Point: Interferon-α for Adjuvant Therapy for Melanoma Patients

Michael S. Sabel, MD, and Vernon K. Sondak, MD, *Ann Arbor, Michigan*

Key Words

Interferon-α, carcinoma, adjuvant therapy, melanoma, immunotherapy.

Abstract

Interferon-α is possibly the most controversial adjuvant therapy for any solid tumor, and multiple trials involving varying doses, routes, schedules, and formulations of interferon-α have increased the confusion. Clinicians are left in a quandary, because high-dose interferon-α-2b (HDI) remains the only FDA-approved adjuvant therapy for high-risk melanoma. Of the three prospective randomized trials involving high-dose interferon-α-2b, all show a significant improvement in disease-free survival and two show a significant improvement in overall survival. Despite this strong evidence, data from studies involving alternate doses, concerns regarding cost and toxicity, and the promise of future therapies have led opponents of interferon to overlook these results. Based on the available clinical evidence, however, high-dose interferon should be offered as standard care for patients with high-risk, resected melanoma. Informed patients who have elected to forego interferon and patients with lower risk lesions can be offered participation in clinical trials with a no-treatment control arm. (*JNCCN* 2004;2:61–68).

After surgical therapy for patients with high-risk melanoma, the outlook is not promising. Patients with thick primary lesions (T4N0M0, American Joint Cancer Committee [AJCC] stage IIB) have a risk of recurrence after surgery of approximately 60%, and those with regional nodal metastases (T1-4N1M0, AJCC stage III) have a 75% risk.[1] Unfortunately, chemotherapy has limited efficacy against melanoma and currently plays no role in the adjuvant setting.[2] Because melanoma is susceptible to immunologic attack by the host, tremendous interest has been expressed in a variety of immunotherapies, including nonspecific immunostimulants, vaccines, and systemic cytokines. However, many of these approaches failed to show significant clinical impact, and the practitioner was left with few options in treating high-risk melanoma patients with adjuvant therapy. One exception to this, however, has been the use of adjuvant interferon-α (IFN-α).

Although the precise mechanism of action remains poorly understood, IFN-α has multiple antitumor effects. These include a direct antiproliferative effect, anti-angiogenesis, the enhancement of natural-killer (NK) cell activity, and the up-regulation of tumor antigens and human leukocyte antigen (HLA) class I and class II antigens.[3,4] Initial phase II clinical studies with IFN-α in metastatic melanoma showed response rates in the 10% to 20% range.[5,6] These response rates were not high enough to lead to routine use in the treatment of metastatic melanoma; however, observations that patients with small tumors and nonvisceral disease were more likely to respond suggested that use of IFN-α may show a greater impact in patients with micrometastases. This prompted multiple clinical trials exploring the use of IFN-α as an adjuvant therapy for melanoma in patients at high risk of recurrence.

In 1995 and based on the earliest of these trials, the adjuvant use of high-dose IFN-α was approved by the United States Food and Drug Administration (FDA). Adjuvant interferon became "standard of care," and its use was widely adopted in the community. However, the results of subsequent trials have not been as clear-cut, and the debate over adjuvant interferon has intensified. This article discusses the arguments supporting adjuvant interferon for the treatment of melanoma.

From the Department of Surgery, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan.

Submitted August 12, 2003; accepted for publication October 31, 2003.

No benefits or funds were received in support of this study.

Correspondence: Michael S. Sabel, MD, University of Michigan Comprehensive Cancer Center, 3304 Cancer Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109. E-mail: msabel@umich.edu

Adjuvant High-Dose Interferon Improves Overall Survival

Improving overall survival is the ultimate goal for any adjuvant therapy, albeit not the only goal. In melanoma, researchers have substantial reason to believe that patients accept adjuvant therapies with considerable toxicity even in the absence of an overall survival benefit. Nonetheless, uncertainty about the effect of adjuvant interferon on overall survival is the most frequently cited criticism of interferon.[7,8] Critics generally cite a recent systematic review[9] and a meta-analysis[10] that question a survival benefit, overlooking a meta-analysis and reviews that conclude the opposite.[11,12]

Important clinical differences among the adjuvant interferon trials could lead to different conclusions about the impact of therapy on overall survival. The most important differences are eligible patient population, trial size, number of study arms (more study arms lead to decreased statistical power for the same overall number of patients entered), potential for crossover from the control group to the study treatment on relapse, and dose and schedule of the study treatment. Efforts to combine all trials without attention to these important differences may yield a statistically valid, but not a clinically correct result. Defining the question precisely is imperative when discussing the clinical use of adjuvant interferon and interpreting data for and against.

