MELANOMA CARE OPTIONS™

APRIL 2009

FOSTERING AN INTERDISCIPLINARY APPROACH TO MELANOMA CARE

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Issue 3: Interpreting Developments in Melanoma Treatment

Editor's Note...

Dear Colleague,

This series of *Melanoma Care Options* was designed to provide expert interpretation of recent and emerging information on melanoma research. Issue 1 focused on the pathogenesis and predictors of prognosis, while Issue 2 explored advances in staging and surgical techniques in patients with pigmented lesions. This issue highlights new findings related to adjuvant and systemic therapies.

High-risk or advanced melanoma cannot always be successfully managed by surgery alone. Patients with stage II/III disease remain at risk of disease recurrence according to tumor microstage and sentinel lymph node findings as summarized in Issue 2 (available at www.MelanomaCare.org). The 10-year survival rates range from 15% to 64%, and the prognosis for patients with metastatic (stage IV) disease is more ominous.[1] Currently, there is only 1 FDA-approved systemic adjuvant therapy for high-risk melanoma—high-dose interferon (IFN) alfa-2b. This therapy is associated with significant improvements in disease-free survival, but considerable toxicity. Systemic treatment options are also lacking for patients with metastatic disease. The 2 FDA-approved therapies—dacarbazine and interleukin-2—have response rates of 7% to 16%, but have never been shown in phase 3 trials to prolong overall survival.[2]

Given this situation, there is intense interest in identifying additional therapeutic options for patients with high-risk or advanced melanoma. For adjuvant therapy, the major focus is on exploiting the confirmed activity of IFN alfa-2b, including efforts to decrease toxicity, improve efficacy, and more precisely target patients most likely to benefit from therapy. For systemic therapy, new options such as agents that disrupt signal transduction pathways of progression are needed. The roles of patient support and symptom management are reviewed, as these represent key facets to successful completion of adjuvant therapy.

The findings presented here provide clinicians with information that may be useful in current treatment decisions and that provides a preview of possible future therapies. We hope this series provides you with a background to evaluate these issues and stimulate discussion concerning the optimal management of melanoma. We welcome your remarks and encourage you to participate in other Melanoma Care Coalition programs available at www.MelanomaCare.org.

Sincerely,

John M. Kirkwood, MD

Additional melanoma information now available at www.MelanomaCare.org or www.MelanomaNurse.org

Clinical Perspectives in Melanoma
A Report on Advances in Melanoma from the 2008 European Society for Medical Oncology (ESMO) Meeting, Stockholm, Sweden, September 12-16, 2008

Insights in Melanoma
Highlights from the Perspectives in Melanoma XII Meeting, The Hague, the Netherlands, October 2-4, 2008

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Target Audience
This activity is directed toward surgical oncologists, oncology nurses, medical oncologists, dermatologists, and other health care professionals who treat or screen for melanoma.

Statement of Need
Management of all stages of melanoma requires a concerted effort on the part of several specially trained members of a healthcare team. Assessing risk, getting patients into the healthcare system, evaluating prognostic information, analyzing and interpreting new therapeutic information and choosing appropriate therapy, working as a team, and educating, guiding, and motivating the patient remain challenging. A core group of specialists are knowledgeable about the optimal management of this malignancy, and this activity provides their insight for practicing healthcare providers.

Learning Objectives
After completing this activity, participants should be able to:
- Interpret the latest data on various adjuvant interferon alfa-2b regimens and extrapolate these findings to clinical practice
- Summarize defects and alterations in signal transduction pathways that contribute to the progression of melanoma
- Evaluate strategies of molecularly-targeted therapy for melanoma
- Identify side effects of interferon alfa-2b therapy and assess approaches to management that may improve patient comfort and adherence

Accreditation and Credit Designation
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1.5 contact hours of Continuing Nursing Education will be granted by the University of Pittsburgh Medical Center. The University of Pittsburgh Medical Center is an approved provider of continuing nursing education by the Pennsylvania State Nurses Association (PSNA), an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

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Adjuvant Interferon Alfa-2b Therapy for High-Risk Melanoma: New Formulations and Regimens

By John M. Kirkwood, MD

Although adjuvant therapy is an area of intense research for melanoma, treatment with high-dose IFN alfa-2b remains the only available US Food and Drug Administration (FDA)-approved option for patients with high-risk operable melanoma.[2] IFN alfa-2a, a closely-related compound, has also been studied in patients with malignant melanoma.[3] IFN alfa-2a and IFN alfa-2b are believed to have comparable effects. IFN alfa-2a is approved for treatment of melanoma outside the United States, but not within the United States.

New studies of IFN alfa in melanoma have focused on evaluating regimens that may offer improved tolerability or antitumor activity, including regimens testing lower doses for longer intervals of treatment, or higher dosages for shorter durations. A pegylated form of IFN alfa-2b (PEG-IFN alfa-2b) has also been tested in patients with operable node-metastatic melanoma. Other studies are attempting to identify prognostic biomarkers and the subsets of patients most likely to benefit from IFN alfa-2b therapy. All of these studies share the common goal of elucidating how best to exploit the therapeutic activity of IFN alfa-2b in patients with high-risk melanoma.

High-Dose IFN Alfa-2b as Adjuvant Therapy in Patients with Melanoma

The FDA-approved high-dose IFN alfa-2b regimen consists of an induction phase, in which IFN is administered intravenously (IV) at a dose of 20 million international units (MU)/m^2 5 times a week on consecutive days for 4 weeks, followed by a maintenance phase, in which IFN alfa-2b is administered subcutaneously (SC) at a dose of 10 MU/m^2 3 times a week for 48 weeks.[4]

High-dose IFN alfa-2b regimens were assessed in 3 Eastern Cooperative Oncology Group (ECOG) trials in patients with high-risk melanoma defined as primary invasion >4 mm Breslow thickness or associated with regional lymph node metastasis.[5-7] All 3 trials found that adjuvant therapy with high-dose IFN alfa-2b significantly improved disease-free survival (DFS) compared with observation (E1684 and E1690)[5,6] or GMK (antiganglioside) vaccine (E1694).[7] A statistically significant improvement in overall survival (OS) was observed in 2 of the trials (E1684 and E1694).[5,7] In the third trial (E1690), patients who experienced disease recurrence during observation were allowed to receive high-dose IFN alfa-2b as salvage therapy.[6] The median OS of patients was longer than expected, and it is possible that the salvage arm served to confound the effect of IFN alfa-2b on OS.[6] In the ECOG and ECOG-led intergroup trials, high-dose IFN alfa-2b therapy was associated with significant adverse events, including flu-like symptoms, myelosuppression, hepatotoxicity, and neuropsychiatric symptoms. With appropriate support and dose modifications, most patients (>90%) were able to tolerate a full year of high-dose IFN alfa-2b therapy.[8]

Data from these and other trials involving IFN alfa-2a/b were included in an individual patient data meta-analysis of 6,067 patients conducted by Ives, Wheatley, and the relevant clinical trial leadership on behalf of the International Malignant Melanoma Collaborative Group.[9] In this analysis, adjuvant IFN alfa-2a/b therapy was found to be associated with a significant increase in DFS and OS compared with no IFN alfa-2a/b therapy; the absolute benefit in survival was about 3% at 5 years, considering all trials of either type of IFN at any dosage or duration. Dose and duration of IFN alfa therapy could not be demonstrated to have a significant effect upon outcome, in contrast to the earlier meta-analysis of published trials of Wheatley and colleagues, in which there was a trend to dose-response correlation.[10] There was no evidence of differences in response on the basis of clinical characteristics such as Breslow thickness or disease stage. However, patients with ulcerated primary melanoma were found to have significantly longer DFS and OS durations than patients with nonulcerated tumors.[9]

On the basis of these studies, it can be concluded that adjuvant therapy with IFN alfa-2b has a favorable although modest effect on patient outcomes. Patient preference surveys have indicated that many patients are willing to accept IFN alfa-2b–associated side effects to realize an improvement in DFS, even if no significant impact upon OS is achieved.[11] Such findings have encouraged ongoing investigations into IFN alfa-2b regimens with improved activity or less toxicity.

