Interferon-α and Chemohormonal Therapy for Patients with Advanced Melanoma

Final Results of a Phase I–II Study of the Cancer Biotherapy Research Group and the Mid-Atlantic Oncology Program

James J. Stark, M.D.[1]
Robert O. Dillman, M.D.[2]
Richard Schulof, M.D.[3]*
Michael C. Wiemann, M.D.[4]
Neil M. Barth, M.D.[2]
Pamela J. Honeycutt, M.D.[5]
Gamini Soori, M.D.[6]

[1] Maryview Medical Center, Portsmouth, Virginia.

[2] Patty and George Hoag Cancer Center, Newport Beach, California.

[3] Presbyterian/St. Lukes Medical Center, Denver, Colorado.

[4] St. Vincent Cancer Center, Indianapolis, Indiana.

[5] Columbia Regional Hospital, Columbia, Missouri.

[6] Bergan Mercy Medical Center, Omaha, Nebraska.

Parts of this work were presented at the 1992 meeting of the Society of Biological Therapy in Williamsburg, Virginia, and portions appeared in abstract form in 1993 in the *Journal of Immunotherapy* (1993;13:72) and the *Proceedings of the American Society of Clinical Oncology* (1993;12:392).

The authors thank various members of the Cancer Biotherapy Research Group central office, including Jerry Arnold, R.N., and Carol DePriest, R.N., for their assistance in data acquisition, Curtis Church, Ph.D., for statistical analysis. They also thank Gini Battle of the Hoag Cancer Center for clerical assistance.

* Deceased.

Address for reprints: Robert O. Dillman, M.D., Hoag Cancer Center, One Hoag Drive, Building 41, Newport Beach, CA 92658.

Received July 2, 1997; revision received November 3, 1997; accepted November 3, 1997.

BACKGROUND. The treatment of metastatic melanoma remains unsatisfactory despite encouraging results with biotherapy and combination chemotherapy. Combining these two modalities may improve outcomes for such patients.

METHODS. Patients who were eligible for this study had metastatic melanoma and were in good medical condition. The following regimen was used: dacarbazine 220 mg/m^2 and cisplatin 25 mg/m^2 administered intravenously (i.v.) daily $\times$ 3 days every 3 weeks, carmustine 150 mg/m^2 i.v. every 6 weeks, tamoxifen 10 mg administered orally twice a day, and interferon-α2b 3.0 thousandths of an International Unit (mIU)/m^2 administered subcutaneously on Days 1, 3, and 5 of each week a patient was on study. Patients were analyzed for toxicity, tumor response, and survival. Because of severe toxicity, partway through the trial the regimen was modified as follows: dacarbazine and cisplatin were given at the same dose every 4 weeks, and carmustine was reduced to 100 mg/m^2 every 8 weeks.

RESULTS. Forty-two patients with a median age of 61 years were enrolled. Twenty had liver metastases and 18 had lung metastases. Forty patients were evaluable for toxicity, 17 at the original dose and 23 at the new dose; of these, 35 were evaluable for response. Hematologic toxicity was severe at the original dose: 10 patients had a nadir $< 500/\mu$L, 10 had platelets $< 25{,}000/\mu$L, and 2 discontinued treatment because of toxicity. At the reduced dose, 5 had a nadir absolute neutrophil count < 500, and 10 had platelets $< 25{,}000$. Of the 35 patients evaluable for response, there were 10 partial responses (29%) and 2 minimal responses. Median duration of disease control was 4 months. Median survival was 8.9 months. One partial and one minimal responder were removed from the study because they experienced toxicity while still responding.

CONCLUSIONS. The addition of interferon-α to this chemohormonal therapy regimen greatly increased toxicity without improving the response rate or survival for patients with metastatic melanoma. ***Cancer* 1998;82:1677–81.**
© 1998 American Cancer Society.

KEYWORDS: melanoma, interferon-α, chemotherapy, biotherapy.

The incidence of malignant melanoma is increasing throughout the world, probably because of changes in life-styles over the past 30 years that have resulted in more sun exposure.[1] Surgery continues to be the mainstay of treatment for patients with newly diagnosed disease, but patients with recurrences and metastases have not responded well to systemic treatment.[2] Until recently, chemotherapy was considered ineffective in the management of metastatic melanoma. However, with the advent of platinum-based combination chemotherapy in conjunction with tamoxifen, various investigators reported an increase in partial and complete responses over those

