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Adjuvant interferon alfa-2a treatment in resected primary stage II cutaneous melanoma. Austrian Malignant Melanoma Cooperative Group. — Source link

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Published on: 01 Apr 1998 - Journal of Clinical Oncology (American Society of Clinical Oncology)

Topics: Cutaneous melanoma, Adjuvant therapy, Breslow Thickness, Melanoma and Interferon alfa

Adjuvant Interferon Alfa-2a Treatment in Resected Primary Stage II Cutaneous Melanoma

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Purpose: **Patients with primary cutaneous melanoma with a Breslow thickness ≥ 1.5 mm have only a 30% to 70% probability of survival after surgery, and no adjuvant therapy has so far improved this outcome. Since interferon alfa-2a (IFNα2a) exhibits antitumor activity in metastatic melanoma, we investigated whether adjuvant IFNα2a diminishes the occurrence of metastases and thus prolongs disease-free survival in melanoma patients after excision of the primary tumor.**

Patients and Methods: **In a prospective randomized study, 311 melanoma patients with a Breslow thickness ≥ 1.5 mm were assigned to either adjuvant IFNα2a treatment (n = 154) or observation (n = 157) after excision of the primary tumor. IFNα2a was given daily at a dose of 3 mIU subcutaneously (SC) for 3 weeks (induction phase), after which a dose of 3 mIU SC three times per week was given over 1 year (maintenance phase).**

Results: **Prolonged disease-free survival was observed in patients treated with IFNα2a versus those who underwent surgery alone. This difference was significant (*P* = .02) for all patients enrolled onto the study (intention-to-treat analysis) at a mean observation time of 41 months. Subgroup analysis showed that Breslow tumor thickness had no influence on treatment results in the groups of patients investigated.**

Conclusion: **Adjuvant IFNα2a treatment diminishes the occurrence of metastases and thus prolongs disease-free survival in resected primary stage II cutaneous melanoma patients.**

J Clin Oncol 16:1425-1429.* © *1998 by American Society of Clinical Oncology.

DURING THE YEARS 1973 to 1991, the incidence of melanoma increased approximately 4% each year, which is faster than that of any other cancer.[1-5] Early recognition and excision of the primary tumor remains the treatment of choice. Although efforts to improve early diagnosis[2,4-7] and education campaigns[5,8,9] have resulted in earlier detection of melanoma, patients with intermediate- and high-risk primary melanoma without clinically detectable metastases still have only a dismal 30% to 70% probability of survival depending on lesion thickness.[4] No adjuvant therapy has been proven so far to prolong significantly the disease-free interval and to increase the probability of survival in primary cutaneous melanoma patients.[2,5]

Interferons (IFNs) are glycoproteins with diverse immunomodulatory effects on tumor cells.[10-12] The mechanism of action includes both direct antiproliferative and immune-mediated effects via enhanced natural-killer cell activity or upregulation of tumor antigens and/or human leukocyte antigen (HLA) class I and class II antigens.[10] However, in a clinical setting, response rates of metastatic melanoma have been shown to range from as little as 10% to 20% in phase II studies that used different IFNα preparations.[13-15] Patients with nonvisceral disease are more likely to respond, which suggests the use of IFNα2a in microscopic early metastatic tumor might have a greater impact.[4]

Preliminary data have already indicated a beneficial therapeutic effect of adjuvant IFN treatment in patients with regional node metastases[16]; however, the significance disappeared in a further follow-up study.[17] Creagan et al[18] found a possible benefit on disease-free survival for selected patients with stage I and II malignant melanoma. On behalf of the Eastern Cooperative Oncology Group (ECOG), Kirkwood et al[19] reported a significant prolongation of relapse-free survival and a marginal prolongation of overall survival with high-dose adjuvant IFNα2b therapy following surgery for high-risk primary (Breslow depth > 4 mm) or regionally metastatic melanoma. The greatest reduction of relapse rate was found among patients with microscopic regional lymph node metastases that were clinically inapparent.[19]

The Austrian Melanoma Cooperative Group conducted a prospective randomized trial in primary cutaneous melanoma patients (Breslow thickness ≥ 1.5 mm) without clinical evidence of metastases to settle the issue whether adjuvant IFNα2a treatment following surgery has any effect on the outcome in these patients as compared with surgery alone. Here, we show, among a cohort of 311 patients monitored for a mean of 41 months, that adjuvant

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Submitted April 10, 1997; accepted November 14, 1997.