Low-Dose IFN Alfa Therapy

Clinical data. Data concerning patient response to low-dose IFN alfa-2a/b adjuvant therapy are inconsistent: some studies have shown improvements in DFS, whereas others have not.[12] The individual patient data analysis by Wheatley and colleagues identified an IFN-associated benefit that could not strictly be correlated with dosage and duration, suggesting that lower-dose regimens might have the potential to improve patient outcomes.[9] In contrast, data from E1690, the only head-to-head phase 3 trial that allows comparison of the benefits of high-dose and low-dose IFN alfa-2b,[13] suggest that low-dose IFN alfa-2b was not associated with durable or significant benefits in high-risk melanoma patients. E1690 randomized patients with stage IIB or III melanoma to observation or treatment with high-dose IFN alfa-2b or low-dose IFN alfa-2b (3 MU/day, 3 times weekly for 2 years). While high-dose IFN alfa-2b significantly and durably prolonged DFS, the low-dose regimen was not associated with significant or durable improvements in DFS or OS compared with observation.[6]

The Cooperative Working Group of the German Cancer Society and German Dermatology Society (DeCOG) has sponsored several trials investigating lower dose IFN alfa-2a/b regimens. In a study of clinically node-negative patients with intermediate- to high-risk melanoma, SC low-dose IFN alfa-2b plus interleukin (IL)-2 for 48 weeks did not show a benefit in DFS or OS compared with observation.[14] A more recent study found that SC low-dose IFN alfa-2a (3 MU 3 times weekly) for 2 years significantly improved both DFS and OS in patients with regional lymph node involvement. For reasons that are not clear, the addition of dacarbazine to this regimen appeared to abrogate the favorable effect of IFN therapy.[15] This trial is not consistent with other study results, and must be interpreted with caution until confirmed.

Intermediate-dose regimens of IFN alfa-2b (10 MU 5 days per week for 4 weeks followed by either 10 MU 3 times weekly for a year or 5 MU 3 times weekly for 2 years) have also been evaluated in patients with stage IIB/III melanoma.[16] Neither of these regimens was found to result in significant improvements in DFS or OS compared with observation. A borderline effect was observed in patients with stage IIB disease, although the authors did not consider this worthy of further pursuit.[16]

While these new studies have added to the knowledge base concerning IFN alfa therapy, the sometimes conflicting data are difficult to apply to clinical practice, except in the case of the E1684 high-dose regimen approved by the US FDA. Studies that have identified a favorable effect of lower-dose IFN alfa-2b regimens upon relapse-free survival (RFS) have not generally been followed to the mature interval of 7 years, where the results of the pivotal E1684 regimen[5,7] were first reported. Since most subsequent trials have included lower-risk groups of patients in whom the interval to relapse is more prolonged, the maturity of these trials would optimally be even greater—but the results have often been reported at a median follow-up of less than 5 years. In addition, the variability of risk groups and specific patient populations (eg, disease stage groups) and the variability of treatment regimens (some of which have extended to 2-5 years), need to be considered. Further research will be required to determine the optimal use of low-dose IFN alfa regimens.

Insights into Molecular Mechanisms of High-Dose Versus Low-Dose Therapy

IFNs exert their effects in part through the Janus-activated kinase (JAK)/signal transducers and activators of transcription (STAT) pathway. Signals transmitted through this pathway impact both tumor progression and immunomodulation.[13] Microarray expression profiles have found that IFN-stimulated gene expression is altered in patients with melanoma compared with healthy controls; one of the most significant defects has been the activation and phosphorylation of STAT1 in response to IFN alfa-2b. Defects in IFN-associated STAT1 signaling could be overcome by stimulation of cells with high concentrations of IFN alfa-2b analogous to ambient serum levels that can be achieved only through IV administration of high-dose IFN alfa-2b therapy.[17]

A trial in which high-dose IFN alfa-2b was utilized as neoadjuvant therapy (before surgical resection) allowed Wang and associates and Moschos and colleagues to conduct in-depth analyses of the in vivo effects of this therapy.[18-20] Wang and associates obtained tissue samples from patients before and after 20 doses of high-dose IFN alfa-2b.[18] IFN alfa-2b increased the expression of phosphorylated STAT1 (pSTAT1) and decreased the constitutive expression of phosphorylated STAT3 (pSTAT3) and total STAT3 levels in the regional lymph node metastases of treated patients who participated in this novel trial. Higher pretreatment ratios of pSTAT1:pSTAT3 were significantly associated with improved outcome.[18] A subsequent study from the same group found that high-dose IFN alfa-2b therapy and low-dose IFN alfa-2b had different effects upon STAT1 and STAT3 in the melanocytic elements of atypical nevi, which are nonobligate precursors of melanoma.[18,19] These data suggest that key signaling pathways, including the mitogen activated protein kinase (MAPK) pathway, are altered in malignant cells.[18,19] Finally, the work of Moschos and colleagues argues that IFN acts as an immunotherapy to drive tumor infiltration by host dendritic cells and T cells, perhaps as a consequence of the profound inhibition of the constitutively activated STAT3 system, which may operate as a mechanism of tumor induction of host tolerance during melanoma progression.[20] Of interest, studies of a range of markers designed to test whether there were any signs of antiangiogenic or proapoptotic effects underlying the neoadjuvant benefits of high-dose IFN alfa-2b disclosed no findings consistent with either of these effects.

IFN-associated changes in immunologic parameters have also been reported. In an analysis of patient subsets participating in E1690, dose-dependent increases in human leukocyte antigen DR expression and decreases in intercellular adhesion molecule-1 (ICAM-1) expression were observed.[21] In addition, patients treated with high-dose IFN alfa-2b showed changes in natural killer and T-cell functions before those who received low-dose therapy.[21]

It thus appears likely that the differences in the effects of IFN administered at different dosages for different intervals may ultimately be understood in terms of the impact of these pleiotropic agents upon both the signaling pathways of melanoma cells and of host immune elements responding to melanoma. The differing clinical efficacy reported with varying doses of IFN alfa-2b may reflect important changes associated with tumor progression, both in molecular mechanisms of the tumor and of the host immunological system. These studies may help researchers identify patients who will benefit from therapy on the basis of pretreatment markers or markers that change early in the course of therapy. In addition, such data may help explain the mechanism of action of high-dose IFN alfa-2b and suggest additional targets or strategies for optimizing adjuvant therapy.

Duration and Timing of IFN Alfa Therapy

Longer courses of IFN therapy have the potential to allow sustained modulation of the mechanisms that drive tumor progression, including angiogenesis, and immunomodulation. Hauschild and colleagues compared an 18-month course of low-dose SC IFN alfa-2a (3 MU 3 times weekly) with 60 months of treatment with the same regimen in patients with node-negative, high-risk melanoma (primary melanoma with a thickness ≥1.5 mm).[22] The 60-month treatment regimen did not improve 5-year outcomes and was associated with significantly more treatment discontinuations than the 18-month regimen.[22]

Shorter durations of IFN alfa-2b have also been assessed, as these regimens could potentially reduce IFN-associated toxicities and enhance treatment convenience and compliance. The Hellenic Cooperative Oncology Group compared a nonstandard induction plus maintenance regimen, consisting of 4 weeks of induction (IV IFN alfa-2b 15 MU/m^2 5 days per week, 75% of the E1684 regimen) followed by 48 weeks of maintenance (flat dose of 10 MU SC 3 times weekly, whereas E1684 dosage was 10 MU/m^2), versus the lower-dose induction regimen alone in 364 patients with stage IIB/III melanoma.[23] The Hellenic Group regimen therefore compared a 1-year regimen attenuated by approximately 25% to 33% with the modified induction regimen alone.[13]

The Hellenic Group study was designed to detect noninferiority of the 1-month regimen, but as there was no control observation group, it cannot be determined what the level of antitumor activity for either of these regimens actually was. The study was relatively small, and underpowered to detect smaller differences of 7.5% or less, which most investigators would now consider relevant. In fact, the biostatistical design of this study would have declared no difference between the 2 treatment arms if a difference of up to 15% were found between the treatment arms (eg, if the 1-month treatment had resulted in 35% RFS and the 1-year regimen had resulted in 50% RFS).[23]

At a median follow-up of 63 months, the median RFS was 27.9 months in patients treated with the 1-year regimen and 24.1 months in patients treated with the 1-month regimen, a difference that was not statistically significant (*P*=.90). Similarly, the difference in median OS was not statistically significant (65.3 months for 1 year of treatment vs 64.4 months for induction alone; *P*=.49).[23] Hepatotoxicity, nausea/vomiting, alopecia, and psychiatric disorders occurred at significantly higher frequencies in the 1-year treatment group, as would be expected.

