



Low-dose adjuvant interferon has not changed overall survival for patients with melanoma, but high doses have improved both disease-free and overall survival.

Jennifer Eisenpresser. *Red Car*. Oil on canvas, 52" × 58".

An Update on Adjuvant Interferon for Melanoma

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Background: *Despite advances in the staging and surgical therapy of melanoma, patients with high-risk resected melanoma still have 5-year recurrence rates of 55% to 80% and 5-year survival rates as low as 25% to 70%. Effective adjuvant therapy is needed for this patient population.*

Methods: *The authors review the literature regarding the use of interferon for the adjuvant therapy of resected melanoma.*

Results: *Low-dose adjuvant interferon regimens have not affected overall survival and have had an inconsistent effect on disease-free survival across different stage groupings. High-dose adjuvant interferon improved disease-free and overall survival in the E1684 and Intergroup E1694 trials. High-dose interferon regimens cause significant morbidity, but quality-adjusted years of life are greater with this therapy.*

Conclusions: *Adjuvant high-dose interferon should be considered standard therapy for all high-risk melanoma patients expected to be able to tolerate the interferon and treated off protocol. In addition, this regimen should serve as the active control in future trials of alternative adjuvant therapies for these patients.*

Introduction

Despite advances in the staging and surgical therapy of melanoma, the 5-year recurrence rates for patients with high-risk resected melanoma are 55% to 80%, and their 5-year survival rates are as low as 25% to 70%. Clearly, there is a need for effective adjuvant therapy in these patients. Historically, adjuvant therapies were developed from those interventions that showed some success in treating advanced melanoma. The premise for this approach is that treatments that are effective against macroscopic melanoma will provide even greater benefit in eradicating micrometastatic disease that is the source of future recurrence and death.

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Traditional cytotoxic chemotherapeutic agents have not proved effective in patients with melanoma, but based on the premise that tumor antigens capable of immune recognition exist in many tumors, including melanoma, attempts have been made to apply immunotherapy to these patients. Early trials suggested some response to a number of these interventions, and interferon alfa therapy produced encouraging response rates of 15% to 20% in metastatic melanoma. Motivated by these results, trials of adjuvant interferon were undertaken for patients with melanoma who were felt to be at high risk for recurrence and death. Following a series of studies of this modality in the Eastern Cooperative Oncology Group (ECOG) and United States Intergroup settings, interferon has emerged as the leading adjuvant therapy for melanoma and a standard against which other approaches are to be compared among patients with good performance status and without contraindications to interferon.

Interferon Biology

Isaacs and Lindenmann¹ identified interferons in 1956. As early as the 1960s, interferons demonstrated antitumor activity in laboratory models. Despite intensive investigation since then, the mechanism of action remains incompletely understood.

Human interferons are classified as alpha, beta, and gamma. Alpha interferons are produced in vitro by leukocytes in response to a viral challenge. This group of interferons has been evaluated most extensively in trials of adjuvant therapy. Interferons function by binding to cell surface receptors, interacting with specific gene sites in both normal and neoplastic cells.² They modulate the expression of host natural killer cells, T cells, monocytes, dendritic cells, and class I and II major histocompatibility (MHC) antigens in both neoplastic and nonneoplastic host tissues. Through this enhancement of MHC expression, interferons have been theorized to render malignant cells more antigenic. Interferons have also been shown to have a growth inhibitory effect when added to tumor cells in vitro. An apparent inhibition of angiogenesis has been demonstrated,^{2,3} and some studies have suggested that interferons may increase infiltration of CD4+ T-cells into melanoma tumors.^{4,5}

Clinical Studies of Adjuvant Interferon

The clinical trials of adjuvant interferon for melanoma have evaluated two broad categories of regimens referred to as low-dose interferon (LDI) and high-dose interferon (HDI). Advantages proposed for LDI

regimens include simplicity of subcutaneous (SC) administration and perhaps lower morbidity, while HDI regimens have been suggested to be more effective.