Supported in part by Hoffmann-La Roche, Vienna, Austria.

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0732-183X/98/1604-0048$3.00/0

IFNα2a therapy diminishes the occurrence of metastases and thus prolongs disease-free survival.

PATIENTS AND METHODS

Patients

All clinical protocols were approved by the respective institutional review boards. The risks and benefits of the treatment regimens were explained to each patient in detail and informed consent was obtained from all patients.

A total of 311 patients with primary cutaneous malignant melanoma stage II according to American Joint Committee on Cancer (1992) criteria[20] from seven institutions were enrolled onto this study over a four-year period from February 1990 to September 1994. In all patients, the primary melanoma was excised with safety margins according to international guidelines.[21] Elective lymph node dissection (ELND) was not performed. Histopathologic diagnosis and microstaging according to Clark's level of invasion[22] and Breslow thickness[23] were performed on hematoxylin and eosin–stained specimens according to established criteria.[24,25] The extent of the disease was determined by a standardized staging protocol, which included physical examination, chest x-ray, abdomen and lymph node ultrasound, complete WBC and RBC counts, chemistry profiles, and urinalysis.

The criteria for eligibility included the following: (1) primary cutaneous malignant melanoma with a tumor thickness ≥ 1.5 mm according to Breslow[23]; (2) no evidence of regional and/or distant metastases; (3) patient age greater than 18 and less than 75 years; (4) and the absence of pregnancy, severe internal disease, cardiomyopathy, secondary neoplasms, and previous chemotherapy and/or immunotherapy.

Treatment

After surgery, patients were randomly assigned to receive either adjuvant treatment with IFNα2a (Roferon A; Hoffmann-La Roche, Vienna, Austria) or observation (control group). Patients assigned to the IFNα2a protocol were instructed how to dose and self-administer IFNα2a by subcutaneous (SC) injection. IFNα2a treatment was initiated within 4 weeks after the excision of the primary melanoma and was administered at a daily dose of 3 mIU by SC application in an induction phase for 3 weeks, followed by a dose of 3 mIU SC three times per week to complete 1 year of treatment. At this time, treatment was discontinued, but follow-up evaluation was continued. Dose modifications were performed in accordance with the common toxicity scale of the World Health Organization (WHO).[26] After the first postoperative year of treatment or observation, both groups of patients underwent identical follow-up procedures.

Determination of Response and Follow-Up

Response to treatment was evaluated by monthly physical examinations. Laboratory examinations included RBC and WBC counts, blood chemistry, and urinalysis, which were performed every 3 months. Chest x-ray and lymph node and abdominal ultrasound were performed every 6 months. Progression was defined as the onset (detection) of melanoma metastases. In this case, IFN treatment was discontinued and patients were monitored by physical examinations every 3 months and laboratory and imaging controls at 6-month intervals.

Statistical Analysis

The primary analyses were performed on an intention-to-treat basis and included all patients who underwent randomization. Brewlow thickness represents the single most important prognostic factor in primary melanoma. Instead of a stratified randomization, it was preplanned to account for this continuous risk factor by the proportional hazards method. Disease-free interval was defined as the period from the date of inclusion to the date of progression. Data of patients who were disease-free or lost to follow-up evaluation were censored as of the last date seen. The probability of remaining free of progression during the follow-up period was analyzed by means of Kaplan-Meier survival estimates, and event curves were compared by the log-rank test. Comparisons between the two treatment groups were performed with χ^2 tests for categorical variables. A P value of $\leq .05$ was considered statistically significant. All tests performed were two-tailed. Subgroup analysis was performed by Cox regression model. SAS software (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS

Intention-to-Treat Analysis

A total of 311 patients with primary cutaneous melanoma (Breslow thickness ≥ 1.5 mm) from seven institutions were enrolled onto this study (intention-to-treat). The clinical and histopathologic characteristics of the patients are listed in Table 1. Following surgery of the primary melanoma, patients were randomly assigned to receive either adjuvant IFNα2a treatment or observation. A prolongation of the disease-free survival time was observed in patients who were treated by surgery plus IFNα2a as compared with those treated by surgery alone. This difference was significant

Table 1. Clinical and Histopathologic Characteristics of Patients Enrolled Onto the Study (intention-to-treat)

Characteristic	IFNα2a		Control		Total	
	No.	%	No.	%	No.	%
No. of patients	154	49.5	157	50.5	311	100.0
Age, years						
Median	55		57		56	
Range	19-75		20-78		19-78	
Sex						
Male	78	50.6	80	51.0	158	50.8
Female	76	49.4	77	49.0	153	49.2
Localization						
Not assessable	2	1.3	2	1.3	4	1.3
Trunk	60	39.0	64	40.8	124	39.9
Extremities	78	50.6	80	51.0	158	50.8
Head and neck	14	9.1	11	7.0	25	8.0
Clark level						
Not assessable	3	1.9	4	2.5	7	2.3
II	1	0.6	1	0.6	2	0.6
III	31	20.1	36	22.9	67	21.5
IV	111	72.0	101	64.4	212	68.2
V	8	5.2	15	9.6	23	7.4
Breslow tumor thickness (mm)						
1.5-2.0	43	27.9	38	24.2	81	26.0
2.01-3.0	40	26.0	45	28.7	85	27.3
3.01-4.0	28	18.2	32	20.4	60	19.3
> 4.01	43	27.9	42	26.7	85	27.4

Note. The clinical and histopathologic characteristics in both groups were comparable in that no statistically significant differences were observed.

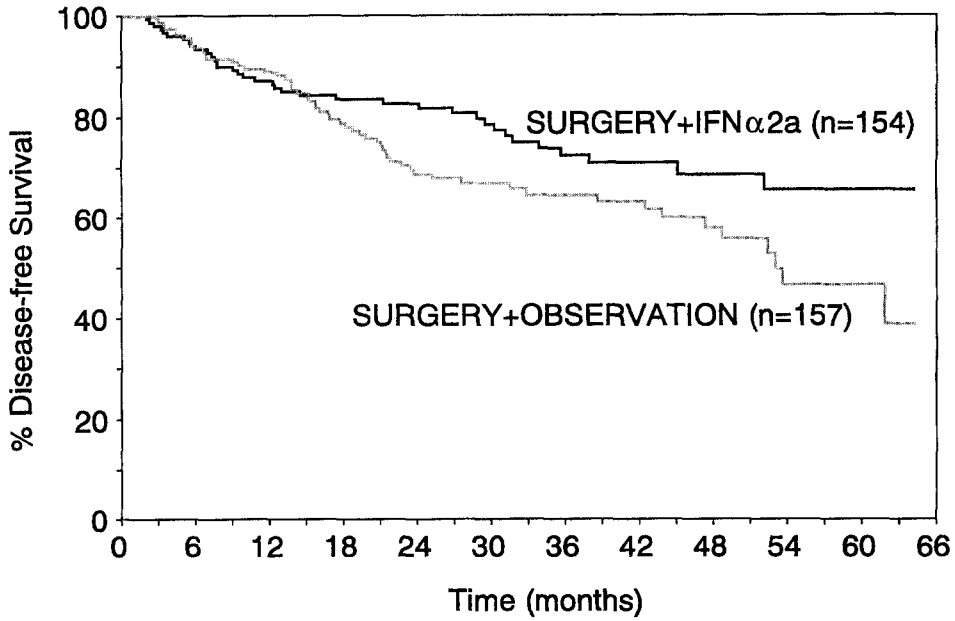

Fig 1. Kaplan-Meier estimates of cumulative disease-free interval in 311 patients (intention-to-treat) randomly assigned to either surgery plus IFNα2a (n = 154) or surgery and observation (n = 157). Disease-free survival was significantly ($P < .02$) prolonged in patients treated with adjuvant IFN.

