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BRIEF COMMUNICATION

Randomized Trial of Adjuvant Human Interferon Gamma Versus Observation in High-Risk Cutaneous Melanoma: a Southwest Oncology Group Study

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The prognosis for patients with cutaneous malignant melanoma worsens considerably if the primary tumor invades deeply (≥1.5 mm, American Joint Committee on Cancer [AJCC] stage II) and/or spreads to regional lymph nodes (AJCC stage III) (*1-3*). Such patients are therefore appropriate candidates for studies of postsurgical adjuvant therapy. Several observations suggest a role for immunologic mechanisms in controlling proliferation and spread of melanoma cells (*4,5*). Nonetheless, clinical trials of nonspecific immunologic stimulants such as BCG, *Corynebacterium parvum*, levamisole, and transfer factor have been disappointing (*6-11*), leading to consideration of more specific immunomodulatory approaches.

Interferon gamma (IFN γ) induces a variety of immunomodulatory effects: increased natural killer cell-mediated cytotoxicity, macrophage activation, and enhancement of human leukocyte antigen class II antigen expression and shedding (*12-15*). Phase I studies showed that IFN γ was well tolerated and favorably affected immune parameters in patients with completely resected melanoma (*16-18*). Although IFN γ has no documented activity against metastatic melanoma, such phase I results argued for its evaluation in the adjuvant setting. Accordingly, the Southwest Oncology Group undertook a randomized, phase III trial (SWOG-8642) to test whether prognosis is improved with recombinant human IFN γ (Genentech, Inc., South San Francisco, CA) compared with observation following definitive surgery for cutaneous melanoma.

Eligible patients were 18 years of age or older, had cutaneous melanoma of AJCC stage II (primary thickness of ≥1.5 mm, N0, M0) or III (any T, N1-2, M0), and a performance status (Eastern Cooperative Oncology Group scale) of 0 or 1. Patients were required to have had complete excision of their tumors (with at least 1-cm margins) within 4 weeks after registration and to have no prior or concurrent nonsurgical therapy. Staging procedures were required to ensure that patients were free of detectable residual disease. After giving written informed consent, patients were randomly assigned to receive either IFN γ or no treatment (observation), stratified by stage. Optimal immunomodulatory effects of IFN γ in melanoma patients at high risk of recurrence following surgery have been reported at an intramuscular or subcutaneous dose of 0.1 mg/m^2 per day (*19*). For practicality, IFN γ was given subcutaneously at 0.2 mg per day for 1 year or until disease recurrence. The slides of the tumors of all patients were reviewed by one pathologist (R. J. Tuthill), and there was central review of all relevant eligibility criteria, including surgical technique, to determine final eligibility. The protocol was approved by the institutional review boards of the participating institutions. The present analysis was based on data available August 2, 1994, and updates an earlier preliminary report (*20*). Since the stated aim of the study was to determine whether treatment with IFN γ improves outcome compared with that seen with observation, one-tailed P values (P_1) are reported except for unplanned post hoc analyses using two-tailed P values (P_2) that were performed to investigate whether treatment with IFN γ might actually be harmful.

From October 1987 through November 1989, 284 patients were randomly assigned (137 IFN γ and 147 observation) by standard cooperative group procedures performed centrally at the Southwest Oncology Group Statistical Center. Eighty-two (29%) were ineligible, primarily because of failure to obtain required prestudy tests or to meet required histologic or surgical criteria. Results for all 284 patients were similar to those for the 202 eligible patients; the latter are emphasized here.

Characteristics of and treatment outcomes for the eligible patients are shown in Table 1. Disease-free survival and overall survival were not significantly better with IFN γ (Fig. 1: for disease-free survival, $P_1 = .81$; for overall survival, $P_1 = .91$; stage-stratified logrank test). Disease-free survival and overall survival were in fact somewhat poorer with IFN γ, but not significantly so in post hoc analyses (disease-free survival, $P_2 = .38$; overall survival, $P_2 = .18$). Proportional hazards regression analysis found no significant interactions between treatment and stage, gender, age, primary site, body surface area, or weight. The study was originally designed for 230 eligible patients. With 202 eligible patients, however, the alternative hypothesis that IFN γ reduces the risk of relapse or death by 25% (i.e., relative risk = 0.75) was convincingly rejected ($P_1 = .007$), constituting strong evidence against any clinically meaningful beneficial effect.

