



William Lee, 1810-1865. *Le Retour de Cypre*. Oil on canvas, 39" × 40 7/8".
Courtesy of the Callan Fine Art gallery, New Orleans, Louisiana.

*Since there is clearly room for improvement
in the adjuvant therapy of melanoma,
physicians should encourage their
patients to participate in clinical trials.*

Choices in Adjuvant Therapy of Melanoma

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Background: High-dose interferon (IFN) is the approved agent for adjuvant treatment of melanoma in the United States. This approval is for high-risk, predominantly stage III patients with cutaneous primaries. There are still decisions to be made in the care of these patients. Also, there are questions about whether the IFN data can be extrapolated to patients with other stages of melanoma and whether adjuvant treatment should be offered to these individuals. Clearly there is room for improvement in this area.

Methods: The literature on this topic and ongoing national trials in the United States were reviewed.

Results: The data are insufficient to recommend other agents in the adjuvant treatment of melanoma outside a clinical trial. Extrapolation of the IFN data to patient populations other than those studied is problematic at best. National trials are available for most patient populations.

Conclusions: The adjuvant treatment of choice for melanoma patients is participation in a clinical trial.

Introduction

The availability of only one agent approved by the US Food and Drug Administration (FDA) for the adjuvant therapy of melanoma would seem to simplify treatment decisions in this area, but in fact there are still choices to be made. This article reviews the evidence in support of some of

these options, including interferon (IFN) alpha-2b, other commercially available agents, and current clinical trials. It is written primarily from the perspective of trials nationally available in the United States, which are predominantly cooperative group trials. Local phase II trials are beyond the scope of this manuscript, as is a discussion of the proper place of these trials in the adjuvant setting. Also included is a discussion of how these options might be used in treatment planning for three different groups of patients based on risk of recurrence.

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Abbreviations used in this paper: IFN = interferon, GM-CSF = granulocyte-macrophage colony-stimulating factor, IL = interleukin.

Currently Available Options

High-Dose Interferon

High-dose IFN alpha-2b is the current FDA-approved therapy for patients at high risk of recurrence of melanoma. In

1995, a multicenter study reported improved long-term and disease-free survival in melanoma patients using IFN alpha-2b as adjuvant therapy.¹ Thus, in 1995 the FDA approved IFN for treatment in patients who are free of disease but are at high risk for recurrence. However, multiple trials have been conducted since then that have provoked controversy regarding appropriate use of this agent.^{2,3} A recent overview combining the two largest trials with observation control arms confirmed an approximate 10% reduction in risk of recurrence with this therapy but showed no effect on overall survival.⁴ A possible reason for the lack of effect on survival despite improvement in freedom from recurrence is that the observation arm included patients with resectable recurrences who then went on to be treated with high-dose IFN. A meta-analysis of several high-dose IFN trials, including one with a vaccine control, also confirmed a reduction in recurrence risk.⁵ Patients who received a high-dose IFN regimen showed an improvement in survival that was approximately 3% in absolute numbers and of borderline statistical significance ($P=.06$). Lower doses of IFN appear to have no benefit and are not recommended.^{5,6} The role of IFN has been extensively debated, due to concerns about efficacy, toxicity, and cost.^{6,9}

Other Options

Systemic options other than IFN include observation, use of commercially available agents not approved for this indication, and participation in a clinical trial. Radiation therapy is an option for some patients (not discussed here). Isolated limb perfusion is not recommended based on lack of effect on distant metastases or survival in a randomized prospective clinical trial.¹⁰ Nonapproved agents commonly considered include interleukin-2 (IL-2), temozolomide with or without thalidomide, and granulocyte-macrophage colony-stimulating factor (GM-CSF). No vaccines are commercially available in the United States, and no trials using this strategy in the adjuvant setting have reported positive results, but some of these agents are approved in Canada and Australia.