observed with single agents.[3,4] Furthermore, McClay et al. suggested that the presence of tamoxifen was necessary to preserve the antitumor effect of the combination.[5] This issue was recently addressed in a randomized trial in Canada, which yielded a response rate of 30% in the treatment arm given chemotherapy plus tamoxifen and 21% in the arm given chemotherapy alone.[6] This difference was not statistically significant, although the sample size was too small to conclude that the response rates were equivalent, and there was not difference in survival between the two arms. Thus, at the time NBSG 90-06 was designed, it appeared appropriate to the investigators to include tamoxifen in the treatment program. We considered data suggesting that interferon-α had activity as a single agent in the treatment of melanoma,[7] the finding that interferon was synergistic in vitro with certain chemotherapy agents,[8,9] and encouraging clinical results reported for the combination of interferon-α and dacarbazine[10–13]; and in light of these findings, it seemed reasonable to try to combine interferon-α with this popular chemohormonal therapy regimen. With this rationale, the Cancer Biotherapy Research Group (CBRG), formerly known as the National Biotherapy Study Group (NBSG),[14] and the Mid-Atlantic Oncology Program (MAOP) launched a Phase I–II trial using the four-drug chemohormonal program in combination with interferon-α to determine whether there was a suggestion of synergy or additive effects. Preliminary results of this trial have been reported in abstract form.[15,16] Final results of the trial are reported herein.

METHODS

NBSG 90-06 was designed as an open-label, single-arm, Phase II trial of combination chemohormonal therapy and interferon biotherapy. All patients enrolled in this trial gave written informed consent, and the protocol itself was reviewed by the appropriate institutional review boards of participating institutions.

Eligibility

Patients were required to have histologically confirmed malignant melanoma and be age $\geq$18 years at the time of study enrollment. They were to have measurable metastatic disease and no prior chemotherapy, biotherapy, or tamoxifen. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and a minimum life expectancy of 3 months. Hematologic parameters included a granulocyte count of $>1500/\mu$L, a platelet count of $>125{,}000/\mu$L, a serum creatinine level of <2.0 mg/dL, and a normal prothrombin time. Patients were specifically excluded for prior clotting diathesis, such as phlebitis or pulmonary embolism; prior myocardial infarction; central nervous system metastases that were not controlled with therapy; active infection; or pregnancy.

TABLE 1
Treatment Schedules

Schedule A	Schedule B
Carmustine 150 mg/m^2 i.v. q 6 wks	Carmustine 100 mg/m^2 i.v. q 8 wks
Dacarbazine 220 mg/m^2 i.v. q.d. $\times$ 3 q 3 wks	Dacarbazine 220 mg/m^2 i.v. q.d. $\times$ 3 q 4 wks
Cisplatin 25 mg/m^2 i.v. q.d. $\times$ 3 q 3 wks	Cisplatin 25 mg/m^2 i.v. q.d. $\times$ 3 q 4 wks
Tamoxifen 10 mg p.o. b.i.d.	Tamoxifen 10 mg p.o. b.i.d.
Interferon alpha-2b 3.0 mu/m^2 s.c. q.o.d. 3 times a wk	Interferon alpha-2b 3.0 mu/m^2 s.c. q.o.d. 3 times a wk

i.v.: intravenously; p.o.: orally; s.c.: subcutaneously; q.d.: daily; q.o.d.: every other day.

Treatment Regimen

Both treatment schedules used in the course of this trial are shown in Table 1. The interferon utilized in this trial was interferon-α2b (Intron A, Schering Corp., Kenilworth, NJ). After an interim analysis of toxicity, the regimen was modified as shown in Schedule B, by decreasing the frequency of dacarbazine and cisplatin to every 4 weeks instead of every 3 weeks and reducing the dose of carmustine to 100 mg/m^2 and the frequency of that agent from every 6 weeks to every 8 weeks. The doses of tamoxifen and interferon-α2b were not altered. There were 17 patients enrolled for Schedule A and 25 for Schedule B.

Assessment of Response

Before initiation of therapy, patients underwent complete history and physical examination, complete blood cell count (CBC), chemistry panel (SMA-12 or the equivalent), prothrombin time, partial thromboplastin time, urinalysis, chest X-ray, electrocardiogram, computed tomography (CT) or magnetic resonance imaging of the brain, and a CT evaluation of the chest and abdomen. CBC was repeated weekly and patients were reexamined monthly. Patients were reevaluated for tumor response at Week 7 on Schedule A and Week 9 on Schedule B. Responses were evaluated using standard criteria for complete and partial response. Complete remission (CR) was defined as the disappearance of all disease for $\geq$4 weeks. Partial response (PR) was defined as at least a 50% reduction in the sum of the products of the cross-sectional greatest dimensions of all measurable lesions without the appearance of new lesions, or an increase in the size of any single existing lesion. Minimal response (MR) was defined as a decrease of $\geq$25% but $<$50% in the sum of cross-sectional greatest dimensions, or the disap-