Low-Dose Adjuvant Interferon

One of the first major trials of LDI was the World Health Organization's WHO-16 trial,⁶ which was recently updated to a median follow-up of 88 months.⁷ This trial randomized 444 node-positive patients with melanoma to postoperative LDI (3 million units [MU] SC 3 times per week for 3 years) vs observation. Five-year disease-free survival (DFS) was 28% for those receiving LDI and 28% for those treated with postoperative observation ($P=.50$). The 5-year overall survival (OS) was 35% for the interferon group vs 37% for the observation group ($P=.72$). The French Interferon trial⁸ randomized 499 patients (489 eligible) with melanomas thicker than 1.5 mm without clinically apparent lymph node metastases to postoperative observation vs LDI (3 MU 3 times per week for 18 months). At a median of 5 years of follow-up, this study showed a significant improvement in the relapse-free interval ($P=.035$) and a trend toward improved OS ($P=.059$) with adjuvant interferon therapy. In the Austrian Interferon trial,⁹ 311 patients were randomized to postoperative observation vs LDI (3 MU daily for 3 weeks followed by 3 MU 3 times per week for 1 year). LDI was shown to increase DFS compared to observation (72% vs 64% at 3 years), but again there was no difference in OS. Finally, the European Organization for Research and Treatment of Cancer (EORTC) trial 18871¹⁰ randomized 830 patients with melanoma thicker than 3 mm or with lymph node metastases to LDI (a very low dose of 1 MU SC 3 times per week) vs interferon gamma vs Iscador (an herbal immunomodulator made of extracts from *Viscum album*) vs observation. There were no significant differences among the groups in DFS or OS.

Thus these four trials, taken together, suggest that adjuvant LDI fails to impact OS. In addition, whether it improves DFS in high-risk melanoma patients remains unclear, although a transient impact on DFS in intermediate-risk patients is suggested by the French and Austrian trials. However, these trials differed significantly in their patient eligibility criteria so that individual trial results should not be considered as one group.

High-Dose Adjuvant Interferon

Three major randomized trials evaluated the role of adjuvant HDI in high-risk melanoma patients (Table). These trials used an intravenous (IV) induction phase of interferon alfa-2b for 4 weeks followed by prolonged SC therapy for 11 months. The design of the regimen

Major Trials Evaluating the Role of Adjuvant HDI in High-Risk Melanoma Patients

Trial	Reference	No. of Patients	Therapy	Median Follow-up	Overall Survival	Disease-free Survival*
E1684	10	287	HDI or observation	6.9 years	HDI: 3.82 yrs Obs: 2.78 yrs	HDI: 1.72 yrs Obs: 0.98 yrs
Intergroup #1690/S9111/C9190	11	642	LDI, HDI, or observation	52 months	HDI: 52% LDI: 53% Obs: 55%	HDI: 44% (5-yr) LDI: 40% Obs: 35%
Intergroup #1694/S9512/C509801*	12	880	HDI or GMK vaccine	16 months	HDI: 78% GMK: 73%	HDI: 62% (2-yr) GMK: 49%

* This trial was closed after interim analysis indicated inferiority of GMK vs HDI.

was based on phase I and II studies that showed interferon to have its greatest effect at high doses against metastatic disease. In addition, when a high-dose induction phase given parenterally has been used in the treatment of other malignancies, the production of anti-interferon antibodies has been minimized.

In the ECOG trial E1684,¹¹ a total of 287 patients with high-risk melanomas were enrolled and 280 were evaluable. High-risk patients were defined to include those designated as stage IIB or III by the former American Joint Committee on Cancer staging system (primary tumor >4 mm depth with or without regional lymph node involvement or shallower lesions with pathologically proven lymphatic metastases or regional lymph node recurrence). Patients were treated with wide local excision and complete regional lymph node dissection and then randomized to adjuvant HDI (20 MU/m² IV 5 days per week for 4 weeks, followed by 10 MU/m² 3 days per week SC for 48 weeks) or observation. After a median follow-up of 6.9 years for survivors, both median DFS and median OS were significantly better for the HDI group when compared to the observation group (DFS 1.72 vs 0.98 years; OS 3.82 vs 2.78 years, respectively). At 5 years, the HDI arm was found to have a DFS rate of 37% and OS of 46%, while the observation arm patients had a DFS rate of 26% and an OS of 37%. Since an attempt was made to administer maximally tolerated doses of interferon, it is not surprising that toxicity was significant among those treated with HDI. Grade III toxicity occurred in 67% of patients, grade IV toxicity in 9%, and two patients died secondary to hepatotoxicity. The most prevalent toxicities were constitutional symptoms, myelosuppression, and hepatotoxicity. Nonetheless, HDI appeared to alter the natural history of melanoma in these patients and extend median DFS and OS by approximately 1 year. This landmark study resulted in the approval of HDI by the US Food and Drug Administration for use in high-risk melanoma patients as defined in this trial.

