. Kirkwood and colleagues have recently reported that these cytotoxic effects are maximal with high-dose IFNα-2b (as compared to low-dose IFNα-2b or no treatment). It is therefore possible, that for IFNα-2b to have any beneficial effects, patients need to be enrolled when their cancer is in a more active state and not simply present at a microscopic level. As to when to initiate treatment with IFNα-2b, experience with aforementioned salvage therapy would suggest that the ideal time would be when there has been clinical evidence of relapse.

The above arguments attempt to explain why the second study may have failed to demonstrate a benefit from treatment with IFNα-2b. It is however, possible that the results of the first study are incorrect, and that IFNα-2b offers little improvement in survival. A major criticism of the first study has been that the patients in the two arms (i.e., observation vs. treatment) may not have been completely matched in terms of predictors of survival. Although every effort was made to match patients according to the usual predictors (e.g., age and sex of the patient, as well as features of the melanoma, i.e., location, level of invasion, tumor thickness, ulceration of the surface), it is not clear whether patients were matched according to the number of positive lymph nodes. It is well known that one's chances of survival are far greater if only one lymph node is involved rather than if multiple nodes are affected. If the control group had a disproportionate number of patients with multiple positive lymph nodes, this group would have had a less favourable outcome, and therefore, any treatment (e.g., even placebo) would appear to have a beneficial effect. Supposedly, this potential confounding factor was controlled for in the second study.

Unfortunately, the confirmatory study has raised more questions than answers to the dilemma of whether IFNα-2b should be used in Stage III melanoma patients. Although oncologists have not abandoned this treatment altogether, many now leave the decision of initiating IFNα-2b to the patient. It would appear that a third prospective, randomized-control study is now required to finally resolve this issue. *TGS*

MELANOMA VACCINE TRIAL

The Cross Cancer Institute has joined forces with the John Wayne Cancer Institute of Santa Monica, California in conducting a Phase III trial assessing the usefulness of a polyvalent melanoma vaccine, *CancerVax*, designed by researchers at the latter cancer center. In a previous ASM newsletter (Spring 1997), we had discussed the various melanoma vaccines under investigation. Vaccines consist of antigens ("foreign" substances) unique to melanoma cells that are capable of triggering an immunological response when injected into the body. In that most melanoma antigens vary in their ability to induce strong immunological responses, co-stimulatory factors called "adjuvants" need to be given simultaneously. *CancerVax* utilizes melanoma antigens expressed on several melanoma cell lines (hence the term "polyvalent" vaccine) that have been rendered inactive by irradiation, in addition to the adjuvant BCG (Bacillus Calmette-Guerin). The latter is an attenuated strain of bacterium (*Mycobacterium bovis*) related to the micro-organism responsible for tuberculosis (i.e., TB). Previous experience with BCG has shown that it is capable of inducing the regression of tumor nodules both at the site of injection and distant sites, presumably by stimulating a systemic immunological response. Furthermore, a World Health Organization (WHO) study found that Stage III patients who received BCG or BCG plus decarbazine (a standard chemotherapeutic agent used in melanoma patients) experienced significantly improved disease-free survival as compared to untreated controls if they initially lacked immunity to BCG, but subsequently developed immunity after BCG vaccination (Cascinelli, N *et al.*. Cancer Immunology & Immunotherapy 1989:28:282-6).

The trial is open to patients with metastatic melanoma that have been rendered free of clinical evidence of disease after surgical resection of involved lymph nodes (Stage III) or distant internal sites (e.g., lung, liver, skin, etc.)(Stage IV). Confirmation of a disease-free stage is based on a physical examination and negative radiologic (e.g., Chest x-ray, CT Scan, ultrasound, nuclear medicine scans, etc.) and serologic (liver function tests) investigations. To be eligible, vaccination must be initiated no more than 90 days after the surgical resection of all known metastatic sites. Patients will be segregated randomly into one of two treatment arms: *CancerVax* plus BCG or placebo and BCG. Due to the aforementioned beneficial effects of BCG alone, regardless of which treatment arm the patient is assigned to, all patients will receive some form of active treatment. Both the patient and physician will be unaware of which treatment the patient is receiving until the conclusion of the study (hence the term "blinded" trial). Treatment will be given over three years; during the first year patients will be vaccinated every two weeks for the first two months, and then monthly. In the second year they will receive "booster shots" every two months, and in the third year every three months (for a total of 25 injections over the three years). More detailed discussion of the eligibility criteria and guidelines of treatment should be obtained from the investigating physician. *TGS*

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