Although multiple trials studied IFN-α in the adjuvant setting, these trials included different doses, routes, and schedules, as well as two different types of recombinant interferon; IFN-α-2a (Roferon-A, Hoffman-LaRoche, Nutley, NJ) and IFN-α-2b (Intron-A, Schering-Plough, Kenilworth, NJ). Six trials have been performed using IFN-α-2a, none of which have shown a survival benefit (Table 1). Although the two IFN-α-2 subtypes are very similar in structure, they are not of identical efficacy. Neutralizing antibodies have been seen in 25% to 30% of patients treated with IFN-α-2a but less than 3% of patients treated with IFN-α-2b.[22,23] The development of neutralizing antibodies has been associated with a loss of response and may explain the relative lack of clinical efficacy of IFN-α-2a.[24]

In addition to different IFN subtypes, trials involving adjuvant IFN-α have involved both low-dose and high-dose regimens. The low-dose IFN-α

Table 1 Trials Not Involving High Dose IFN-α-2b

Author	Year	# Pts.	Arms	IFN Schedule	F/U (yr)	Results
Trials involving Interferon α-2a						
Cascinelli et al.[13]	1994	444	IFN-α vs Obs	3 MU SC 3×/wk × 3 yr	7.3	DFS NSD OS NSD
Creagan et al.[14]	1995	262	IFN-α vs Obs	20 MU/m² IM 3 × /wk × 3mo	6.1	DFS NSD OS NSD
Pehamberger et al.[15]	1998	311	IFN-α vs. Obs	3 MU SC qd × 3wk then 3 MU SC 3×/wk × 1 yr	3.4	DFS[a] OS NSD
Grob et al.[16]	1998	489	IFN-α vs. Obs	3 MU SC 3×/wk × 18mos	5.0	DFS[b] OS NSD
Hancock et al.[17]	2001	654	IFN-α vs Obs	3 MU SC 3×/wk × 2 yr	1.3	DFS NSD OS NSD
Kleeberg et al.[18]	2001	830	IFN-α vs IFNγ vs Iscador vs Obs	1 MU SC QOD × 1 yr	5.5	DFS NSD OS NSD
Trials involving Interferon α-2b (low or intermediate dose)						
Cameron et al.[19]	2001	96	IFN-α vs Obs	3 MU SC 3×/wk × 6mo	6.5	DFS NSD OS NSD
Kirkwood et al.[20]	2000	642	IFN-α vs Obs	3 MU SC 3×/wk × 2yr	4.3	DFS NSD OS NSD
Eggermont et al.[21]	2002	1418	1 yr IFN-α vs. 2 yr IFN-α vs. Obs	10 MU SC 5/7d × 4wk then 10 MU SC 3×/wk × 1 yr **or** 5 MU SC 3/wk × 2 yr	1.6	DFS[c] OS[d]

[a]$P = .02$, [b]$P = .04$, [c]$P = .01$, [d]Not reported.

regimen consists of 2 to 3 MU administered two to three times per week for anywhere from one to three years. Although early results suggested some effectiveness to the low-dose regimens,[13,25] re-analysis and additional trials have shown no benefit to survival and inconsistent or transient effects on relapse-free survival.[26,27] A shorter-duration regimen of 20 MU/m^2 administered intramuscularly three times per week for three months also failed to result in an overall survival benefit.[14] Table 1 summarizes the non-high dose interferon trials. Low or intermediate doses of interferon never have shown any durable impact on overall survival and have not been approved or even advocated for routine clinical use in high-risk melanoma patients.