In the Intergroup trial E1690/S9111/C9190,¹² 642 patients (608 eligible) with high-risk melanoma similar to those enrolled in E1684 were treated with wide local excision followed by randomization to HDI, LDI (3 MU 3 times per week SC for 2 years) or observation. It is important to note that unlike in E1684, regional lymph node dissection was not mandated. After a median follow-up of 52 months, the study was unblinded. There were no significant differences in OS for HDI (52%), LDI (53%), or observation (55%). HDI improved DFS (44%) when compared to observation (35%). LDI did not significantly change DFS when compared to observation (40% vs 35%, respectively). A major difference between the results of this trial and E1684 was the 5-year OS rates for those patients in the observation arms (55% in E1690, 37% in E1684). This difference in OS is significant at the $P=.001$ level. A post-hoc analysis revealed that 31% of patients in the observation arm who relapsed received interferon salvage therapy, including all but one of the patients with resectable regional recurrences. These patients had a prolonged OS when compared to those not receiving salvage interferon therapy (mean 2.2 years vs 0.8 year, $P=.0024$), but these patients were not randomized to these therapies so selection bias may have played a role in this difference. It is important to note that approximately one third of the observation patients who experienced a relapse had disease confined to a regional lymph node basin that had not been previously evaluated pathologically. These patients then had a second opportunity for surgical cure in the form of lymphadenectomy and a second opportunity to receive adjuvant systemic therapy with HDI as “salvage therapy.” However, it does not appear that this HDI salvage therapy alone sufficiently explains the prolonged post-relapse survival of patients on the observation arm when compared with patients on the observation arm of E1684. Significant toxicity was again observed with interferon therapy, but there were no deaths due to complications among those treated with HDI.

In the Intergroup trial E1694/S9512/C509801,¹³ 880 patients with resected high-risk melanoma were randomized to HDI or GMK vaccine. GMK vaccine is a formulation containing ganglioside GM2, a melanoma antigen that is the most immunogenic ganglioside expressed on melanoma cells.^{14,15} The trial was closed by the external safety monitoring committee after an interim analysis indicated significant inferiority of GMK vaccine compared to HDI for both survival and disease-free interval. After a median follow-up of 16 months, there was a significant increase in 2-year DFS for the HDI group vs the GMK vaccine group (62% vs 49%) as well as in 2-year OS (78% vs 73%). HDI yielded superior outcomes in all patient subsets. Again, significant toxicity was associated with HDI. A delay or dose reduction was required in 33% of patients during the induction phase and in 38% during the maintenance phase, but only 10% of patients required discontinuation of therapy. This trial is the largest reported study of adjuvant therapy for high-risk melanoma and confirms the positive impact of HDI on both DFS and OS compared with GMK vaccine. This positive effect was demonstrated in reference to a promising vaccine selected for evaluation in this cooperative group trial on the basis of a prior phase III trial. The promise of the GM2 vaccine had been demonstrated by Livingston et al¹⁶ in a randomized, controlled trial conducted at Memorial Sloan Kettering Cancer Center. Some have raised concerns that the GMK vaccine may have adversely influenced the outcome of patients in the E1694 trial, making HDI appear more advantageous than it would have been against an observation control. No data support this suggestion in the original analysis, as recipients of GMK vaccine who showed an antibody response at 1 month were found to have a strong trend toward prolonged survival ($P=.06$). In addition, a subsequent update of the trial data¹⁷ presented at the 2001 American Society of Clinical Oncology meeting showed improved outcome for GMK vaccine recipients in this trial when compared to the observation control patients in a pooled analysis of E1694, E1690, and E1684. This study, therefore, provides strong evidence for the efficacy of HDI with a 33% reduction in relapses and deaths and a benefit that is independently significant in the large, clinically node-negative group in this trial.

While some argue that the benefits of HDI may not outweigh its toxicity, HDI has also been shown to provide significant benefit when measured by a quality-adjusted time without symptoms or toxicity (Q-TWIST) analysis of E1684.¹⁸ In this study, patients treated with adjuvant HDI gained a mean of 8.9 relapse-free months and 7 months of OS. The HDI group experienced a mean of 5.8 months qualified by treatment-related toxicity. Thus the adjuvant HDI-treated patients enjoyed

more quality-of-life adjusted survival time than the observation group regardless of the relative valuations placed on time with toxicity and time with relapse. It is notable that, on average, patients with intermediate-thickness melanomas rate quality of life associated with melanoma recurrence much lower than even severe treatment-related toxicity. However, there is significant variability among patients so that treatment must be tailored to the individual.^{19,20} In addition, an economic analysis of the E1684 data found that the projected cost of adjuvant HDI per quality-adjusted year of life gained is less than \$16,000.²¹ This cost is less than even the rigorous Canadian benchmark of \$20,000 per quality-adjusted year of life gained and much less than the cost of several widely accepted adjuvant therapies employed in other malignancies such as breast and colon cancer.

