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

Permalink
https://escholarship.org/uc/item/3hb043v4

Journal
Journal of the National Cancer Institute, 87(22)

ISSN
0027-8874

Authors
Meyskens, Frank L
Kopecky, Kenneth J
Taylor, Charles W
et al.

Publication Date
1995-11-15

DOI
10.1093/jnci/87.22.1710

Copyright Information
This work is made available under the terms of a Creative Commons Attribution License, available at https://creativecommons.org/licenses/by/4.0/

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

Frank L. Meyskens, Jr., Kenneth J. Kopecky, Charles W. Taylor, R. Dirk Noyes, Ralph J. Tuthill, Evan M. Hersh, Lynn G. Feun, James H. Doroshow, Lawrence E. Flaherty, Vernon K. Sondak*

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/m² 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 (P₁) are reported except for unplanned post hoc analyses using two-tailed P values (P₂) 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 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, P₁ = .81; for overall survival, P₁ = .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, P₂ = .38; overall survival, P₂ = .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 (P₁ = .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

*Affiliations of authors: F. L. Meyskens, Jr., Southwest Oncology Group Statistical Center, Seattle, WA; C. W. Taylor, E. M. Hersh, University of Arizona Cancer Center, Tucson; R. D. Noyes, University of Utah Medical Center, Salt Lake City; R. J. Tuthill, Cleveland Clinic Foundation, OH; L. G. Feun, University of Miami School of Medicine, FL; J. H. Doroshow, City of Hope National Medical Center, Duarte, CA; L. E. Flaherty, Wayne State University Medical Center, Detroit, MI; V. K. Sondak, University of Michigan Medical Center, Ann Arbor. Correspondence to: Vernon K. Sondak, M.D., 2920 Taubman Center, 1500 East Medical Center Dr., Ann Arbor, MI 48109-0331. Reprint requests to: Southwest Oncology Group (SWOG-8642), Operations Office, 14980 Omicron Dr., San Antonio, TX 78245-3217. See "Notes" section following "References."
suggested benefit, particularly improved survival of adjuvant interferon alfa (IFN-α) for patients with primary cutaneous malignant melanoma. In contrast to negative results from the current study (21,22), an adverse effect of IFN-α was borne out in the present analysis of patients with stage II disease. This was an adverse effect of IFN-α, which was not found to be significant in the current analysis.

### 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.

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.

### References

1. Breslow A, Cascinelli N, van der Esch EP, Morabito A. Stage I melanoma of the limbs: assessment of prognosis by levels of invasion and maximum thickness. Tumori 1978;64:273-84.

2. Meyskens FL Jr, Berdeau DH, Parks B, Tong T, Loescher L, Moon TE. Cutaneous malignant melanoma (Arizona Cancer Center experience). I. Natural history and prognostic factors influencing survival in patients with stage I disease [published erratum appears in Cancer 1989;63:1436]. Cancer 1988;62:1207-14.

3. Berdeau DH, Meyskens FL Jr, Parks B, Tong T, Loescher L, Moon TE. Cutaneous malignant melanoma. II. The natural history and prognostic factors influencing the development of stage II disease. Cancer 1989;63:1430-6.

4. Shikin H, Takahashi T, Resnick LA, Oettgen HF, Old LJ. Cell surface antigens of human malignant melanoma. III. Recognition of autoantibodies with unusual characteristics. J Exp Med 1977;145:784-9.

5. Houghton AN, Eisinger M, Albino AP, Cairncross JG, Old LJ. Surface antigens of melanocytes and melanomas. Markers of melanocyte differentiation and melanoma subsets. J Exp Med 1982;156:1755-66.

6. Morton DL, Eilber FR, Joseph WL, Wood WC, Trahan E, Ketcham AS. Immunologic factors in human sarcomas and melanomas: a rational basis for immunotherapy. Ann Surg 1970;172:740-9.

7. Gutterman JU, Mavligit G, McBride C, Frei E 3d, Freireich EJ, Hersh EM. Active immunotherapy with B.C.G. for recurrent malignant melanoma. Lancet 1973;1:1208-12.

8. Barth A, Morton DL. The role of adjuvant therapy in melanoma management. Cancer 1992;75(2 Suppl):726-34.

9. Spiteri LE, Sagebiel R. A randomized trial of levamisole versus placebo as adjuvant therapy in malignant melanoma. N Engl J Med 1980;303:1143-7.

10. Blume MR, Rosenbaum EH, Cohen RJ, Gershew J, Glassberg AB, Shepley E. Adjuvant immunotherapy of high risk stage I melanoma with transfer factor. Cancer 1981;47:882-8.

11. Lipton A, Harvey HA, Balch CM, Antle CE, Heckard R, Barolucci AA. Corynebacterium parvum versus bacille Calmette-Guerin adjuvant immunotherapy of stage II malignant melanoma [see comment citation in Medline]. J Clin Oncol 1991;9:1151-6.