($P = .02$) based on log-rank analysis (Fig 1). Thirty-seven of 154 patients developed metastases in the surgery-plus-IFNα2a group, whereas in the control group, 57 of 157 patients showed progressive disease. The mean observation period was 41 months (SD = 14) and every patient had at least 1 year of follow-up evaluation.

Per-Protocol Analysis

Eighteen of 311 patients enrolled onto this study were withdrawn due to non–melanoma-related death, loss to follow-up evaluation, or adverse effects (Table 2). Among 293 assessable patients, 143 received IFNα2a treatment and 150 belonged to the observation group. In the per-protocol analysis, adjuvant IFNα2a treatment was again found to provide a significant ($P = .02$) disease-free survival increase as determined by log-rank analysis.

Table 2. Reasons for Withdrawal From the Study (ineligible patients)

Reason for Withdrawal	Surgery + IFNα2a	Surgery + Observation
Non–melanoma-related death	2	2
Lost to follow-up	4	5
Adverse effects	5	0
Total	11	7

Note. Numbers of patients withdrawn from the study within the first year were comparable in both groups. Adverse effects occurred only in the IFN group. Adverse effects that resulted in treatment violation included persistent thrombocytopenia (n = 1), leukopenia (n = 1), cardiac arrhythmia (n = 1), hyperthyroidism (n = 1), the onset of diabetes (n = 1), and arthralgia (n = 1).

Sites of Relapses and Mortality

The sites of relapses are listed in Table 3. The mortality rate (death related to melanoma) was 17 patients in the IFN group versus 21 patients in the observation arm.

Subgroup Analysis

In a subgroup analysis, the benefit of the IFNα2a treatment was independent of tumor thickness as calculated by Cox regression analysis ($P = .001$) using Breslow thickness[23] as the single most important prognostic factor in primary cutaneous melanoma.

Side Effects

The symptoms commonly attributed to IFNα2a therapy were generally mild or moderate and consisted primarily of leukopenia, headache, malaise, nausea, weakness, fever, and mild psychogenic depression. In eight patients, a dose reduction was necessary (WHO toxicity scale II) for a median period of 14 days (range, 3 to 30), and in 12 patients, IFN therapy had to be transiently discontinued for a median of 11 days (range, 1 to 21). In five patients, IFN treatment

Table 3. Primary Sites of Relapse

	Surgery + IFNα2a		Surgery + Observation	
Site	No.	%	No.	%
Lymph node	27	17.5	37	23.5
Skin	6	3.8	12	7.6
Visceral	4	2.5	8	5.0
Total	37	24.0	57	36.3

had to be permanently discontinued (Table 2) due to adverse effects, such as persistent thrombocytopenia and leukopenia, onset of diabetes, hypertension, cardiac arrhythmia, hyperthyroidism, arthralgia, or other symptoms not necessarily related to IFN therapy.

DISCUSSION

A significant proportion of patients with primary cutaneous melanoma develop metastatic disease, despite curative attempts by surgical procedures. In fact, patients with primary lesions thicker than 1.5 mm have a greater than 50% likelihood of progression (metastasis) within 10 years after excision.[3-5,10] For those who develop distant metastases, life expectancy is limited (median survival, ~ 6 months) and existing chemotherapeutic regimens have not been demonstrated to increase survival.[4,5,10] The development of postoperative adjuvant therapies to decrease the likelihood of progression and prolong survival therefore assumes a high level of priority.[10] Here, we report on the beneficial effect of adjuvant IFNα2a treatment on the main end point variable of the study, postsurgical disease-free survival in primary cutaneous melanoma patients.

A prolongation of the disease-free survival interval was observed in patients treated with IFNα2a as compared with those who underwent surgery alone. This effect was seen in both assessable patients (per-protocol analysis), as well as in the analysis of all patients entered onto the study (intention-to-treat analysis). The primary sites of metastases was the lymph nodes in both groups of patients investigated (Table 3).