The only clinically indicated adjuvant treatment for high-risk melanoma is high-dose IFN-α-2b (HDI). This regimen involves an "induction" phase of IFN-α-2b 20 MU/m^2 intravenously five days a week for four weeks followed by a "maintenance" phase of 10 MU/m^2 subcutaneously three days a week for the remainder of a year. Three trials have studied HDI, two with an observation arm and one comparing HDI to a vaccine (Table 2).

The most mature study of adjuvant interferon is ECOG 1684, performed by Kirkwood et al.[28] Patients randomized to the treatment group had a significant improvement in disease-free and overall survival compared with the control group. High-dose IFN-α-2b therapy for one year increased the median relapse-free survival by nine months (1.72 years for IFN-α-2b patients vs. 0.98 years for observation patients) and produced a 42% improvement in the five-year relapse-free survival rate (37% for IFN-α-2b patients vs. 26% for observation patients). In addition, IFN-α-2b therapy significantly increased median survival by one year and produced a 24% improvement in the five-year survival rate (46% for IFN-α-2b patients vs. 37% for observation patients). The FDA approved IFN-α-2b for the adjuvant treatment of high-risk melanoma based on these results.

To verify the findings of E1684, an ECOG-coordinated Intergroup trial was initiated that could not only reaffirm the overall benefit of adjuvant IFN-α, but allow a more precise appraisal of the benefit of therapy in the group of patients with thick, node-negative melanomas. E1690 compared high-dose IFN-α-2b and a two-year low-dose IFN-α-2b regimen with observation after complete resection of all known disease.[20] Results of this trial confirmed the disease-free survival advantage for high-dose IFN-α seen in E1684 but not the survival advantage.

The failure of E1690 to verify the findings of E1684 intensified the interferon debate. Advocates of adjuvant interferon therapy point out that this discrepancy is probably the result of differences in eligibility criteria and, more importantly, the subsequent availability of post-relapse IFN-α-2b crossover therapy in the E1690 trial but not in E1684. These crossover data have not been convincingly established and must be considered an unproven hypothesis.

With evident differences between E1684 and E1690, the importance of a third prospective randomized trial involving high-dose interferon is magnified. This trial was designed after the results of E1684 were known, but before E1690 was analyzed. Intergroup E1694 compared one year of high-dose IFN-α-2b with two years of a promising melanoma vaccine; no observation arm was used because adjuvant interferon was considered the standard for high-risk patients desiring adjuvant therapy. For the investigational arm, a vaccine derived from the ganglioside GM2 was used. A pilot randomized trial suggested a disease-free survival benefit in patients treated with purified GM2 plus BCG compared with those treated with BCG alone after resection of stage III disease.[30]

Table 2 Adjuvant Trials Involving High Dose IFN-α-2b

Author	Year	# Pts.	Arms	IFN Schedule	Med F/U (yr)	Results
Kirkwood et al.[28]	1996	280	IFN-α vs Obs	HDI	6.9	DFS (P = .004) OS (P = .046)
Kirkwood et al.[20]	2000	642	IFN-α vs Obs	HDI	4.3	DFS (P = .05) OS NSD
Kirkwood et al.[29]	2001	880	IFN-α vs. Vaccine	HDI	1.3	DFS (P = .0015) OS (P = .009)

Notwithstanding the prior promising data regarding the GM2 vaccine, in May 2000, the E1694 trial's independent Data Safety Monitoring Committee concluded that the high-dose interferon arm was associated with significantly improved relapse-free and overall survival, and mandated that the study be terminated early and the results disclosed.[29]