Interleukin-2

The long-term complete remissions seen with high-dose IL-2 suggest that this agent might have activity in the adjuvant setting,¹¹ but this has not been tested in melanoma. One course (2 cycles) of adjuvant high-dose IL-2 was evaluated in renal cell carcinoma with negative results.¹² Low-dose IL-2 plus IFN has been tested as an adjuvant treatment for melanoma, again with negative results.¹³ Given the toxicity and expense of IL-2 and these negative results, empiric use of this agent as an adjuvant treatment for melanoma is not recommended.

Temozolomide With or Without Thalidomide

No data are available on temozolomide with or without thalidomide in the adjuvant setting, but the results with dacarbazine are negative.^{14,15} Dacarbazine and temozolo-

midate are equivalent in stage IV melanoma.¹⁶ Since temozolomide penetrates the blood brain barrier its use in patients with treated solitary brain metastases is sometimes considered. In patients with clinically evident brain metastases temozolomide has a 7% partial response rate in previously untreated patients (including those with no previous brain irradiation).¹⁷ Responses do not appear to be significantly better with concurrent temozolomide and whole brain irradiation.¹⁸ In light of this, the empiric use of temozolomide, alone or in combination, even in patients with treated solitary brain metastases, would seem unwarranted, although the toxicity of temozolomide alone is relatively modest.

Granulocyte-Macrophage Colony-Stimulating Factor

Adjuvant use of GM-CSF is supported by one phase II trial and by extensive data demonstrating a prominent role for this drug as an immunopotentiator.¹⁹ In this trial, 48 high-risk patients rendered free of disease either by surgery or chemotherapy were treated with GM-CSF on a classic regimen of 125 $\mu\text{g}/\text{m}^2$ subcutaneously on a schedule of 14 days on/14 days off. Progression-free and overall survival results were compared with matched patients from the University of Alabama data base. The median overall survival was 37.5 months in treated patients vs 12.2 months in controls ($P<.001$).

Toxicity in this trial was generally mild, but 92% of patients had at least one adverse event. Transient myalgias, weakness, and mild fatigue were reported by 27 (56%) of 48 patients, and 28 (58%) experienced injection site reactions, usually erythema. Five (10%) reported a more generalized rash. Of note, 1 patient reported grade 3 asthenia requiring a 50% dose reduction, and 1 patient discontinued treatment because of a grade II injection site reaction. There are no known long-term ill effects of GM-CSF, but this possibility should not be dismissed out of hand, especially in light of recent findings about estrogen supplementation in postmenopausal patients, COX-2 inhibitors, and high-dose vitamin E, to name a few.

The favorable toxicity profile and possibility of benefit to high-risk patients has led many physicians to recommend this agent outside a trial. Some of the arguments against this are considered below in the discussion about participation in a clinical trial.

Clinical Trials

Three large national adjuvant trials for melanoma patients are currently under way, as well as institutional trials not listed here. A trial evaluating the allogeneic vaccine developed by Donald Morton, MD, at the John Wayne Cancer Institute for stage III patients has met its accrual goal and has been closed. A trial evaluating the same vaccine for stage IV patients has been discontinued after an independent Data and Safety Monitoring Board determined that

Table 1. — Eligibility Criteria for E1697

- initial presentation of primary cutaneous melanoma
- primary melanoma ≥ 1.5 mm
- no more than one microscopically positive node
- children ≥ 10 years of age may enter through Children's Oncology Group

the vaccine was unlikely to significantly improve survival in these patients. In the discussion below, note that trials starting with E are led by the Eastern Cooperative Oncology Group and those starting with S are led by the Southwest Oncology Group.

E1697, an Eastern Cooperative Oncology Group (ECOG) trial for intermediate-risk patients, is comparing 1 month of high-dose IFN with observation. This trial is also available through Southwest Oncology Group (SWOG), NCI Canada (CAN-NCIC-ME.10), Cancer and Leukemia Group B (CALGB 500103), in various centers in Australia, and through the Children's Oncology Group (COG). The rationale for this trial is the observation that relapse-free survival curves separate early in the randomized high-dose IFN trials, suggesting an effect of the first high-dose month. Furthermore, this high-dose month is the primary difference between the positive trials and other IFN trials that have been negative. This study was activated in December 1998. Thus far over 500 patients of an accrual goal of 1,420 have entered the trial. Eligibility criteria are listed in Table 1.