The mortality rate, ie, death related to melanoma, was 17 patients in the IFNα2-treated group and 21 patients in the group treated by surgery alone. The difference was not expected to be significant due to the limited numbers of events and the limited observation period, since the treatment was initiated in an early stage of the disease.

Our data support the conclusions drawn from the ECOG trial,[19] which reported significant prolongation of disease-free survival by high-dose adjuvant IFNα2b treatment in patients with deep primary Breslow depth greater than 4 mm or regional metastatic disease. Creagan et al[18] reported a possible benefit for selected patients with melanomas greater than 4 mm in thickness and regional disease, but no benefit for patients with melanomas greater than 4 mm without clinically detectable regional metastases. The investigators argued that this might be due to the limited number of patients studied.[18] Our study on a prospectively treated group of high-risk candidates with primary melanomas without clinically detectable metastases supports the hypothesis[4] that the use of IFNα might have a preventive impact on the progression of early microscopic metastatic disease and our data are in concordance with a recently presented French multicenter trial.[27]

The rationale for the treatment schedule chosen in this study was drawn from investigations on advanced disease,[28] which have indicated a beneficial effect of IFNα2a also when administered in a low-dose schedule, as well as from previous studies.[16] IFNα2a 3 mIU daily for 3 weeks in an induction phase and, thereafter, IFNα2a 3 mIU three times per week for 1 year was found to be well accepted as a SC self-application home therapy regimen. IFNα2a treatment was arbitrarily terminated at 1 year, as this period was considered sufficiently long to provide an answer to whether adjuvant IFN therapy delays metastatic disease and also appeared acceptable with regard to tolerance and compliance by patients with metastatic disease. Discontinuation of treatment was not followed by immediate disease progression, as occasionally observed in other studies (N. Cascinelli, personal communication). Whether an extension of the duration of treatment beyond 1 year could further improve the therapeutic efficacy of IFN remains to be answered.

It should be noted that ELND was not performed in any of our patients. This decision was based on the fact that prospective randomized studies[29,30] had failed to demonstrate a beneficial effect of ELND on the disease-free interval and/or survival. We are aware that other, nonrandomized, studies claim a beneficial effect of ELND for at least some subgroups of patients and this question is still under debate.[5,31] In addition, a recently published prospective randomized study[32] indicates a possible benefit of ELND for a subgroup of intermediate-risk patients.

Treatment-related side effects were limited primarily to WHO grade I and II toxicity, with most patients experiencing flulike symptoms, such as malaise, fever, and nausea. Only five of 154 patients had treatment discontinued due to adverse reactions (Table 2), but the symptoms were not necessarily related to IFN therapy.

The results of this study demonstrate that IFNα2a is capable of influencing the outcome of the disease in resected primary cutaneous melanoma patients. We are aware of the fact that data on overall survival and longer follow-up evaluation will further improve our knowledge on adjuvant IFN treatment in melanoma, but for the time being, our data indicate that IFNα2a should be considered as adjuvant treatment in patients with primary stage II cutaneous melanoma.

ACKNOWLEDGMENT

The clinical care of the patients of Ingrid Kallinger, MD, Bahareh Kechavarz, MD, Eva Kindermann-Glebowski, MD, Anita Kirchmayr-

Grabner, MD, Robert Müllegger, MD, Bernhard Partsch, MD, Regina Pfeifer, MD, Margot Püspöck-Schwarz, MD, Erika Richtig, MD, Johanna Staubmann-Kury, MD, Beatrice Thurner, Alexander Winkler, MD, Ingrid H. Wolf, MD, and Martina Zingg-Schir, MD, is acknowledged. We are indepted to Günther Nirnberger, PhD, and Anna Millendorfer, PhD, who performed the statistical evaluation of the data and Dr P. Bauer for critical statistical advice. The excellent monitoring of Verena Stapf, PhD, is acknowledged.

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