Of these three trials, two (E1684 and E1694) showed statistically significant improvement in overall survival, and the third (E1690) did not. At face value, assuming all three trials were equally valid, reconciling such discordant results is possible. Clinical trials are conducted in a manner that minimizes the likelihood of a fallacious conclusion of efficacy where none exists (called the alpha error), by setting the threshold for accepting a positive result at the stringent $P = .05$ level. This means that, by chance alone, the likelihood of a clinical trial being positive when no real difference exists is only one in 20. To achieve this stringency, a compromise is made regarding the likelihood of an erroneous conclusion of lack of efficacy where efficacy actually exists (beta error): this is routinely designed to be between one in ten and one in five (10% to 20%). These numbers have particular importance when the results of multiple trials are considered: the probability of two clinical trials to both reach a positive conclusion at the $P = .05$ level by chance alone is miniscule. Conversely, if a trial designed with an 80% power to detect a significant difference (20% beta error) were repeated in the identical patient population three times, the likelihood that one trial would be negative when a difference actually exists is high: 48.8% (probability of at least one false-negative trial is $1 - (0.8 \times 0.8 \times 0.8) = 0.488$). This means that, by chance alone, at least one of three identical trials of an active agent will be negative nearly half the time. Of course, the three high-dose interferon-α-2b trials were not exactly identical. The E1690 trial was a three-arm trial and was clearly affected to some degree by crossover from the observation arm to the study treatment on relapse and repeat resection. Thus, we should be least surprised that it was the E1690 trial that diverged in regard to overall survival and more than usually reluctant to accept that lone conclusion in the face of the other two positive results.

Critics contend that the E1684 trial was the smallest study and shows a loss of survival benefit with long-term follow-up. Small size limits the ability to detect a positive result, but doesn't invalidate the positive result after it occurs. A recent, unplanned long-term analysis of the E1684 trial at 12.6 years median follow-up (compared with the original analysis at 6.9 years median follow-up) did show persistence of the relapse-free and survival differences between the interferon and observation arm, but only the relapse-free survival difference remained statistically significant.[11] This "loss of survival benefit" has been touted as evidence that the effect of high-dose interferon was not a durable one, but careful examination of the relapse-free survival curves after more than a decade of clinical follow-up clearly demonstrate that is not the case. Competing causes of mortality and smaller numbers of patients followed beyond a decade are far more plausible explanations, and there is no compelling reason to consider that the long-term data in any way invalidates the originally published observations.

E1694 is in many ways the most clinically significant: it was the largest trial and incorporated patients with sentinel lymph node biopsy-proven micrometastases (who now constitute the majority of patients considered as candidates for adjuvant interferon outside the protocol setting). Opponents of interferon argue that it did not incorporate an observation control arm; in fact, high-dose interferon *was* the control arm for a study that compared it to a promising defined antigen vaccine. This trial was stopped early by the independent ECOG Data Safety and Monitoring Committee because of highly significant improvement in both relapse-free and overall survival for patients on the interferon arm. Early closure of a trial is the strongest statistical evidence of benefit possible in an experiment involving human beings, so it is amazing how frequently this dramatic event is actually dismissed as a negative ("if they'd only waited longer, the results would be more valid"). When a study is closed early, it is because independent monitors believe it is now unethical to continue to withhold the more active arm from study patients, so it stands to reason that the same therapy should generally not be withheld from non-study patients while longer follow-up is awaited! However, the absence of an observation arm raised the specter that it wasn't the benefit of interferon but the detrimental effect of the investigational vaccine that led to the early closure, and this must be addressed.

There is, in fact, little or no basis for considering that the investigational GM2 ganglioside vaccine used

in E1694 was potentially deadly, so this argument is difficult to accept. First, because there was an improvement in both disease-free and overall survival, the argument supposes that the vaccine not only led to increased deaths, but increased deaths by melanoma. The likelihood that vaccination with a ganglioside antigen can result in a markedly increased risk of early dissemination of and death from metastatic melanoma is difficult to believe: preclinical testing and early phase clinical trials noted no such hazardous effect. In fact, there is credible evidence that anti-GM2 antibodies, either spontaneous or vaccine-induced, are protective against melanoma relapse, including evidence from the E1694 trial itself. No credible descriptions of antibody-induced exacerbations of any form of human cancer exist. A previous, randomized controlled phase III trial of the GM2 ganglioside given with BCG actually showed a potential benefit, providing the rationale for conducting the trial in the first place.[30] The Europeans, who have frequently cited the lack of proven overall survival benefit as a reason not to accept high dose interferon, evidently don't believe that this identical ganglioside vaccine is harmful because they are using it in a large, randomized trial in melanoma patients at lower risk of recurrence and as of this writing, the EORTC Data Safety and Monitoring Committee has not stopped that trial because of a detrimental effect of the vaccine. As it is likely that the ganglioside vaccine is not harmful, and may even be somewhat beneficial, then the results of E1694 provide the strongest evidence to date that adjuvant high-dose interferon improves overall survival in high-risk melanoma patients.