S0008, a SWOG trial for higher-risk patients, compares standard high-dose IFN for 1 year with 3 cycles of biochemotherapy. This trial is also available through ECOG, CALGB, and the COG. Evaluation of biochemotherapy in the adjuvant setting is based on high response rates and some durable complete responses (9% greater than 2 years) seen in stage IV disease.²⁰ A less toxic regimen more suited to widespread use and to use in the adjuvant setting was developed,²¹ and detailed guidelines for safe administration of this regimen have been published.²² This trial was activated in August 2000 and has accrued 285 of the 410 patients needed. Eligibility criteria are listed in Table 2.

Table 2. — Eligibility Criteria for S0008

- cutaneous or unknown primary melanoma
- ulcerated primary with ≥ 1 positive nodes, micro or macro
- non-ulcerated primary with:
 - 1 macro-positive node
 - or
 - ≥ 2 micro- or macro-positive nodes
 - or
 - satellite/intransit metastases
- regional nodal recurrence at site of previous complete lymphadenectomy
- no adjuvant radiation
- children ≥ 10 years of age may enter through Children's Oncology Group

Table 3. — Eligibility Criteria for E4697

- Overlap with S0008 (S0008 preferred)
 - satellite/intransit disease
 - stage III with gross extracapsular extension
 - recurrence in previously resected nodal basin
 - ≥ 4 involved lymph nodes, or matted lymph nodes
 - ulcerated primary and any involved lymph nodes
- No overlap with S0008
 - locoregional recurrence after prior IFN or S0008
 - local recurrence after adequate excision of the original primary
 - any mucosal melanomas
 - completely resected stage IV melanoma (cutaneous, mucosal, ocular, unknown primary)

E4697, which has some overlap with S0008 but also includes higher-risk patients (completely resected stage IV cutaneous melanoma as well as some ocular and mucosal melanoma patients) compares GM-CSF with placebo. For patients with the HLA-A2 phenotype, there is also a randomization between peptide vaccines representing epitopes of gp-100, MART-1, and tyrosinase, also compared with placebo. The impetus for the trial came from the data from Spittler et al¹⁹ outlined above and the extensive data suggesting a role of GM-CSF in immunomodulation. The peptide vaccinations were added based on extensive data showing the immunogenicity of these particular epitopes. This trial is also open in SWOG and in CALGB (CALGB 500101). It was activated in December 1999. Almost 600 patients have enrolled; the accrual goal has been increased to 800. The eligibility criteria are listed in Table 3, and the schema is in Table 4.

Patients and physicians still struggle with the concept of clinical trials, especially with randomization and placebo controls. Classically, trials have been opposed on the grounds that they violate the physician's obligation to choose the treatment that is best for the individual patient rather than leaving this to chance. Trials are viewed as experimentation and not treatment. It is argued that experienced physicians should not be in the position of not knowing whether a new treatment, or one of a set of competing treatments, is best for the patient; their observations, coupled with the experiences of colleagues, should be sufficient.²³ However, a large body of data clearly show that these arguments are not true. Recent experiences with COX-2 inhibitors, postmenopausal estrogen use, and high-dose vitamin E are painful reminders of the fact that

Table 4. — Treatment Arms for E4697

HLA-A2-positive patients:	HLA-A2-negative patients:
• GM-CSF + placebo	• GM-CSF
• vaccine + placebo	• placebo
• GM-CSF + vaccine	
• placebo only	

patients can be harmed by too early acceptance of drugs and treatments.²⁴ Such harm is particularly indefensible when there is no benefit and when drugs are given to patients without evidence of active disease, such as in the adjuvant setting.

Patients can be harmed by use of drugs without adequate proof of benefit and adequate study of ill effects. Conversely, what are the data that patients are harmed by participation in clinical trials? There have been high-profile instances of patients harmed by risky experimental procedures, and patients who receive an inferior arm of a trial, or observation or placebo, are arguably not as well off as they might be had they received the treatment later shown to be superior. Similarly, though, patients on an observation arm of a trial evaluating a treatment that is shown to be ineffective are better off because they avoided the side effects of the agent being tested. Overall, there are no data to show that patients are systematically harmed by participation in clinical trials. Some of this is clearly related to the careful supervision of these trials, with data and safety monitoring and early stopping rules. These safeguards are not available to patients who are taking unproven agents outside of trials.