Although the authors concluded that the 1-month modified IFN alfa-2b induction regimen was not inferior to the modified 1-year regimen,[23] the data from this study are difficult to interpret. In addition to using a different dosage regimen than the ECOG trials, the generous noninferiority criteria and the relatively small study population make it impossible to know what the actual benefit of the 1-month regimen actually was, since we have no controlled data regarding the efficacy of the 1-month or 1-year modified treatment regimens that were studied. If the noninferiority parameter had been set at 9% or less, noninferiority criteria would not have been met.[23] It may thus be more reasonable to conclude that RFS rates with this unconventional induction-only regimen are not 15% higher than RFS rates with the unconventional induction plus maintenance regimen. Until we have data that suggest what the actual level of therapeutic benefit from 1 month of induction therapy is, clinicians should be extremely cautious in adopting truncated regimens of induction-only IFN alfa-2b therapy for the treatment of patients with high-risk melanoma.

The impacts of induction therapy were also assessed in a recent DeCOG trial.[24] Patients were randomized to low-dose treatment with IFN alfa-2b with or without an induction phase (10 MU/m^2). Preliminary data from this trial suggest that DFS and OS rates were similar for the 2 regimens.[24]

The scheduling of IFN alfa-2b therapy could also potentially be modified to improve efficacy or tolerability. A phase 3 trial sponsored by DeCOG is comparing conventional high-dose IFN alfa-2b therapy to high-dose pulsed IFN alfa-2b (3 induction cycles of 20 MU 5 days per week for 4 weeks every 4 months for a period of 12 months). An interim analysis of this trial found that both regimens had similar efficacy, but that the pulsed regimen was better tolerated.[25]

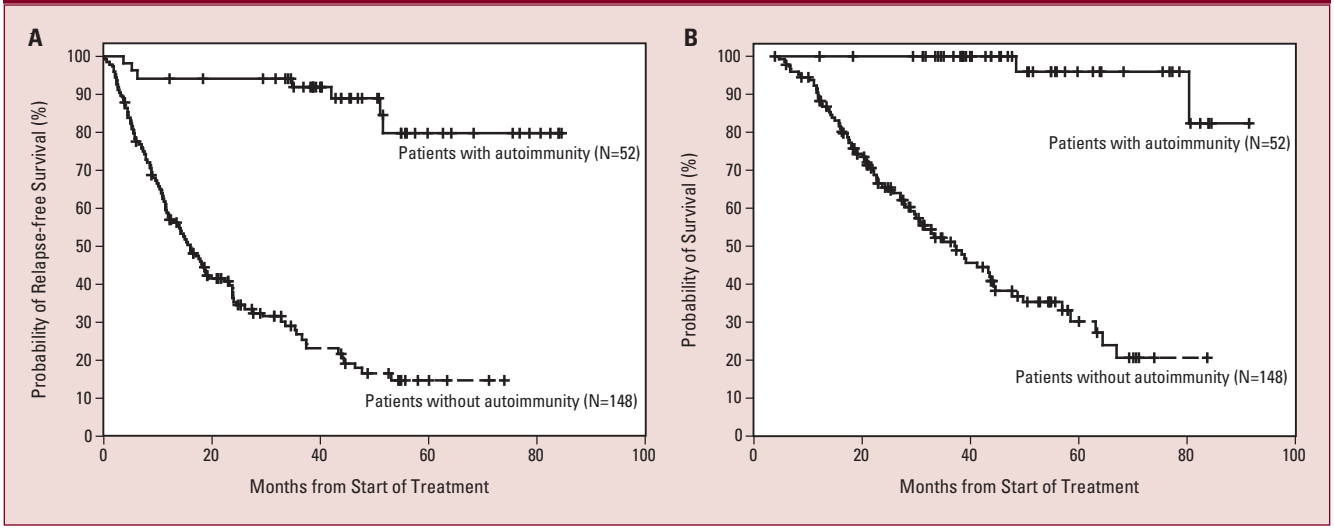
PEG-IFN Alfa-2b as Adjuvant Therapy for Melanoma

The pharmacokinetic properties of PEG-IFN alfa-2b allow weekly, self-administered, SC treatment, improving convenience by avoiding any high-dose component requiring office visits. Eggermont and colleagues recently published data from a phase 3 trial in 1,256 patients with resected stage III melanoma.[26] The trial was undertaken based on preclinical murine data that suggested antiangiogenic effects of IFN alfa-2b would be optimal with a prolonged regimen employing lower dosages that could be sustained in vivo. Patients were randomized to either observation or treatment with PEG-IFN alfa-2b at 6 µg/kg per week for 8 weeks followed by 3 µg/kg per week for an intended duration of 5 years. At a median follow-up of 3.8 years, the PEG-IFN alfa-2b group had a 4-year RFS rate of 45.6% compared with 38.9% in the observation group (*P*=.01). The difference in OS between the 2 groups was not significant. PEG-IFN alfa-2b showed the greatest activity in patients with microscopic nodal disease, designated by European Organisation for Research and Treatment of Cancer (EORTC) as N1.[26] In patients with N1 disease, RFS was significantly improved in the PEG-IFN alfa-2b group compared with the observation group (57.7% vs 45.4%; *P*=.016).

In contrast, patients with clinically palpable lymph node involvement (designated by EORTC as N2) had no benefit from this regimen, and similar RFS rates were noted in the PEG-IFN alfa-2b and observation arms (36.3% vs 33.9%).[26] Ulceration of the primary tumor correlated with therapy benefit. Patients with both N1 microscopic nodal involvement and ulceration of the primary tumor receiving PEG-IFN alfa-2b had a lower risk of recurrence, distant metastasis, and death than those in the observation group. Improvement of outcome was not seen in N1 patients with nonulcerated primary tumors. These results indicate that PEG-IFN alfa-2b improves RFS in patients with stage III melanoma, and the subset analyses demonstrate that this RFS benefit is confined to patients with microscopic nodal involvement and ulcerated primary tumors.[26]

These data may pose new opportunities for patients with resectable melanoma and for physicians who care for them—but they raise concerns regarding how they will be incorporated into current practice. First, the data as published are not adequately mature—results were reported at a median follow-up of 3.8 years compared with 5 years for the stipulated treatment (76% of the treatment interval). No IFN trials in the literature have been adequately interpreted until 2 or more years following the conclusion of therapy—and while the median interval of therapy was little over 1 year, the analysis of benefit among patients more than 2 years off therapy is needed. Second, the patients who appear to be the only beneficiaries of this proposed regimen of prolonged

Figure 1. Kaplan-Meier Estimates of (A) RFS and (B) OS Among Patients With or Without Autoantibodies or Clinical Manifestations of Autoimmunity



therapy are those who have the lowest risk of relapse and mortality—and who would have been predicted from the 6th Edition of the American Joint Committee on Cancer staging system for cutaneous melanoma to have a 65% RFS at 5 years.[1] Thus, this therapy would be administered to patients whose likelihood of relapse without therapy is less than 40%, and a focus upon this group of patients would lead to treatment of patients more often than not who had been cured by their initial surgery.