Adjuvant Interferon Clearly Prolongs Disease-Free Survival

Even those who question the impact of high-dose interferon on overall survival acknowledge its impact on relapse-free survival.[8,9] Although an improvement in overall survival is the strongest evidence in favor of adjuvant therapy, it is not the only one. Two studies of high-dose chemotherapy with autologous stem-cell rescue, published in the *New England Journal of Medicine*, reported improvements in relapse-free survival but not overall survival.[31,32] The accompanying editorial outlined reasons why relapse-free survival improvement should be considered important and sufficient to justify this extremely toxic and costly adjuvant therapy in a disease (breast cancer) where there are effective (albeit non-curative) therapies that clearly prolong survival for patients who relapse after initial surgical therapy.[33] Prolongation of the relapse-free state has even more significance when there are no therapies capable of prolonging survival for the average patient, as is the case for metastatic melanoma. Most importantly, our patients agree: the average patient would accept a toxic adjuvant therapy if it were associated with a reproducible 10% improvement in five-year relapse-free survival in the absence of any prolongation of overall survival.[34] Based on the available meta-analysis[10] and pooled analysis,[11] the impact of adjuvant interferon is between 24% and 30%, and is reproducible ($P = .0009$ and $P < 0.006$, respectively).

The Benefit Justifies Toxicity and Cost

Several examples show adjuvant chemotherapy accepted as "standard treatment" despite controversial or inconclusive evidence.[35-37] So why is adjuvant cytotoxic chemotherapy often accepted easily, while treatment shown to significantly improve disease-free survival in three published randomized trials and overall survival in two still considered controversial? One reason may be that interferon is a biologic therapy, with which oncologists are less familiar than standard cytotoxic chemotherapies. Additionally, the mechanism of action of interferon on melanoma is not completely understood.

Another more likely reason is the level of care necessary to successfully administer IFN-α-2b. Serious side effects occur, including fatigue, flu-like symptoms (malaise, fevers, chills, arthralgias), liver function abnormalities, neutropenia, nausea and vomiting, and psychiatric symptoms such as depression and suicide. Complete therapy takes a year, and careful attention to dose reduction criteria and liberal use of intravenous fluids, antiemetics, and antidepressants are necessary. The successful administration of high-dose IFN-α-2b adjuvant therapy often requires a committed team, including oncologists, nurses, pharmacists, social workers and psychiatrists/psychologists. However, these toxicities appear to be justified by the potential benefit. A quality-of-life-adjusted survival analysis (Quality-Adjusted Time Without Symptoms and Toxicity [Q-TWiST]),[38] on the basis that quality of life with toxicity during therapy was valued more highly than quality of life with relapse found that the

interferon group had significantly greater quality of life adjusted time than did the observation group. Clinically, the Q-TWiST data can be helpful in promoting a discussion with patients regarding the relative risks and benefits of adjuvant interferon.

Patients must receive the information they need to decide if the potential benefits of interferon justify the risks, and physicians should present all information in a balanced, objective fashion, as with other routinely used adjuvant therapies. Patients strongly averse to the side effects of IFN-α, particularly those who perceive their risk of recurrence to be low, often decide against interferon treatment and seek alternatives in clinical trials or chose to forgo adjuvant therapy altogether.