Of the 137 patients randomly assigned to receive IFN γ, 133 were assessable for toxic effects. There were no

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See "Notes" section following "References."

Table 1. Characteristics of and treatment outcomes for eligible patients

Characteristic*	IFN γ (n = 97)	Observation (n = 105)
Age, median (range), y	45 (21-79)	46 (21-74)
Sex, No. (%)		
Female	25 (26)	38 (36)
Male	72 (74)	67 (64)
Primary site, No. (%)		
Trunk	46 (47)	47 (45)
Extremity	29 (30)	30 (29)
Head or neck	16 (16)	17 (16)
Other or unknown	6 (6)	11 (10)
Stage, No. (%)		
II	39 (40)	35 (33)
III	58 (60)	70 (67)
Disease-free survival		
Estimate at 2.5 y		
Stage II, % (95% CI)	64 (49-79)	66 (50-81)
Stage III, % (95% CI)	31 (19-43)	41 (30-53)
Relative risk of relapse or death (95% CI)	1.18 (0.82-1.68)	1.00 (—)
Overall survival		
Estimate at 2.5 y		
Stage II, % (95% CI)	79 (67-92)	89 (78-99)
Stage III, % (95% CI)	47 (34-59)	57 (46-69)
Relative risk of death (95% CI)	1.31 (0.88-1.95)	1.00 (—)

*CI = confidence interval.

fatal or grade 4 toxic effects (Common Toxicity Criteria, Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute). Twenty-four patients (18%) had grade 3 toxic effects, including neurologic effects (confusion, insomnia, and personality change) in three and myelosuppression in four. Other grade 3 toxic effects were depression, migraine, elevated levels of liver enzymes, pruritus, and flu-like symptoms. Sixteen patients (12%) had grade 1 neurologic toxic effects. Other frequent toxic effects included chills and fever (71%), headache (64%), and nausea/anorexia (35%).

We conclude that adjuvant treatment with daily subcutaneous injection of IFN γ at a known immunomodulatory dose was well tolerated but did not improve disease-free survival or overall survival of patients with high-risk cutaneous melanoma resected with curative intent. Although an interim analysis raised concern about the possibility of an adverse effect of IFN γ (*20*), this was not borne out in the present analysis with its longer follow-up. In contrast to our results with IFN γ, two trials (*21,22*) of adjuvant interferon alfa (IFN α) for the treatment of melanoma patients have suggested benefit, particularly improved disease-free survival. An important difference between the two interferons is that the α-form is active against advanced melanoma (approximately 16% response rate) (*23*), whereas the γ-form is basically inactive (*24,25*). The use of IFN α is also accompanied by substantial toxicity, including treatment-related deaths. Nonetheless, if this reported benefit is confirmed, we would be wise to examine the clinical and biological differences between these two similar molecules for lessons that might apply to future adjuvant trials in melanoma and other malignancies. In view of the negative results from the current study and previous randomized trials using transfer factor, levamisole, and vitamin A (*8,26*), we should question whether agents that have favorable immunologic and biologic properties, but that lack therapeutic efficacy against measurable disease, are indeed appropriate for adjuvant trials in melanoma.