Adverse events occurring in the PEG-IFN alfa-2b–treated patients were similar to those observed with conventional IFN alfa-2b therapy, including fatigue, hepatotoxicity, and depression.[26] During the study, 31% of patients in the PEG-IFN alfa-2b arm discontinued treatment due to toxicity[26]—a frequency of treatment discontinuation that exceeds the frequency observed in the initial and all subsequent trials of high-dose IFN (E1684, 26%; E1690, 13%; E1694, 10%).[5-7] While the intended duration of PEG-IFN alfa-2b therapy was 5 years, the actual median length of treatment was only slightly longer than 12 months, so we cannot make firm conclusions about the long-term effects of this modality in half of the subjects.[26] A comparison of adverse events in melanoma patients receiving SC PEG-IFN alfa-2b at a dose of 100 µg per week or SC IFN alfa-2b at a dose of 3 MU 3 times weekly found that the tolerability of these 2 regimens was comparable, although leukopenia and granulocytopenia were more common in the PEG-IFN alfa-2b group.[27]

Predicting Response to IFN Alfa-2b Therapy: Patient Characteristics and Prognostic Biomarkers

As mentioned, ulceration of the primary tumor has been identified as a favorable predictive factor in patients treated with conventional IFN alfa-2a/b therapy studied previously[9] and with PEG-IFN alfa-2b as more recently studied by EORTC.[26] On the basis of these findings, the EORTC has planned a randomized phase 3 clinical trial of PEG-IFN alfa-2b in patients with stage III disease and an ulcerated primary melanoma <1 mm in thickness.[28] An earlier disease stage (IIB or N1) may also be associated with an improved response to IFN alfa-2b and PEG-IFN alfa-2b.[16,26] If these observations are confirmed, ulceration and extent of nodal involvement could potentially focus future therapy upon these patients, who may be more likely to respond to IFN alfa-2b therapy.

One of the most promising predictors of a favorable response to IFN alfa-2b therapy is the induction of clinical and serological findings of autoimmunity during therapy. Gogas and colleagues evaluated autoimmune responses, as indicated by autoantibodies and clinical manifestations of autoimmunity such as vitiligo and hypothyroidism, in 200 patients receiving adjuvant IFN alfa-2b therapy.[29] Overall, 26% of patients developed autoantibodies or manifestations of autoimmunity during therapy; the most common sign of autoimmunity was antithyroid antibodies, seen in 22% of patients. Autoimmunity was found to be a significant independent prognostic marker for improved RFS and OS ($P<.001$). Patients with signs of autoimmunity showed prolonged RFS and OS compared with patients without autoimmunity (**Figure 1**).[29] At a median follow-up of 45.6 months, the median survival of patients without signs of autoimmunity was 37.6 months, while the median survival had not been reached in patients with the development of autoimmunity during therapy.[29]

A subsequent report with a median follow-up of 72 months confirmed and extended these findings: median survival was 37 months in patients without autoimmunity and had still not been reached in patients with autoimmunity.[30] The median DFS in patients without autoimmunity was 16 months compared with 115 months for patients with autoimmunity.[30] These data have also been corroborated in analyses of high-dose IFN as studied in the US Intergroup trial E1694,[31] and strongly support the importance of the evaluation of signs of autoimmunity as a prognostic factor in patients receiving adjuvant therapy with IFN alfa-2b. Curiously, studies of the EORTC within trials of lower dosages of IFN without an induction IV therapy component have failed to demonstrate the development of autoimmunity with treatment in EORTC 18952.[32]

A recent report from our laboratory highlighted the measurement of levels of serum protein S100B as a potential prog-

nostic risk factor for patients with high-risk, surgically resected melanoma. We found that high baseline or increasing S100B levels were associated with an increased risk of relapse and death.[33] This finding may allow us to refine the selection of patients most likely to benefit from adjuvant therapy.

Multiplex immunobead assays have more recently been used to assess serum cytokine and chemokine profiles in patients treated with IFN alfa-2b.[34] Patients with resected melanoma were found to have significantly higher serum concentrations of 6 proinflammatory and angiogenic factors, including IL-1 alfa, IL-1 beta, IL-6, IL-8, tumor necrosis factor (TNF) alfa, and vascular endothelial growth factor (VEGF). IFN alfa-2b therapy resulted in significant decreases in growth stimulatory factors such as VEGF, epidermal growth factor, and hepatocyte growth factor. High pretreatment levels of proinflammatory cytokines (including IL-1 alfa, IL-1 beta, IL-6, and TNF alfa) and the chemokines MIP 1 alfa and MIP 1 beta were significantly associated with longer DFS in patients receiving adjuvant IFN alfa-2b treatment.[34] These cytokines may thus provide a means for predicting response to IFN alfa-2b therapy in patients with advanced melanoma. These studies are being expanded with other high-throughput serum protein array techniques amenable to the quantitative assessment of larger numbers of receptors and ligands.

Adjuvant IFN Alfa-2b Therapy: Looking Ahead

In multiple studies, adjuvant therapy with high-dose IFN alfa-2b has been associated with improvements in DFS and, in 2 studies of high-dose IFN,[5,7] improvements in OS. Numerous phase 3 trials have demonstrated the benefit of this regimen in relation to RFS, and it thus remains the gold standard for adjuvant therapy in melanoma. Nevertheless, the search for more effective and better tolerated therapies continues.

While lower-dose IFN alfa regimens have not demonstrated consistent and durable activity, there may be a subset of patients who can derive benefit from this form of treatment. The polar possibilities of lower dosages of therapy administered indefinitely, and of short, high-intensity therapy are obvious. The EORTC effort to deliver 5 years of therapy did not appear to influence survival, but has an impact upon relapse frequency in stage III disease, particularly among patients with ulcerated primary tumors and microscopic nodal dissemination. What is the biology of this differential impact at the nodal station and in the primary melanoma? Ulceration has been considered a pathological covariate of lymphovascular invasion.[35] We need to understand the angiogeneic impact of this therapy to more intelligently interpret the results of this trial.

An initial study of adjuvant treatment with induction high-dose therapy regimen produced promising results and data from additional trials of permutations of this regimen are eagerly awaited. For at least this regimen, there is little to argue for an underlying mechanism of antiangiogenesis. Adjuvant therapy with PEG-IFN alfa-2b has also been shown to improve DFS, and was particularly beneficial in patients with microscopic nodal involvement and an ulcerated primary tumor. Other potential prognostic factors for IFN alfa-2b response include autoimmunity, S100B, and specific cytokine profiles. As we become more proficient in exploiting the therapeutic activity of IFN alfa-2b through more tolerable regimens and improved patient selection, the benefit:risk ratio of this therapy is likely to increase substantially.

New Frontiers in Targeted Therapies for Advanced Melanoma

By Keith T. Flaherty, MD

Despite decades of research, none of the chemotherapy, biochemotherapy, or vaccine regimens evaluated have consistently demonstrated a survival benefit in patients with advanced metastatic melanoma.[36]

Melanoma derives its malignant properties from genetic alterations that affect cell division, survival, and proliferation. The unraveling of the genetic map and studies of the molecular biology of melanoma have revealed several pathways involved in these events. In particular, melanoma cells have demonstrated the ability to co-opt signal transduction pathways to stimulate cell growth and proliferation and to avoid apoptosis (programmed cell death). Agents that block the activity of proteins involved in these dysregulated signaling pathways may thus have therapeutic potential for the treatment of melanoma.