Another aspect affecting the use of interferon is the cost. Cost-effectiveness of high-dose IFN-α-2b for patients with high-risk resected melanoma was assessed based on the results of the original E1684 trial. The cost of a year of IFN-α-2b was estimated to be just under $29,000. This is comparable to other recognized medical therapies.[39,40] A cost-effectiveness analysis of adjuvant interferon in Spain, also based on the E1684 data, also showed its use to be within limits established in health economics and comparable with other interventions with acceptable cost-effectiveness.[41] Nonetheless, cost considerations appear to be a major impediment to the use of high-dose interferon in some parts of the world.[42,43]

No Other Effective Adjuvant Therapies Are Available

Patients who have just undergone surgical treatment for thick primary melanomas (>4 mm) or melanoma metastatic to the regional lymph nodes are facing a high likelihood of relapse. After unresectable distant metastases develop, median survival is as little as nine months. The use of adjuvant cytotoxic chemotherapy has never been established to reduce this risk and is not a current option outside of a clinical trial setting. Although adjuvant interferon is not the ideal therapy, the only alternative other than clinical trials is "watch and wait."

Many who argue against interferon point toward melanoma vaccines as holding promise to improve disease-free and overall survival with minimal toxicity. However, the promise of melanoma vaccines has been touted for decades without any established clinical benefit. To date, no large prospective randomized trial has shown an improvement in overall survival associated with vaccine therapies. Many questions regarding vaccines remain unanswered, and none are ready for off-protocol use. Several approaches to vaccine therapy also are presently in clinical trials.[44-48] To discover the potential benefits of vaccines, informed patients with high-risk melanoma who are not interested in interferon should be encouraged to participate in clinical vaccine trials. However, many patients either do not want to participate in randomized trials or are not able to participate in trials primarily accruing at major academic institutions.

Conclusions

Based on currently available clinical evidence, can we consider high-dose interferon standard care for patients with high-risk, resected melanoma? Yes. Too many clinical trials show improved relapse-free survival to deny the fact that high-dose IFN-α-2b alters the natural history of high-risk melanoma. Unless one believes that the ganglioside vaccine may have a detrimental effect, E1694 should be accepted as a clinical trial that documents a significant impact of high-dose IFN-α-2b on overall survival, confirming the findings of E1684. It is then impossible not to conclude that adjuvant therapy with high-dose IFN-α-2b is potentially beneficial and should be routinely offered to healthy melanoma patients at high-risk of relapse. Clinical trials continue to be essential to our efforts to make further progress in the treatment of this difficult and refractory disease, and patient participation in clinical trials must be encouraged. Clinical trials of high-risk patients desiring adjuvant therapy should offer high-dose interferon as the control arm; informed patients who have elected to forego interferon can be offered participation in trials with a no-treatment control. Outside the clinical trial setting, patients who want adjuvant therapy should receive high-dose interferon from a dedicated and qualified health care team who can deliver this therapy with the fewest possible side effects.

References

1. Balch CM, Buzaid AC, Soong S-J, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 2001;19:3635–3648.
2. Dickler MN, Coit DG, Myers ML. Adjuvant therapy of malignant melanoma. Surg Oncol Clin N Am 1997; 6:793–812.