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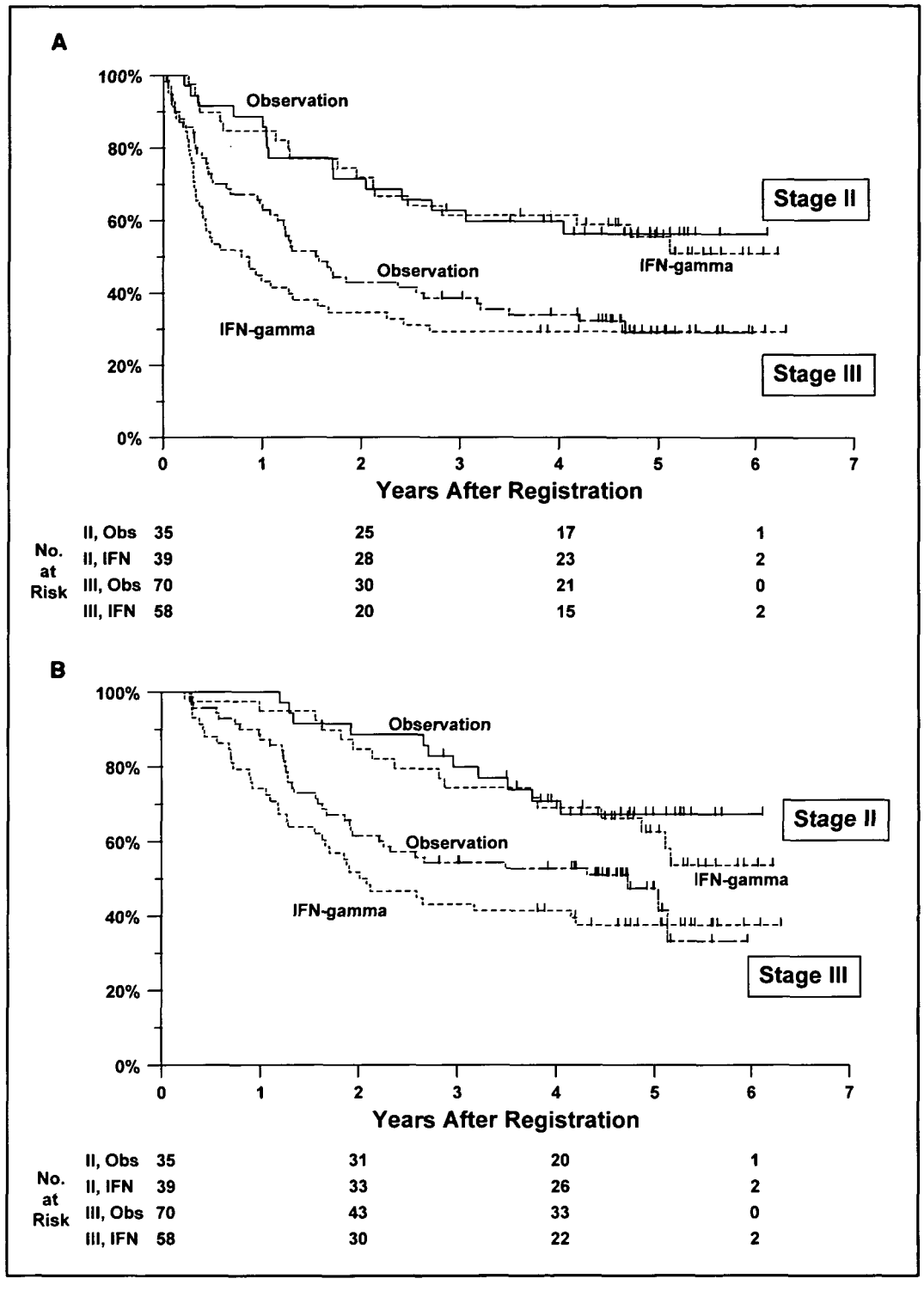

Fig. 1. A) Disease-free survival of eligible patients by stage and treatment arm. Thirty-three patients with stage II disease (15 observation, 18 interferon gamma [IFN γ]) and 89 patients with stage III disease (48 observation, 41 IFN γ) have relapsed or died. B) Overall survival of eligible patients by stage and treatment arm. Twenty-seven patients with stage II disease (11 observation, 16 IFN γ) and 73 patients with stage III disease (37 observation, 36 IFN γ) have died. Tickmarks indicate censored observations. Obs = observation; IFN = IFN γ.

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Notes

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