TABLE 2
Patient Characteristics

Patients	Site of metastatic involvement
42 patients studied: 28 males, 14 females	Liver: 20
All had ECOG <2 (23 were ECOG 0)	Lung: 18
Median age: 61 yrs	Bone: 5
40 had no prior chemotherapy or biotherapy	Subcutaneous/lymph nodes: 19
	Brain: 0
	Many patients had 2 or 3 of above

ECOG: Eastern Cooperative Oncology Group performance status.

pearance of some lesions while others grew. Progressive disease (PD) was defined as an increase in the sum of the products of the cross-sectional greatest diameters of measurable lesions. Stable disease (SD) was defined as any condition between an MR and a PD.

Statistical Analysis

Comparisons of response rates between the two dose regimens were made with a chi-square test of homogeneity. Actuarial survival was estimated using the Kaplan–Meier method,[17] and comparison of survival distributions for the two dose regimens were made with a Wilcoxon log rank test.

RESULTS

Patient accrual to NBSG 90-06 took place between September 26, 1990, and June 30, 1994. Forty-two patients were enrolled; their characteristics are depicted in Table 2. There were 40 patients evaluable for toxicity and 35 evaluable for response. Two patients from MAOP sites were inevaluable for toxicity or tumor response because no data regarding these two patients was ever submitted after they were enrolled. The other five patients were inevaluable for response for the following reasons: One patient was on study for 16 days but discontinued because of various toxicities; 1 patient went off study after 20 days because of delirium/dementia that was attributed to other medications; 1 patient discontinued treatment after 21 days because of myalgias; 1 patient stopped treatment after 21 days to pursue unorthodox treatment in Mexico; and 1 patient was on study for 31 days, then died of pulmonary embolism. One patient on Schedule B reported that she was ceasing treatment after 43 days because of nausea, vomiting, and malaise. Even though the protocol would not have required tumor measurements until Week 9, a scan on Day 47 did show PD in her liver; thus, she was considered to have PD.

TABLE 3
Treatment Toxicities for 40 Patients with Metastatic Melanoma Who Were Enrolled in the NBSG 90-06 Trial of Dacarbazine, Carmustine, Cisplatin, Tamoxifen, and Interferon-α2b

Schedule A	Schedule B
No. of patients: 16	No. of patients: 24
ANC <1000: 3	ANC <1000: 9
ANC <500: 5	ANC <500: 3
ANC <200: 5	ANC <200: 2
Platelets <75,000: 2	Platelets <75,000: 3
Platelets <50,000: 4	Platelets <50,000: 5
Platelets <25,000: 10	Platelets <25,000: 10
Toxic deaths: 0	Toxic deaths: 0
Other toxicities: none severe	Other toxicities: 1 pulmonary embolus

ANC: absolute neutrophil count; DVT: deep venous thrombosis.

TABLE 4
Response Rates for 42 Patients with Metastatic Melanoma Who Were Enrolled in NBSG 90-06

	PR[a]	MR[b]	SD	PD	Inevaluable	Total
All patients	10	2	10	13	7	42
Schedule A	6	2	3	4	3	18
Schedule B	4	0	7	9	4	24

PR: partial response; MR: minimal response; SD: stable disease; PD: progression of disease; CI: confidence interval.
For evaluable patients:
[a] PR rate of 29% (95% CI, 15–43%).
[b] PR + MR of 34% (95% CI, 20–50%).

Toxicity

After an interim analysis revealed severe hematologic toxicity, drug doses were modified as shown in Table 1. Toxicity data for each schedule of drug administration are shown in Table 3. Despite the reduction in drug doses, there was still significant toxicity associated with Schedule B. Two patients went off study because of drug-related toxicities, and both were being treated per Schedule A.