3. Pfeffer LM, Dinarello CA, Herberman RB, et al. Biological properties of recombinant alpha-interferons: 40th anniversary of the discovery of interferons. Cancer Res 1998;58: 2489–2499.
4. Frank SJ, Meyers M. Interferon as adjuvant therapy for high risk melanoma. Melanoma Lett 1995; 13:1–4.
5. Legha SS. Current therapy for malignant melanoma. Semin Oncol 1989;16:34–44.
6. Steiner A, Wolf CH, Pehamberger H. Comparison of the effects of three different treatment regimens of recombinant interferons (r-IFN alpha, r-IFN gamma and r-IFN alpha + cimetidine) in disseminated malignant melanoma. J Cancer Res Clin Oncol 1987;113:459–465.
7. Eggermont AM. The role interferon-alpha in malignant melanoma remains to be defined. Eur J Cancer 2001;37: 2147–2153.
8. Punt CJA, Eggermont AM. Adjuvant interferon-alpha for melanoma revisited: news from old and new studies. Ann Oncol 2001;12:1633–1666.
9. Lens MB, Dawes M. Interferon alfa therapy for malignant melanoma: a systematic review of randomized controlled trials. J Clin Oncol 2002;20:1818–1825.
10. Wheatley K, Hancock B, Gore M. Interferon-alpha as adjuvant therapy for melanoma: a meta-analysis of the randomized trials (Abstract). Proc Am Soc Clin Oncol 2001;20:349a.
11. Kirkwood JM, Manola J, Ibrahim J, et al. Pooled analysis of four ECOG/Intergroup trials of high-dose interferon alpha-2b (HDI) in 1916 patients with high-risk resected cutaneous melanoma (Abstract). Proc Am Soc Clin Oncol 2001; 20:350a.
12. Thome' SD, Loprinzi CL, Heldebrandt MP. Determination of potential adjuvant systemic therapy benefits for patients with resected cutaneous melanoma. Mayo Clin Proc 2002;77:913–917.
13. Cascinelli N, Bufalino R, Morabito A, Mackie R. Results of adjuvant interferon study in WHO melanoma programme (letter). Lancet 1994;343:913–914.
14. Creagan ET, Dalton RJ, Ahmann DL, et al. Randomized, surgical adjuvant clinical trial of recombinant interferon alpha-2a in selected patients with malignant melanoma. J Clin Oncol 1995;13:2776–2783.
15. Pehamberger H, Soyer HP, Steiner A, et al. Adjuvant interferon alfa-2a treatment in resected primary stage II cutaneous melanoma. Austrian Malignant Melanoma Cooperative Group. J Clin Oncol 1998;16(4):1425–1429.
16. Grob JJ, Dreno B, de la Salmoniere P, et al. Randomised trial of interferon alfa-2a as adjuvant therapy in resected primary melanoma thicker than 1.5mm without clinically detectable node metastases. Lancet 1998;351:1905–1910.
17. Hancock BW, Wheatley K, Harrison G, et al. Aim high: Adjuvant interferon in melanoma (high risk), a United Kingdom Cooordinating Committee on Cancer Research (UKCCCR) randomized study of observation versus adjuvant low-dose extended duration intereron alpha-2a in high risk resected malignant melanoma (Abstract). Proc Am Soc Clin Oncol 2001;20:349a.
18. Kleeberg UR, Brocker EB, Lejeune FJ, et al. Adjuvant trial in melanoma patients comparing rIFN-α to rIFN-γ to Iscador to a control group after curative resection of high risk primary (>3mm or regional lymph node metastasis (EORTC 18871). Eur J Cancer 1999; 35 (Suppl 4):S82.
19. Cameron DA, Cornbleet MC, Mackie RM, et al. Adjuvant interferon alpha 2b in high risk melanoma—the Scottish study. Br J Cancer 2001;84:1146–1149.
20. Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol 2000;18:2444–2458.
21. Eggermont AMM, Gore M. A critical appraisal of the role of interferon-α in the treatment of malignant melanoma. Principles and Practice of Biologic Therapy of Cancer Updates. Philadelphia: Lippincott Williams and Wilkins, 2002: p 3.
22. Itri LM, Sherman MI, Palleroni AV, et al. Incidence and clinical significance of neutralizing antibodies in patients receiving recombinant interferon-alpha 2a. J Interferon Res 1989;9(suppl1):S9–S15.
23. Speigel RJ, Jacobs SL, Treuhaft MS. Anti-interferon antibodies to interferon-alpha 2b: Results of comparative assays and clinical perspective. J Interferon Res 1989;9(suppl1):S17–S24.
24. Wussow PV, Jakschies D, Freund M, et al. Treatment of anti-recombinant interferon-alpha 2 antibody positive CML patients with natural interferon-alpha. Br J Haematol 1991;78:210–216.
25. Kokoschka EM, Trautinger F, Knobler RM, et al. Long-term adjuvant therapy of high risk malignant melanoma with interferon a2b. J Invest Dermatol 1990;95:S193–197.
26. Cascinelli N. Evaluation of efficacy of adjuvant rIFN-α 2a in melanoma patients with regional node metastases (Abstract). Proc Am Soc Clin Oncol 1994;14:410.
27. Rusciani L, Petraglia S, Alotto M, et al. Postsurgical adjuvant therapy for melanoma. Evaluation of a 3-year randomized trial with recombinant interferon-alpha after 3 and 5 years of follow-up. Cancer 1997;79:2354–2360.
28. Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 1996;14:7–17.
29. Kirkwood JM, Ibrahim JG, Sosman JA, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. J Clin Oncol 2001;19:2370–2380.
30. Livingston PO, Wong GY, Adluri S, et al. Improved survival in stage III melanoma patients with GM2 antibodies: a randomized trial of adjuvant vaccination with GM2 ganglioside. J Clin Oncol 1994;12:1036–1044.
31. Rodenhuis S, Bontenbal M, Beex LVAM, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for high-risk breast cancer. N Engl J Med 2003;349:7–16.
32. Tallman MS, Gray R, Robert NJ, et al. Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer. N Engl J Med 2003;349:17–26.