Ongoing Trials

Many questions remain regarding the optimal application of adjuvant interferon. One of these questions is whether the 1-month induction phase of HDI, given alone, might be both necessary and sufficient to achieve the benefit of the full 1-year regimen. This question is fueled by the early separation of event curves in the HDI trials E1684 and E1690, as well as the fact that adjuvant HDI for 3 months (20 MU intramuscularly 3 days per week for 12 weeks) without the intensive induction phase has not been shown to be as effective in the North Central Cancer Treatment Group trial 93-7052.²² This question is being formally evaluated in the Intergroup trial E1697, in which patients with melanomas at intermediate risk for recurrence will be randomized to adjuvant 1-month IV induction HDI vs observation. Patients eligible for this trial include those with melanomas thicker than 1.5 mm who are clinically or pathologically node-negative. The trial also includes patients who have only microscopic nodal disease, as these patients were included in the eligibility prior to the availability of data from E1694. Since that time, the trial has been amended to assure that this subgroup of patients is considered for study only if they are unwilling to pursue standard HDI. The study is planned to accrue 1,420 patients.

Another question being evaluated is the role of sentinel lymph node biopsy and the efficacy of interferon in the adjuvant treatment of patients with microscopic and submicroscopic regional lymph node metastases. In the ongoing Sunbelt Melanoma Trial, patients with melanomas thicker than 1 mm who undergo sentinel lymph node mapping and biopsy are eligible. All patients with histologically proven metastases undergo completion lymphadenectomy. Patients with only one

lymph node involved by metastatic disease are randomized to adjuvant HDI vs observation. Patients with histologically negative sentinel lymph nodes have polymerase chain reaction (PCR) analysis of the lymph node(s). Those with lymph nodes showing only PCR evidence of metastases are randomized to observation, completion lymphadenectomy, or completion lymphadenectomy plus adjuvant 1-month induction HDI as in the E1697 trial. This trial will help reveal the biological significance of PCR-detected lymphatic metastases and may provide evidence of HDI efficacy in a wider range of disease than is currently known.

The mechanism of action of HDI in high-risk patients is of interest since the identification of this mechanism will allow more rapid development of new approaches to improved melanoma adjuvant therapy. Candidate mechanisms include direct antitumor activity, immunomodulatory effects, and antiangiogenic effects. Prior studies have evaluated the general phenotypic and functional attributes of peripheral blood lymphocytes over time during interferon treatment. No definitive correlations between these factors and the clinical benefit of interferon therapy have been established. Current studies by ECOG are examining the effects of interferon alfa-2b, granulocyte-macrophage colony-stimulating factor, or the combination of these agents on antigen presentation by dendritic cells and specific T-cell responses in patients who receive a multi-epitope peptide vaccine. New tools of immunologic evaluation allow the measurement of peptide-specific responses in the peripheral blood and tumor. It is hoped that these more specific studies will delineate the immunomodulatory impact of interferon alfa-2b. Antiangiogenic mechanisms of interferon are currently under study at the University of Pittsburgh Cancer Institute (M. Wong, principal investigator).

Conclusions

The lack of effective therapies for advanced metastatic melanoma makes effective surgical and adjuvant treatment regimens essential for high-risk patients. It is apparent from the trials conducted to date that the only adjuvant therapy for high-risk melanoma patients that results in consistent improvement in both DFS and OS is interferon alfa-2b administered intravenously for 1 month and then subcutaneously for 11 months at maximally tolerated doses. Adjuvant LDI at a range of doses has been associated with an inconsistent impact on DFS and no significant change in OS. Treatment of patients with high-risk melanoma with HDI clearly improves DFS, and the preponderance of evidence suggests that it improves OS as well. Currently, the adjuvant HDI regimen as defined

in the E1684 trial should be viewed as the reference standard for therapy of patients with melanomas thicker than 4 mm or with regional lymph node metastases. This regimen should be considered for these patients if they are unable to enter formal trials. It should serve as the active control in studies of alternative adjuvant therapies for high-risk patients.

Because of the significant morbidity associated with HDI, elderly patients and those with significant comorbidities may not be appropriate candidates for this regimen. In addition, patients undergoing HDI therapy must be carefully monitored for neuropsychiatric toxicity, hepatotoxicity, myelotoxicity, nephrotoxicity, and constitutional symptoms. Any significant toxicity should result in dose delay or modification.

Future efforts focus on the identification of patients who are most likely to benefit from HDI and supportive measures that will maximize the benefit:toxicity ratio. The ongoing E1697 and Sunbelt Melanoma Trials will allow us to better understand the role of adjuvant interferon for patients who are at somewhat lower risk of recurrence than the patients evaluated in past studies.

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