Tumor Response

Table 4 shows the response rates for all patients treated as well as for Schedules A and B. The overall response rate was 29%, which was similar to that observed in the multi-institutional Canadian randomized trial utilizing these chemotherapy agents with or without tamoxifen, but without interferon-α.[6]

Survival

Failure free and overall survival for all patients enrolled in this study are shown in Figure 1. There was

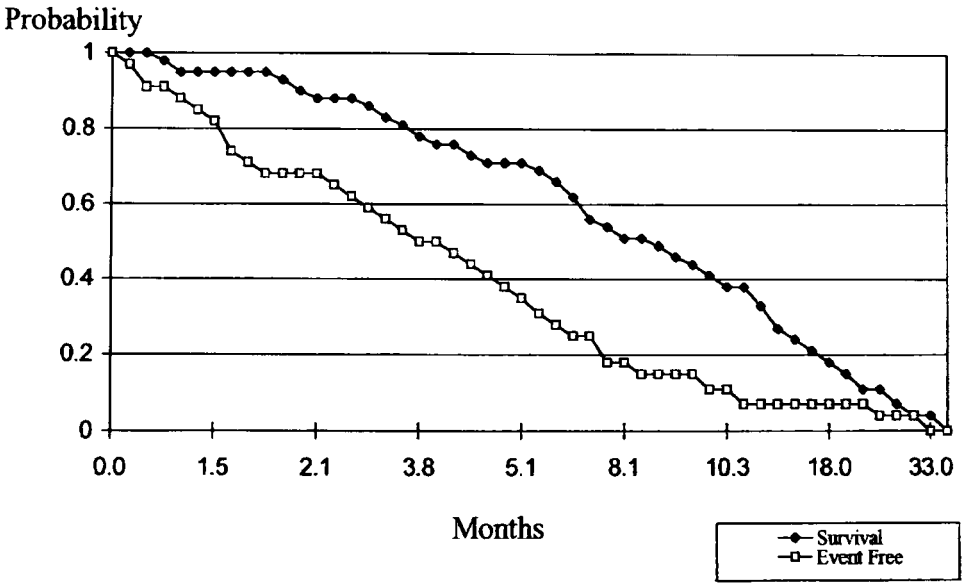

FIGURE 1. Event free and overall survival are shown for 40 patients with metastatic melanoma who were enrolled in the NBSG 90-06 trial of dacarbazine, carmustine, cisplatin, tamoxifen, and interferon-α.

no survival difference for patients treated with the two different regimens. The median duration of response with Schedule A was 3.7 months compared with 4.5 months for Schedule B and 4.1 months for all responders. The median duration of survival was 8.9 months for Schedule A, 9.4 months for Schedule B, and 8.9 months for all patients. Median survival for patients who had a CR or PR was 10 months compared with 8.5 months for nonresponders.

DISCUSSION

We added interferon-α2b to what was then considered the best available chemohormonal therapy in the treatment of metastatic melanoma, in an effort to improve the response rate and duration of response. Prior experience with chemotherapy-interferon combinations suggested that this approach would not lead to excessive toxicity.[10–13] After the initiation of this study, Pyrhönen et al. reported that the addition of interferon-α to the four-drug combination of dacarbazine, vincristine, bleomycin, and lomustine resulted in an overall response rate of 62% and a CR rate of 13%.[18] In that trial, patients who had a CR had a median duration of response of 26.7 months, whereas patients who had a PR had a median duration of response of 6.6 months. Three of the six with CR were still alive at the time of publication. In that study, the investigators used doses of chemotherapy and interferon that were lower than those used in NBSG 90-06.

In another trial, McLeod et al. combined dacarbazine (DTIC) and recombinant interferon-α2a and reported a response rate of 34%.[10] A subsequent confirmation study resulted in a response rate of 26%.[12] In a randomized trial, Faulkson et al. observed a higher response rate and survival advantage with the combination of interferon-α2b and DTIC than with DTIC alone.[13] Investigators at City of Hope Medical Center, Duarte, California, reported a 24% objective response rate for the combination of cisplatin and interferon-α in patients with metastatic melanoma.[19] Based on the disparate results emanating from these trials, it is unclear whether combination chemotherapy is actually better than single-agent DTIC, and the precise role of interferon-α in combination with or sequenced with chemotherapy is still unclear.

The failure of the addition of interferon, as used in this study, to increase the response rate or duration of disease control was disappointing, especially in light of the increased toxicity observed. The response rate among patients who were evaluable for response was similar to that observed in the multicenter Canadian trial of chemohormonal therapy.[6] If one were to analyze response rate in our trial on the basis of intent to treat, the observed response rate would drop from 29% to 25% because 5 patients failed to continue the treatment, primarily because of toxicity.

Since this study was initiated, several groups have reported noteworthy chemobiotherapy combinations. A group at the M. D. Anderson Cancer Center in Houston, Texas, has reported their experience using cisplatin, vinblastine, and DTIC together with interferon-α and interleukin-2 (IL-2) in a variety of schedules.[20] Based on their sequential trials, they feel that it is important to give chemotherapy followed by biologic therapy.