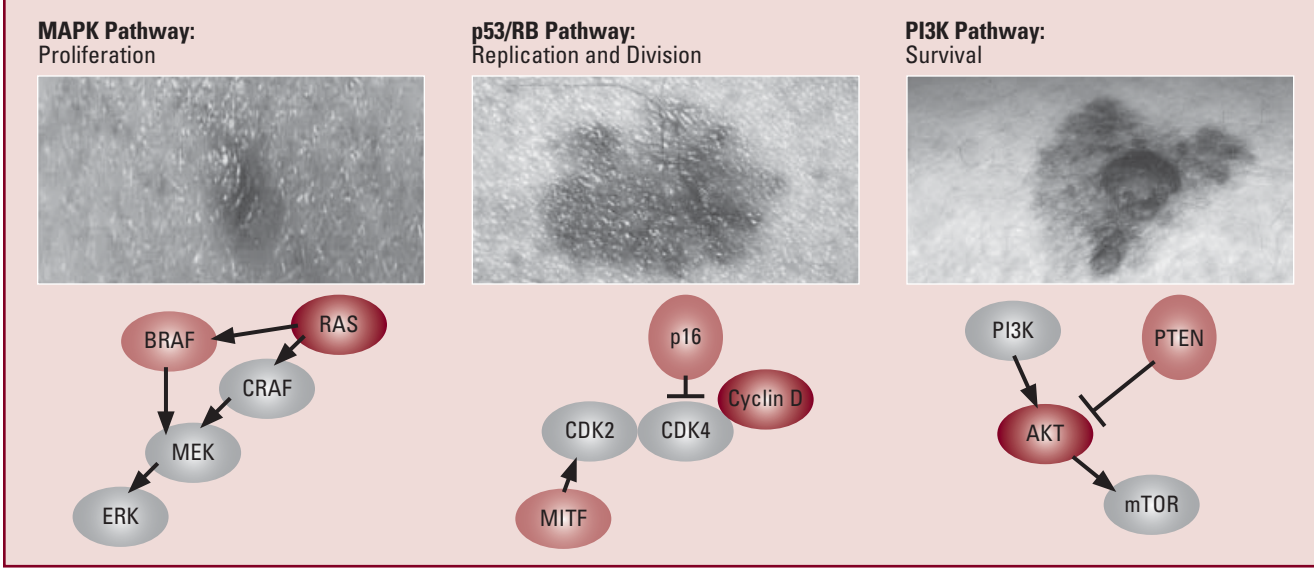
Potential Therapeutic Targets in Melanoma Cells

Three major signaling transduction pathways are believed critical to development of metastatic melanoma: the mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol-3 kinase (PI3K) pathway, and the p53/retinoblastoma (RB) pathway. The MAPK and PI3K pathways are both activated by receptor tyrosine kinases on the cell surface, including the growth factor receptor c-KIT. Signals from these receptors are transmitted through members of the RAS superfamily, proteins that function as membrane-bound guanosine triphosphatases, to activate both the MAPK and PI3K pathways. In patients with melanoma, NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) is the RAS family member that is most frequently mutated.[37]

The MAPK pathway involves BRAF, a serine/threonine kinase, MAPK/extracellular-signal-related kinase (MEK), and extracellular-related kinase (ERK); phosphorylation of these proteins ultimately results in activation of transcription factors and stimulation of cell growth.[38] The PI3K pathway acts through AKT and mammalian target of rapamycin (mTOR) and is primarily involved in cell survival. Phosphatase and tensin homolog (PTEN) is a negative regulator of this system.[39] The p53/RB signal transduction system, located downstream of these other pathways, regulates cell cycle progression.[40] Alterations in the gene encoding p16 disrupts both the p53 and RB pathways.[41] Mutations in the MAPK and PI3K pathways promote malignancy by allowing unregulated cell proliferation, while mutations in the p53/RB pathway abrogate the tumor suppressor activities of these proteins.

The importance of these pathways is

Figure 2. Progression of Melanocytic Lesions From Benign Moles to Malignant Melanoma



CDK2, cyclin-dependent kinase 2; CDK4, cyclin-dependent kinase 4; ERK, extracellular signal-related kinase; MEK, MAPK/ERK kinase; MITF, microphthalmia associated transcription factor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3 kinase; PTEN, phosphatase and tensin homolog; AKT, BRAF, CRAF, and RAS are proto-oncogenes whose names are derived from the viral oncogenes to which they are related.

suggested by frequent mutations observed in key signaling proteins. Proto-oncogenes that are frequently the target of mutations in melanoma cells include BRAF (50% - 70%), AKT (40% - 60%), and NRAS (15% - 25%). Mutations are also observed in tumor suppressor genes, particularly, p16 (40% - 87%) and PTEN (5% - 40%).[42] Melanoma cells with BRAF mutations generally do not have NRAS mutations, suggesting that either one is sufficient to activate the MAPK pathway. Similarly, NRAS and PTEN mutations seldom coincide; 1 mutation is presumably sufficient to activate the PI3K pathway. In contrast, BRAF and PTEN mutations, which affect different pathways, are frequently found together.[43,44]

Different types of melanoma exhibit distinct melanoma mutation patterns. BRAF and NRAS mutations are highly prevalent in melanomas that occur in skin without chronic sun-induced damage (as determined by the absence of solar elastosis) and in acral melanomas, but are less common in skin with chronic sun-induced damage and in mucosal melanomas. In contrast, c-KIT mutations are extremely common in melanomas occurring on mucosal and acral tissues and in skin with chronic sun-induced damage, but are almost never observed in skin without chronic sun-induced damage.[45]

Progression of Melanoma. At the molecular level, melanoma involves a stepwise progression of genetic alterations (**Figure 2**). The initial step appears to involve the MAPK pathway. Mutations in BRAF can be identified in approximately 70% to 80% of benign melanocytic nevi.[46,47] However, the majority of these lesions remain benign, so it appears that activation of the MAPK pathway through BRAF mutation is necessary, but not sufficient, for malignant transformation. Mutations in BRAF promote growth, but proliferation is blocked when cells are driven into senescence, an important barrier to uncontrolled growth.

The next step in the progression to malignant melanoma is believed to involve disruption of the senescence barrier through alterations in the p53/RB pathway. In melanocytic cells, this is most frequently accomplished through inactivation of p16, a tumor suppressor that interacts with cyclin-dependent kinase 4 (CDK4). Genetic mutations in the locus encoding p16 are observed in about 30% of cases of inherited melanoma. The p53/RB pathway can also be disrupted by mutations in CDK4 that make the protein insensitive to p16-mediated inhibition. Although less common than p16 mutations, CDK4 mutations have been observed in both sporadic and familial melanoma.[42]

Another way to circumvent the senescence barrier is through induction of microphthalmia-associated transcription factor (MITF). Amplification of this gene is observed in some melanoma cell lines, and forced expression of MITF in melanocytes with a BRAF mutation results in transformation.[48]

The final step in the progression of melanoma appears to involve the PI3K pathway. Mutations in PTEN, a tumor suppressor, play a major role in activation of the PI3K pathway. Phosphorylation of various molecules by PI3K leads to activation of AKT; this process is negatively regulated by PTEN. When PTEN activity is lost, AKT becomes constitutively activated, allowing unchecked cellular proliferation.[42]

Targeting Signal Transduction Pathways

Our improved understanding of the signaling transduction pathways involved in the progression of melanocytes from benign lesions to malignant melanoma has suggested a number of potential molecular targets suitable for therapeutic intervention (**Table 1**). Many of the agents directed at these targets are in very early stages of development. Others, however, are in late-stage clinical trials, and some have been approved by the FDA for the treatment of other malignancies. In particular, sorafenib and temsirolimus have been approved for advanced renal cell carcinoma, and imatinib is approved for a number of different conditions, including gastrointestinal stromal tumor and certain types of leukemia.[49-51]

There is evidence, however, that blocking a single target or pathway may not be sufficient to treat melanoma. In cell culture studies, agents that inhibited MEK slowed the growth of melanoma cell lines in the

early stages of malignancy, but did not alter the growth of metastatic cell lines. Metastatic cell lines were also resistant to agents that targeted the PI3K pathway. However, combined treatment with PI3K and MEK inhibitors resulted in inhibition of the growth and invasion of the metastatic cell lines, suggesting that blockade of multiple signaling pathways will be required for therapeutic efficacy.[52] It should not be surprising, therefore, if single-agent clinical trials show limited benefit in patients with melanoma. Clinical trials with a combination of agents will probably be required to fully examine the potential of targeted therapy in melanoma.