Are patients helped by taking drugs outside of trials before efficacy is formally proven? Arguably yes, if the agent proves to have a favorable risk-to-benefit ratio, which can be shown only in careful trials. However, the record does not suggest that this is a good bet.²⁴ Arguably the most harmful example of this was the rush to adjuvant bone marrow transplantation for breast cancer, with all the attendant suffering for no added benefit that resulted.

All of this harks back to the argument that physicians who put their patients on randomized trials are failing in their obligation to choose a treatment for their patients. A clinical trial is a choice, and, based on the examples above, one could argue that in the absence of clear evidence of efficacy and knowledge of toxicity, a policy of entering patients on trials rather than a policy of choosing treatments based on early data assures the best odds of advising that patient well.

Choosing agents on the basis of early data and shunning trials is like throwing Hail Mary passes on first down every time. Occasionally you will get a score, and it will be a memorable event when you do, but it is no way to consistently win football games.

An example from the melanoma experience is worth pondering. The ganglioside vaccine GM2 was carefully developed by an excellent group and shown to have promising activity. The vaccine was then tested in a randomized phase III trial involving 122 patients. Patients were randomized to receive the GM2 vaccine plus Bacille Calmette-Guérin (BCG) or BCG alone. Analysis of the trial was complicated by the presence of antibodies to the vaccine in 7 of 64 patients on the control (BCG) arm. In patients with antibody to GM2, either pre-existing or arising during treatment, statistically significant

improvements in disease-free and overall survival were seen. When patients were analyzed by treatment as randomized, there was an 18% absolute improvement in disease-free survival and an 11% absolute increase in overall survival for vaccinated patients; both results were of borderline statistical significance. Elimination of the control and treated patients with pre-existing antibody to the vaccine resulted in statistical significance for the disease-free survival endpoint.²⁵ Based on these data, trial E1694 was designed to compare standard high-dose IFN with a newer version of this vaccine. In this trial GM2 was given with a different adjuvant than used in previous studies (which may have affected the outcome). The results of this showed that IFN was clearly superior to the vaccine.³ One might argue that this is an example of patients being harmed by participating in a trial, in that the patients who received vaccine had a decreased chance of avoiding recurrence than they would have had if they had chosen standard therapy. However, consider what would have happened if the vaccine had been available outside the trial. Many physicians would have recommended the vaccine on the basis of high-quality phase II trials and the phase III data above coupled with a favorable toxicity profile. In so doing, they would have clearly been harming their patients and the many other patients who would have taken this vaccine before trials could finally be completed.

Application to Patients

How, then, should we approach patients with melanoma? For this discussion we will try to apply the above to intermediate-risk, high-risk, and very high-risk patients. Based on the above, each patient has a choice of high-dose IFN, GM-CSF, participation in a trial, or observation.

At the outset a comment about discussing IFN with patients may be in order. Useful suggestions have been published to help individual patients decide whether the toxicity of IFN is worth the benefit to them. Perhaps the most helpful approach is to explain the side effects of IFN and then ask the patient if a 10% improvement in relapse-free survival and a lesser effect on survival are worth experiencing those side effects for a year. Other factors in choosing IFN must include performance status of 0-1 and, in our opinion, life expectancy of 10 years or more. Published results²⁶ and experience at our institution suggest that approximately half of patients presented with this choice will opt to take the IFN.

Intermediate-Risk Patients

Patients with intermediate-risk disease — T2-T4a, N0 (and possibly N1a) — have a 10-year risk of recurrence that covers a wide range but is less than 50%. Classically, high-dose IFN is offered to patients with T4 and/or N1 disease and higher. There is no evidence of a consistent relation-

ship between risk and benefit¹⁻³ as there is for adjuvant treatment of breast cancer: so far as is known, all patients would have a 10% reduction in risk of recurrence, regardless of what that risk might be. This, however, has not been formally demonstrated. Whether it is reasonable to take a treatment with some proven efficacy in one risk stratum and extrapolate that to patients in another risk stratum is an open question. It has not been the policy at our institution to offer IFN to these patients. There are no data to support GM-CSF in this setting, and the risk would not seem to justify the use of any unproven agent. The trial E1697 is designed for this population.