After the closure of NBSG 90-06, the CBRG embarked on a new protocol, NBSG 94-11, alternating this same four-drug chemohormonal therapy with in-

terferon-α and IL-2 in moderate doses in the outpatient setting. The early results of that trial suggest that when the biologic therapy is given after the chemohormonal therapy, rather than at the same time, the hematologic toxicity is much less severe.[21]

REFERENCES

1. Glass AG, Hoover RN. The emerging epidemic of melanoma and squamous cell skin cancer. *JAMA* 1989;262:2097–100.
2. Johnson TM, Smith JW II, Nelson BR, Chang A. Current therapy for cutaneous melanoma. *J Am Acad Dermatol* 1995; 32:689–707.
3. Del Prete S, Maurer L, O'Donnel J, Forcier RJ, LeMarbre P. Combination chemotherapy with cisplatin, carmustine, dacarbazine, and tamoxifen in metastatic melanoma. *Cancer Treat Rep* 1984;68:1403–5.
4. McClay E, Mastrangelo M, Bellet RE, Berd D. Combination chemo/hormonal therapy in the treatment of malignant melanoma. *Cancer Treat Rep* 1987;71:465–9.
5. McClay EF, Mastrangelo MJ, Sprandio JD, Bellet RE, Berd D. The importance of tamoxifen to a cisplatin-containing regimen in the treatment of metastatic melanoma. *Cancer* 1989;63:1292–5.
6. Rusthoven JJ, Quirt IC, Iscoe NA, McCulloch PB, James KW, Lohmann RC, et al. Randomized, double-blind, placebo-controlled trial comparing the response rates of carmustine, dacarbazine, and cisplatin with and without tamoxifen in patients with metastatic melanoma. *J Clin Oncol* 1996; 14:2083–90.
7. Kirkwood JM. Systemic therapy of melanoma. *Curr Opin Oncol* 1994;6:204–11.
8. Bridgewater JA, Gore ME. Biological response modifiers in melanoma. *Br Med Bull* 1995;51:656–77.
9. Wadler S, Schwartz EL. Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies: a review. *Cancer Res* 1990; 50:3473–86.
10. McLeod GRC, Thomson DB, Hersey P. Recombinant interferon alpha-2a in advanced malignant melanoma; a phase I–II study in combination with DTIC. *Int J Cancer* 1987; 1(Suppl):31–5.
11. McLeod GRC, Thomson DB, Hersey P. Clinical evaluation of interferons in malignant melanoma. *J Invest Dermatol* 1990;95(Suppl):185–7.
12. Kirkwood JM, Ernstoff MS, Giuliano A, Gams R, Robinson WA, Costanzi J, et al. Interferon α-2a and dacarbazine in melanoma. *J Natl Cancer Inst* 1990;82:1062–3.
13. Falkson CL, Falkson G, Falkson HC. Improved results with the addition of interferon alpha-2b to dacarbazine in the treatment of patients with metastatic malignant melanoma. *J Clin Oncol* 1991;9:1403–8.
14. Dillman RO, Crispin R, Oldham RK. The Cancer Biotherapy Research Group (CBRG), formerly the National Biotherapy Study Group (NBSG): a 10-year perspective. *Cancer Biother* 1997;12:229–42.
15. Stark JJ, Schulof R, Wiemann M, Barth N, Honeycutt P, Soori G. Alpha interferon and chemo-hormonal therapy in advanced melanoma: a phase I–II NBSG/MAOP study [abstract]. *J Immunother* 1993;13:72.
16. Stark JJ, Schulof R, Wiemann M, Barth N, Honeycutt P, Soori G. Alpha interferon and chemo-hormonal therapy in advanced melanoma: a phase I–II NBSG/MAOP study [abstract]. *Proc Am Soc Clin Oncol* 1993;12:236.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
18. Pyrhönen S, Hahka-Kemppinen M, Muhonen TA. A promising interferon plus four-drug chemotherapy regimen for metastatic melanoma. *J Clin Oncol* 1992;10:1919–26.
19. Margolin KA, Doroshow JH, Akman SA, Leong LA, Morgan RJ, Somlo G, et al. Phase II trial of cisplatin and α-interferon in advanced malignant melanoma. *J Clin Oncol* 1992; 10:1574–8.
20. Anderson CM, Buzaid AC, Legha SS. Systemic treatments for advanced cutaneous melanoma. *Oncology* 1995;9:1149–58.
21. Honeycutt P, Wiemann M, Bury M, Soori G, Boggs JL, Granick C, et al. Phase II trial of BCNU, DTIC, cisplatin, tamoxifen and outpatient interleukin-2 and interferon-α in the treatment of metastatic melanoma [abstract]. *Proc Am Soc Clin Oncol* 1997;16:506a.