It will also likely be important to design therapies based on genetic defects in the patient's melanoma. For instance, patients with a BRAF mutation and deletion of PTEN would likely require therapy with agents that inhibit both the MAPK and PI3K pathways. Alternately, patients with a c-KIT mutation may benefit most from a drug that inhibits c-KIT. Based on our current knowledge, we do not believe that "one size fits all." Rather, each subgroup of patients is likely to require a unique combination of agents. The following sections discuss some of the more promising drug candidates.

c-KIT inhibitors. Imatinib is an oral drug that inhibits several kinases, including c-KIT. This agent has shown excellent activity in the treatment of gastrointestinal stromal tumors, where *c-kit* mutations are very common.[53] Preclinical studies with imatinib suggest that it can block activation of both the MAPK and PI3K pathways and that it is cytotoxic to mucosal melanoma cells in vitro that overexpress c-KIT.[54] Melanoma cell lines that co-overexpressed both c-KIT and CDK4 were also highly sensitive to imatinib, suggesting that this subgroup of melanomas might be suitable to imatinib treatment.[55] Phase 2 trials of imatinib in patients with melanoma who were unselected on the basis of *c-kit* mutation or amplification have found efficacy only in a small subset of patients with high c-KIT expression.[56,57] Current investigations in melanoma are focused on identifying *c-kit* mutations status prospectively and enrolling only those patients into c-KIT inhibitor phase 2 trials.

MAPK pathway inhibitors. Sorafenib was originally selected as a c-RAF inhibitor,[58] but subsequent studies showed that it was also a potent inhibitor of receptor tyrosine kinases, including VEGF receptors.[59] Because sorafenib blocks both angiogenesis and signals mediated through the RAF family, it has been the focus of a number of trials in patients with melanoma.

Table 1. Clinical Development of Therapeutic Agents Targeted at Molecules Involved in Melanoma Signaling Transduction Pathways

Target	Clinical Trial Phase		
	Phase 1	Phase 2	Phase 3
Receptor tyrosine kinase			
c-KIT		Imatinib	
MAPK pathway			
BRAF	RAF-265 PLX4032		Sorafenib
MEK	GSK1120212 PD0325901	AZD6244	
PI3K pathway			
mTOR		AP23573 Temsirolimus Everolimus	
PI3K	BEZ235 GDC0941 SF1126 XL147		
AKT	GSK690693 VQD-002		

MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal-related kinase (ERK) kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3 kinase. c-KIT, AKT, and BRAF are proto-oncogenes whose names are derived from the viral oncogenes to which they are related.

For information on these and other clinical trials, see www.ClinicalTrials.gov.

As a single agent, sorafenib had little antitumor activity in patients with advanced melanoma.[60] Single-arm phase 1 and 2 trials of sorafenib in combination with conventional chemotherapeutic agents (carboplatin and paclitaxel or temozolomide) have produced more encouraging results.[58,61] In the phase 1 study, the response rate was the same irrespective of whether the patients had a mutated or wild-type version of BRAF.[61] A randomized phase 2 trial in which the combination of sorafenib plus dacarbazine was compared with placebo plus dacarbazine in chemotherapy-naïve patients with advanced melanoma found that the sorafenib combination showed a trend toward improving progression-free survival (PFS; 21.1 vs 11.7 weeks; P=.068) and an improvement in objective response rate (24% vs 12%).[62]

Data from phase 2 trials of sorafenib in combination with chemotherapy were sufficiently encouraging to warrant initiation of phase 3 trials. In a randomized trial of carboplatin, paclitaxel, and sorafenib compared with carboplatin, paclitaxel, and placebo in 270 chemotherapy-refractive patients with advanced melanoma, the addition of sorafenib did not significantly improve PFS or OS.[63] An ongoing phase 3 trial, E2603, will compare these regimens in 800 patients who have not received prior chemotherapy.[58] The potential role of sorafenib in the treatment of metastatic melanoma thus remains unclear.

In addition to sorafenib, other BRAF inhibitors with greater selectivity are also being assessed. RAF-265 blocks RAF and VEGF receptor kinase activity and is a more potent inhibitor of MAPK phosphorylation than sorafenib. A phase 1 trial of RAF-265 in unresectable stage III or IV melanoma is currently recruiting patients. PLX4032 is a highly selective small-molecule inhibitor of mutant BRAF. In melanoma cell lines, PLX4032 induces an apoptotic response, leading to cell death, but in those that harbor a BRAF mutation. The therapeutic utility of this agent is currently being assessed in patients with advanced tumors, with a focus on melanoma. Both the RAF-265 and PLX4032 trials will include serial tumor biopsies in a subset of patients to ascertain whether the drugs effectively block the activity of BRAF.[37,64,65]

The therapeutic utility of MEK inhibitors is also being explored in patients with melanoma. AZD6244 is selective inhibitor of MEK. Studies in cell cultures and animal models found that this agent induces cell cycle arrest. Combining it with docetaxel enhanced cell death and tumor regression observed with docetaxel alone.[66] In an open-label phase 2 trial, 200 chemotherapy-naïve patients with advanced melanoma were randomized to receive either temozolomide or AZD6244.[67] No difference in PFS was observed between the 2 treatment arms. Of the

6 patients with a confirmed partial response in the AZD6244 arm, 5 were positive for a BRAF mutation (a 12% response rate to AZD6244 in those whose tumors harbored a BRAF mutation).[67] These data thus suggest that AZD6244 may have antitumor activity in select patients. MEK inhibitors in phase 1 trials include PD0325901 and GSK1120212.

PI3K pathway inhibitors. The PI3K pathway provides additional targets for therapeutic intervention, but the clinical utility of blocking this pathway in patients with melanoma has not yet been demonstrated. Two mTOR inhibitors that have shown efficacy in other forms of malignancy, temsirolimus and everolimus, have produced disappointing results as single-agents in melanoma.[53,68] Several other agents targeting this pathway are at early stages of development.

Additional Therapeutic Strategies

Agents that inhibit angiogenesis have been successful in other solid malignancies (including colorectal cancer), and are now being tested in patients with melanoma. Other strategies are designed to promote apoptosis or to overcome the abrogation of apoptosis observed in cancer cells.

Antiangiogenic agents. In addition to sorafenib, several other antiangiogenic agents are being evaluated in patients with melanoma. Much attention has been focused on bevacizumab, a recombinant anti-VEGF human monoclonal antibody.[53] As of December 2008, the National Institutes of Health-sponsored clinical trials web site, www.clinicaltrials.gov, listed 19 different trials of bevacizumab combination regimens in patients with melanoma. Agents being tested in combination with bevacizumab include dacarbazine, carboplatin and paclitaxel, IFN alfa, and sorafenib.[50]

Axitinib, an oral VEGF receptor inhibitor, is also being assessed. In a phase 2 trial in 32 patients with metastatic melanoma, axitinib showed promising activity, particularly in patients who experienced elevated diastolic blood pressure during therapy, a pharmacodynamic effect seen with VEGF signaling inhibitors.[69] Other angiogenesis inhibitors in early stages of clinical development include sunitinib and TKI-258 (CHIR-258).[50]

Proapoptotic agents. Elesclomol is an agent that results in increased relative species in cancer cells. While the mechanism for this effect is unknown, this agent appears to enhance the cytotoxicity of several chemotherapies. In a small phase 2 study of 81 patients with metastatic melanoma, elesclomol plus paclitaxel significantly prolonged median PFS compared with paclitaxel alone (3.7 vs 1.8 months; P=.035). The difference in median PFS was particularly striking in chemotherapy-naïve patients (8.3 vs 2.4 months, respectively).[70] A subsequent report presented 2-year follow-up data from this study.[71] Although survival data were likely confounded by the crossover from single-agent to combination therapy allowed, the elesclomol plus paclitaxel group still showed a trend toward improved median OS compared with paclitaxel alone (11.9 vs 7.8 months).[71]