33. Elfenbein GJ. Stem-cell transplantation for high-risk breast cancer. N Engl J Med 2003;349:80–82.

34. Kilbridge KL, Weeks JC, Sober AJ, et al. Patient preferences for adjuvant interferon alfa-2b treatment. J Clin Oncol 2001;19:812–823.

35. Spira AI, Ettinger DS. The use of chemotherapy in soft-tissue sarcomas. Oncologist 2002;7:348–359.

36. Davidson NE. Ongoing US cooperative groups trials using taxanes in the adjuvant setting. Clin Breast Cancer 2002;3(Suppl2):S53–S58.

37. Saltz LB, Minsky B. Adjuvant therapy of cancers of the colon and rectum. Surg Clin North Am 2002;82:1035–1058.

38. Cole BF, Gelber RD, Kirkwood JM, et al. Quality-of-life-adjusted survival analysis of interferon alfa-2b adjuvant treatment of high-risk resected cutaneous melanoma: an Eastern Cooperative Oncology Group study. J Clin Oncol 1996;14:2666–2673.

39. Hillner BE. Cost-effectiveness assessment of interferon alfa-2b as adjuvant therapy of high-risk resected cutaneous melanoma. Eur J Cancer 1998;34(suppl3):S18–S21.

40. Hillner BE, Kirkwood JM, Atkins MB, et al. Economic analysis of adjuvant interferon alfa-2b in high-risk melanoma based on projections from Eastern Cooperative Oncology Group 1684. J Clin Oncol 1997;15:2351–2358.

41. Gonzalez-Larriba JL, Serrano S, Alvarez-Mon M, et al. Cost-effectiveness analysis of interferon as adjuvant therapy in high-risk melanoma patients in Spain. Eur J Cancer 2000;36:2344–2352.

42. Cook J, Zitelli JA. Treating patients with melanoma with interferon (letter). Arch Dermatol 1997;133:387.

43. Russell-Jones R. Interferon-α therapy for melanoma. Clin Exp Dermatol 2000;25:1–6.

44. Morton DL, Hsueh EC, Essner R, et al. Prolonged survival of patients receiving active immunotherapy with Canvaxin therapeutic polyvalent vaccine after complete resection of melanoma metastatic to regional lymph nodes. Ann Surg 2002;236:438–449.

45. Morton DL, Barth A. Vaccine therapy for malignant melanoma. CA Cancer J Clin 1996;46:225–244.

46. Hsueh EC, Essner R, Foshag LJ, et al. Active immunotherapy by reinduction with a polyvalent allogeneic cell vaccine correlates with improved survival in recurrent metastatic melanoma. Ann Surg Oncol 2002;9:486–492.

47. Sondak VK, Liu PY, Tuthill RJ, et al. Adjuvant immunotherapy of resected, intermediate-thickness, node-negative melanoma with an allogeneic tumor vaccine: overall results of a randomized trial of the Southwest Oncology Group. J Clin Oncol 2002;20:2058–2066.

48. Sosman JA, Unger JM, Liu PY, et al. Adjuvant immunotherapy of resected, intermediate-thickness, node-negative melanoma with an allogeneic tumor vaccine: impact of HLA class I antigen expression on outcome. J Clin Oncol 2002;20:2067–2075.