Our recommendation is that all patients in this group with life expectancy of 10 years or more and ECOG performance status 0-1 be offered trial E1697 if they are eligible. Patients with T4 and/or N1 disease should also discuss high-dose interferon. For the others we would recommend observation. Institutional protocols might be considered if available, but the need for assurance of safety in this group of relatively low risk patients is high.

High-Risk Patients

High-dose IFN has been most thoroughly studied in patients with high-risk disease (T4a, T4b, N1a and higher, including all Stage III patients). This group has a risk generally greater than 50% up to as high as 80% for the highest risk Stage III patients. (Note that although T4a disease was included in the original IFN trials these patients would be considered intermediate risk using the 50% risk of recurrence cut-off). All patients who are candidates for IFN should have a discussion about this treatment. For those who are also eligible for S0008, we would recommend that trial as first option and IFN as second. For patients who are not suitable for IFN or S0008 but who are eligible for trial E4697 (N2c and N3 disease), we would recommend participation in that study. For patients not suitable for any of these options, we have recommended observation. This group, with increasing risk, is a group where the pressure to consider use of GM-CSF outside of a trial is higher, but this has not been our policy for reasons discussed above. As above, institutional protocols might be considered where available.

Very High-Risk Patients

This group includes patients with ulcerated primary lesions plus positive nodes, patients with 4 or more positive nodes, and patients with intransit/satellite lesions. Patients with completely resected Stage IV disease are also included in this group. Recurrence rates are generally 75% or higher. Interferon has not been tested in patients with completely resected Stage IV disease; arguably its use in these patients is not evidence-based. The question of whether IFN data obtained from study of predominantly stage III patients can be extrapolated to other groups is especially relevant in these patients. The absence of data in Stage IV must be balanced against the

fact that IFN is an approved agent for adjuvant treatment of Stage III melanoma and these patients are at very high risk. We therefore believe that IFN should at least be discussed with these patients, with the caveat that data in Stage IV are lacking. For patients who are not suitable or who decline, we would recommend participation in the E4697 trial. We have wanted to be sure that patients never feel that a potentially active treatment (IFN) is being withheld in order to enroll them in a trial with a placebo arm. The pressure to use GM-CSF outside a study can be especially intense in this population, but we have not been recommending it. Institutional trials can also be considered, but the same discussion about IFN, in our opinion, should take place.

Ocular and Mucosal Melanoma

There are no data on adjuvant treatment of primary ocular and mucosal melanomas. We have not recommended adjuvant IFN or any other adjuvant treatment of ocular melanomas except to patients with completely resected stage IV disease who are eligible for E4697 and are offered that trial. Because of the very high risk associated with resected mucosal melanoma, we discuss adjuvant IFN with these patients, much as per the discussion above with Stage IV cutaneous melanoma patients. These patients are also offered participation in trial E4697 if they decide against IFN. Institutional trials can also be considered.

Conclusions

Although high-dose IFN is now an accepted adjuvant treatment for melanoma, there is considerable room for improvement. This improvement will come only through carefully designed and conducted clinical trials. Given the relatively poor track record of observational/empiric approaches to evaluation of both efficacy and toxicity, an individual patient is more likely to be helped by a physician who enrolls the patient on a clinical trial than by one who tries to make decisions on premature data outside a trial. The treatment of choice for a melanoma patient, especially in the adjuvant setting, is a clinical trial.

References

1. 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.
2. 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.
3. 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.
4. Kirkwood JM, Manola J, Ibrahim J, et al. A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res.* 2004;10:1670-1677.
5. Wheatley K, Ives N, Hancock B, et al. Does adjuvant interferon-alpha for high-risk melanoma provide a worthwhile benefit? A meta-analysis of the randomised trials. *Cancer Treat Rev.* 2003;29:241-252.