On the basis of data from this trial, a phase 3 multinational clinical trial of elesclomol plus paclitaxel versus paclitaxel alone was initiated and completed.[71] Unfortunately, this trial was closed prematurely due to safety concerns regarding the combination therapy, and the promising phase 2 data appear not to have been borne out in the larger phase 3 study. This suggests that renewed attention to larger phase 2 trials, in which the results may be more robust, is important.[72]

Several agents in development target Bcl-2, an antiapoptotic protein that plays an important role in tumor cell survival.[53] Oblimersen, a Bcl-2 antisense oligonucleotide, binds to Bcl-2 mRNA, resulting in cleavage of the resulting double-stranded molecule by RNase H. Addition of oblimersen to dacarbazine in chemotherapy-naïve patients with advanced melanoma resulted in significant increases in PFS, complete responses, and durable responses compared with dacarbazine alone, although a significant difference in OS was not observed.[73] However, in a subgroup analysis, a significant improvement in overall survival (11.4 vs 9.7 months; P=.02) was noted in patients whose baseline serum lactic dehydrogenase (LDH) was not elevated.[73] A second phase 3 trial comparing oblimersen and dacarbazine to dacarbazine alone in patients with an LDH ≤0.8 times the upper limit of normal (ULN) is ongoing. Two small molecular inhibitors of Bcl-2, ABT-265 and GX15-070, are currently in early development and may offer more potent Bcl-2 inhibition leading to greater enhancement of cytotoxic therapies.

Future Directions in Targeted Therapy for Melanoma

Our improved understanding of the molecular pathways that underlie the progression of melanoma has revealed numerous potential therapeutic approaches. We now face the challenge of developing targeted therapies directed at signaling pathways that are activated through mutations. Single-agent therapy is unlikely to be markedly successful, so there is also a pressing need to evaluate combination therapies, both with multiple targeted therapies and with targeted therapies plus conventional chemotherapeutic agents. It is hoped that these approaches will result in effective treatment options for patients with metastatic melanoma.

Preventing Pitfalls to Therapy: Managing Adverse Effects and Improving Patient Compliance

By Rosemary Giuliano, ARNP, MSN

Surgical treatment results in high survival rates for patients with early stage melanoma and favorable histologic characteristics. However, patients with more advanced disease have a diminished prognosis. Choosing the optimal treatment becomes more difficult with advanced disease, as available options are associated with modest improvements in outcomes and may have significant side effects.[2] Patients with advanced melanoma thus need considerable support in choosing a treatment plan and in coping with adverse effects during therapy. Appropriate management of side effects may also improve patient compliance and enhance long-term survival.

Patient Empowerment

Surgery remains the mainstay of treatment for patients with advanced disease. Patients with stage IIB or IIC melanoma or with regional nodal disease (stage III) should also consider postsurgical adjuvant therapy. Active treatment options recommended by the National Comprehensive Cancer Network consist of

IFN alfa and clinical trials.[12] Clinical trials are an important opportunity for patients to receive promising therapies that are not yet approved by the FDA, including vaccines, biochemotherapy, targeted therapy, and immunotherapy. Nontherapeutic trials involve analyses of the genetics of melanoma or identification of prognostic markers. Radiotherapy to the nodal basin is a possible option for patients with stage IIIC disease and multiple nodal involvement or extranodal extension.[12]

The success of adjuvant therapy depends, in part, on the patient's commitment and ability to complete treatment. When possible, the patient's healthcare team should discuss possible supportive options, and give the patient choices when presenting the treatment plan. The primary choice is typically between standard of care and a clinical trial, although some patients may prefer observation only. Each choice has benefits and risks, and these should be thoroughly described. This approach empowers patients, thus improving their commitment to care.

Knowledge plays an important role in helping patients make optimal decisions, in securing their compliance with therapy, and in decreasing their anxiety. The healthcare team should provide patients with an individualized care plan that includes a summary of all surgeries and therapies, including specific drug dosages. Patients who have completed their treatment regimen should be given a plan for ongoing care, with instructions on how they should monitor their health, guidance on follow-up testing, future doctor visits, and potential long-term side effects of surgeries and/or drug therapy. During discussions with patients, it is important to assess the family structure, since family members may play an active role in the overall care, and some treatment options may be difficult to complete without strong family/caregiver support.

Interferon Alfa-2b as Adjuvant Therapy for Melanoma

High-dose IFN alfa-2b is the only FDA-approved adjuvant therapy for high-risk malignant melanoma. The approved treatment regimen consists of a 4-week IV induction phase followed by a 48-week SC maintenance phase.[4] High-dose IFN alfa-2b regimens are associated with significant improvements in RFS; some trials have also found improvements in OS.[74] Although several studies have investigated the utility of low-dose IFN alfa regimens, to date these have not been consistently associated with clinical efficacy.[74]

IFN alfa-2b-associated toxicities. While some toxicities associated with IFN alfa-2b therapy (**Table 2**)[8,75] may occur throughout treatment (such as dermatologic reactions and laboratory abnormalities), others typically emerge on a fairly predictable time course (**Figure 3**).[75] In particular, flu-like symptoms are usually observed immediately following initiation of IFN therapy and diminish over time, while fatigue and symptoms of depression and anxiety generally appear later in the course of therapy.

Laboratory assessments. Because laboratory abnormalities are frequently found in patients receiving high-dose IFN alfa-2b, the FDA recommends the following regular tests:

- Standard hematologic tests, including hemoglobin, complete and differential white blood cell counts, and platelet counts; and
- Blood chemistry, including electrolytes, liver function tests, and thyroid-stimulating hormone.[4]

Differential and white blood cell counts and liver function tests should be performed weekly during the induction phase and monthly during the maintenance phase.[4]

Because drug-induced thyroid disorders are a possible side-effect of IFN alfa-2b therapy, experts recommend that patients be tested for pre-existing thyroid conditions before therapy is initiated, and that tests for triiodothyronine (T3) and thyroxine (T4) and for thyroid autoantibodies be included in regular lab assessments. IFN alfa-2b therapy has been associated with exacerbation of autoimmune endocrine diseases, and thyroid autoantibodies are detected in the majority of IFN alfa-2b-treated patients who develop thyroid disorders.[75] IFN-induced thyroid disorders include hypothyroidism and hyperthyroidism.[76] Many patients are clinically asymptomatic, however, with thyroid disorders only revealed through lab testing.[75]

Dose modification schemes. In the ECOG clinical trials that established efficacy of the high-dose IFN alfa-2b regimen, delays or dose reductions due to toxicity were required in 28% to 44% of patients during the induction phase and 36% to 52% of patients during the maintenance phase.[8] These trials used a 3-step dose modification scheme: after the first treatment interruption for toxicity, a 33% dose reduction was imposed; after the second treatment interruption, the dose was reduced by 66%; and after a third treatment interruption, the patient was removed from the study.[6]

The dose adjustment scheme recommended by the FDA has 2 steps: a 50% dose reduction is suggested if specific granulocyte cell counts (>250 but <500 cells/mm^3) or liver toxicity (serum glutamic pyruvate transaminase [SGPT] or serum glutamic oxaloacetic transaminase [SGOT] from 5-10× ULN) criteria are met.[4] IFN alfa-2b should be permanently discontinued if toxicity does not abate after withholding the drug, severe adverse reactions recur, granulocyte counts fall below 250 cells/mm^3, or if SGPT/SGOT levels exceed 10× ULN.[4]

Table 2. Toxicities Associated With IFN Alfa-2b

Acute (early) toxicities
Flu-like symptoms
Laboratory abnormalities
Dermatologic reactions
Chronic (late) toxicities
Fatigue
Anorexia
Depression
Laboratory abnormalities
Autoimmunity
Dermatologic reactions
Sexual dysfunction

Data from Kirkwood J et al[8] and Hauschild A et al.[75]