12. Stewart WE II. The interferon system. New York: Springer-Verlag, 1981.

13. Nathan CF, Horowitz CR, de la Harpe J, Vaidhan-Raj S, Sherwin SA, Oettgen HF, et al. Administration of recombinant interferon γ to cancer patients enhances monocyte secretion of hydrogen peroxide. Proc Natl Acad Sci U S A 1983;82:8068-90.

14. Herlyn M, Guerry D, Kowalski H. Recombinant γ-interferon induces changes in expression and shedding of antigens associated with normal human melanocytes, nevus cells, and primary and metastatic melanoma cells. J Immunol 1985;134:4226-30.

15. Houghton AN, Thomson TM, Gross D, Oettgen HF, Old LJ. Surface antigens of melanoma and melanocytes. Specificity of induction of α antigens by human γ-interferon. J Exp Med 1984;160:255-69.

16. Foon KA, Sherwin SA, Abrams PG, Stevenson HC, Holmes P, Maluish AE, et al. A phase I trial of recombinant gamma interferon in patients with cancer. Cancer Immunol Immunother 1985;20:193-7.

17. Kurzrock R, Rosenblum MG, Sherwin SA, Rios A, Telpaz M, Quesada JR, et al. Pharmacokinetics, single-dose tolerance, and biological activity of recombinant γ-interferon in cancer patients. Cancer Res 1985;45:2866-72.

18. Kleinerman ES, Kurzrock R, Wyatt D, Quesada JR, Guterman JU, Fidler IJ. Activation or suppression of the tumoricidal properties of monocytes from cancer patients.
following treatment with human recombinant y-interferon. Cancer Res 1986;46: 5401-5.

(19) Maluish AE, Urba WJ, Longo DL, Overton WR, Coggin D, Crisp ER, et al. The determination of an immunologically active dose of interferon-gamma in patients with melanoma. J Clin Oncol 1988;6:434-45.

(20) Meyskens Fl Jr, Kopecky K, Samson M, Hersh E, Macdonald J, Jaffe H, et al. Recombinant human interferon gamma: adverse effects in high-risk stage I and II cutaneous malignant melanoma [letter]. J Natl Cancer Inst 1990;82:1071.

(21) Cascinelli N, Bufalino R, Morabito A, Mackie R. Results of adjuvant interferon study in WHO melanoma programme [letter]. [see comment citation in Medline]. Lancet 1994;1:913-4.

(22) Kirkwood J, Hunt M, Smith T, Ernstoff M, Borden E, Blum R. A randomized controlled trial of high-dose IFN alfa-2b for high-risk melanoma: the ECOG trial EST-1684. Proc ASCO 1993;12:390.

(23) Balch CM, Houghton AN, Peters LJ, Cutaneous melanoma. In: De Vita VT Jr, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 4th ed. Philadelphia: Lippincott, 1993:1612-61.

(24) Creagan ET, Ahmann DL, Long HJ, Frytak S, Sherwin SA, Chang MN. Phase II study of recombinant interferon-gamma in patients with disseminated malignant melanoma. Cancer Treat Rep 1987;71:843-4.

(25) Ernstoff MS, Trauman T, Davis CA, Reich SD, Winman P, Balser J, et al. A randomized phase I/II study of cutaneous versus intermittent intravenous interferon gamma in patients with metastatic melanoma. J Clin Oncol 1987;5:1804-10.

(26) Meyskens Fl Jr, Liu PY, Tuohill RJ, Sondak VK, Fletcher WS, Jewell WR, et al. Randomized trial of vitamin A versus observation as adjuvant therapy in high-risk primary malignant melanoma: a Southwest Oncology Group study. J Clin Oncol 1994;12:2060-5.
Notes

Supported in part by the following Public Health Service Cooperative Agreement grants awarded by the National Cancer Institute, National Institutes of Health, Department of Health and Human Services: CA13612, CA46368, CA42028, CA20319, CA45377, CA46282, CA45560, CA35128, CA58861, CA12644, CA46113, CA35192, CA4919, CA35261, CA35084, CA35200, CA35262, CA27057, CA16385, CA35281, CA58882, CA35178, CA58416, CA04920, CA03389, CA35429, CA12213, CA38926, and CA32102.

Manuscript received April 6, 1995; revised August 15, 1995; accepted August 15, 1995.

 Depository Libraries . . .

Your Source of Government Information

Information from the Federal Government — on subjects ranging from agriculture to zoology — is available at more than 1,380 Depository Libraries throughout the United States.

These libraries allow you free access to thousands of publications issued by your Government and connect you to a variety of information resources to help answer your questions.

To locate the Depository Library in your area, contact your local library or write to the Federal Depository Library Program, Office of the Public Printer, Washington, DC 20401.

The Federal Depository Library Program

This program is supported by The Advertising Council and is a public service of this publication.