6. Moschos SJ, Kirkwood JM, Konstantinopoulos PA. Present status and future prospects for adjuvant therapy of melanoma: time to build upon the foundation of high-dose interferon alfa-2b. *J Clin Oncol.* 2004;22:11-14. Epub 2003 Dec 9.
7. Pawlik TM, Sondak VK. Malignant melanoma: current state of primary and adjuvant treatment. *Crit Rev Oncol Hematol.* 2003;45:245-264.
8. Sabel MS, Sondak VK. Pros and cons of adjuvant interferon in the treatment of melanoma. *Oncologist.* 2003;8:451-458.
9. Schuchter LM. Adjuvant interferon therapy for melanoma: high-dose, low-dose, no dose, which dose? *J Clin Oncol.* 2004;22:7-10. Epub 2003 Dec 9.
10. Koops HS, Vaglini M, Suci S, et al. Prophylactic isolated limb perfusion for localized, high-risk limb melanoma: results of a multicenter randomized phase III trial. European Organization for Research and Treatment of Cancer Malignant Melanoma Cooperative Group Protocol 18832, the World Health Organization Melanoma Program Trial 15, and the North American Perfusion Group Southwest Oncology Group-8593. *J Clin Oncol.* 1998;16:2906-2912.
11. Rosenberg SA, Yang JC, White DE, et al. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. *Ann Surg.* 1998;228:307-319.
12. Clark JI, Atkins MB, Urba WJ, et al. Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. *J Clin Oncol.* 2003;21:3133-3140. Epub 2003 Jun 16.
13. Hauschild A, Weichenthal M, Balda BR, et al. Prospective randomized trial of interferon alfa-2b and interleukin-2 as adjuvant treatment for resected intermediate- and high-risk primary melanoma without clinically detectable node metastasis. *J Clin Oncol.* 2003;21:2883-2888.
14. Veronesi U, Adamus J, Aubert C, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. *N Engl J Med.* 1982;307:913-916.
15. Hill GJ II, Moss SE, Golomb FM, et al. DTIC and combination therapy for melanoma: III. DTIC (NSC 45388) Surgical Adjuvant Study COG PROTOCOL 7040. *Cancer.* 1981;47:2556-2562.
16. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol.* 2000;18:158-166. Erratum in: *J Clin Oncol.* 2000;18:2351.
17. Agarwala SS, Kirkwood JM, Gore M, et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *J Clin Oncol.* 2004;22:2101-2107.
18. Margolin K, Atkins B, Thompson A, et al. Temozolomide and whole brain irradiation in melanoma metastatic to the brain: a phase II trial of the Cytokine Working Group. *J Cancer Res Clin Oncol.* 2002;128:214-218. Epub 2002 Mar 12.
19. Spittle LE, Grossbard ML, Ernstoff MS, et al. Adjuvant therapy of stage III and IV malignant melanoma using granulocyte-macrophage colony-stimulating factor. *J Clin Oncol.* 2000;18:1614-1621.
20. Legha SS, Ring S, Eton O, et al. Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. *J Clin Oncol.* 1998;16:1752-1759.
21. McDermott DF, Mier JW, Lawrence DP, et al. A phase II pilot trial of concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin 2, and interferon alpha-2B in patients with metastatic melanoma. *Clin Cancer Res.* 2000;6:2201-2208.
22. Buzaid AC, Atkins M. Practical guidelines for the management of biochemotherapy-related toxicity in melanoma. *Clin Cancer Res.* 2001;7:2611-2619.
23. Retsas S. Treatment at random: the ultimate science or the betrayal of Hippocrates? *J Clin Oncol.* 2004;22:5005-5008.
24. Wieand S, Murphy K. A commentary on treatment at random: the ultimate science or the betrayal of Hippocrates? *J Clin Oncol.* 2004;22:5009-5011.
25. 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.
26. Kilbridge KL, Weeks JC, Sober AJ, et al. Patient preferences for adjuvant interferon alfa-2b treatment. *J Clin Oncol.* 2001;19:812-823.