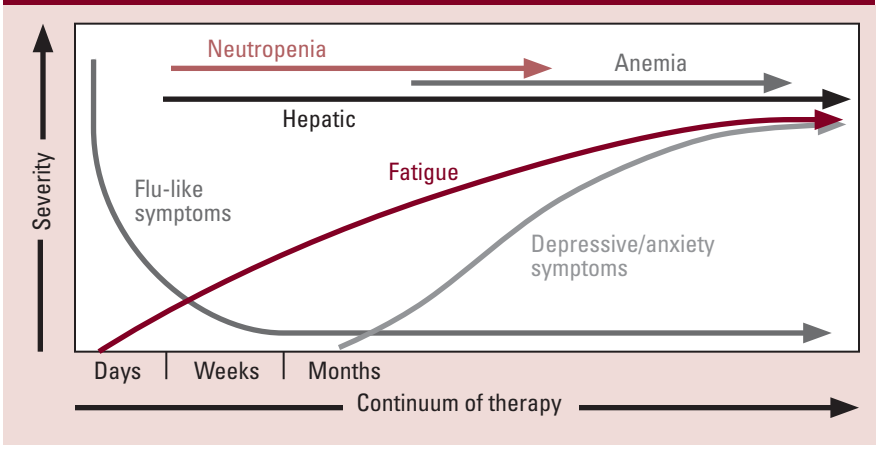
Managing Treatment-Associated Toxicities

Most melanoma patients are willing to tolerate severe toxicity for a 10% improvement in 5-year DFS and to tolerate mild-to-moderate toxicity for a 4% improvement in 5-year DFS associated with IFN alfa-2b therapy.[11] Combining these data on relative values with outcome data from 2 of the ECOG adjuvant IFN alfa-2b clinical trials, Kilbridge and associates reported that most patients in these trials experienced an increase in quality of life (QOL)-adjusted survival and that the benefit was statistically significant in 16%.[77] These QOL data further support the use of adjuvant IFN alfa-2b therapy in high-risk melanoma patients beyond improved DFS.

With appropriate symptom management, most patients can successfully complete a full 52-week course of IFN alfa-2b therapy.[78] In the ECOG clinical trials, an improved understanding of IFN alfa-2b-associated toxicities and more effective management helped reduce toxicity-related discontinuation rates from 26% in the first trial to 10% in the third.[75]

A multidisciplinary team approach—including primary care physicians, surgical and medical oncologists, nurses, the pharmacist, and a psychiatrist when appropriate—ensures patient safety and optimal symptom

Figure 3. Typical Time Course of Adverse Events Associated With IFN Alfa-2b



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management. Involvement of the pharmacist is particularly important when the patient is taking multiple drugs for comorbid conditions. The nurse can play a key role in assisting with the coordination of care, thus enabling improved quality of care, enhanced communication, and reduced patient loss to follow-up or discontinuation of therapy.

Flu-like symptoms. Appropriate management strategies include alterations in the timing of therapy, use of over-the-counter or prescription medications, and attention to proper fluid intake. Since flu-like symptoms generally last from 1 to 12 hours after treatment administration, tolerability may improve with evening administration of IFN alfa-2b accompanied by prophylactic analgesics and antipyretics as necessary.[8,75] We usually recommend prophylactic oral acetaminophen (1 g, 3-4 times daily), but liver function tests should be closely monitored. If elevated liver enzymes are observed, acetaminophen should be discontinued and the patient switched to oral ibuprofen (400 mg, 3 times daily). At our institution, we have found that oral diphenhydramine (25 mg) given prior to infusion helps reduce flu-like symptoms, but care should be taken to ensure the patient has no plans to drive. If nausea and vomiting are a problem, an antiemetic such as chlorpromazine or metoclopramide may be useful. A warm room and warm blankets may help the patient cope with severe chills. Oral meperidine at a dose of 25 mg is an option for severe rigors.[8]

Hydration is a key component in the successful management of flu-like symptoms. Fever and vomiting may cause dehydration, which can exacerbate other symptoms. In a recent study of high-risk melanoma patients who received high-dose IFN alfa-2b adjuvant therapy, those with a daily fluid intake ≥1.5 L were significantly more likely to complete the 1-year treatment course than those with a lower fluid intake.[78] Appropriate beverage choice should be discussed, with a reminder that coffee, tea, soda, and alcoholic beverages may actually increase dehydration. The daily fluid requirement (in ounces) is easily calculated by dividing the patient's weight (in pounds) by 2. We recommend that daily nondiuretic fluid intake exceed 2 L. If necessary, IV hydration can be used in patients with decreased oral fluid intake.[8]

Hepatotoxicity. As with many drugs, IFN alfa-2b can cause liver injury. While rare, drug-associated hepatic injuries can be severe: more than 75% of idiosyncratic liver injuries caused by drugs result in liver transplantation or death. Overall, drug-induced liver toxicity accounts for more than 50% of cases of acute liver failure in the United States.[79]

To help avoid IFN alfa-2b-associated hepatotoxicity, it is important to identify comorbidities and potential drug interactions. The aid of a pharmacist should be enlisted in recognizing possible drug interactions. Conditions that may predispose to liver damage include pre-existing renal or liver disease, infection with hepatitis C or human immunodeficiency virus, malnutrition, obesity, alcohol use, or diabetes.[79-81]

Fatigue. Almost all (96%) patients treated with high-dose IFN alfa-2b experience fatigue—the most common dose-limiting chronic toxicity. While the mechanism is unclear, IFN alfa-2b may cause fatigue by inducing the release of nitric oxide and cytokines such as IL-1, IL-2, IL-6, and TNF alfa. These substances can affect endocrine cells and alter the hypothalamic-pituitary-adrenal axis, potentially causing fatigue.[8]

Fatigue associated with IFN alfa-2b treatment may further compound cancer-related fatigue from other causes (including direct effects of the malignancy, comorbid medical conditions, additional symptoms such as chronic pain, and psychosocial factors such as anxiety and depression).[82] Fatigue has a significant impact on QOL and may increase in intensity during IFN alfa-2b maintenance therapy.[75] Effective management may therefore help patients complete the course of therapy.

The first step in evaluating fatigue is to examine the patient for other possible causes, including anemia, poor nutrition, depression, and hypothyroidism.[75] If fatigue persists after other causes have been addressed, behavioral interventions should be implemented. Patients should be counseled on energy conservation and the need to prioritize important activities for times when their energy level is high. Regular light exercise has been shown to alleviate fatigue in cancer patients. Intellectual stimulation may also help combat fatigue. Patients should keep in close contact with their family members and friends and remain involved in their regular activities as much as possible.[8] At our institution, we have observed that evening administration of IFN alfa-2b helps reduce fatigue. We also recommend that our patients add refreshing, restful activities to their routine, such as reading, listening to relaxing music, meditating, and taking warm baths.

If behavioral interventions are not adequate, pharmacologic therapies may be useful. Methylphenidate in combination with light aerobic exercise was found to improve fatigue in melanoma patients treated with IFN alfa-2b in a small, uncontrolled study.[83] Other possibilities include the antiemetic agent granisetron and antidepressants.[75] The use of corticosteroids is controversial as the immunosuppressive effects could potentially reduce therapeutic immune-mediated effects of IFN alfa-2b. Another hormonal agent, megestrol acetate, improves appetite but may increase the risk of venous thrombosis and pulmonary thromboembolism in patients with melanoma who have anorexia and weight loss while undergoing high-dose IFN alfa-2b therapy.[8,75]

Treatment of fatigue requires accurate diagnosis and measurement. A number of fatigue assessment tools are available.[84] Some QOL instruments, including the Profile of

Mood States and Functional Assessment of Cancer Therapy, contain subscales that assess fatigue. These tools allow fatigue to be tracked over time and can assess the efficacy of interventions designed to reduce fatigue.

Mood disorders. A range of neuropsychiatric adverse effects have been observed in patients treated with IFN alfa-2b, including depressive symptoms, an acute confusional state, and manic symptoms.[85] Appropriate screening for prior psychiatric disorders and early expectant behavioral and pharmacological interventions for patients with early signs of depression or other affective disorders on treatment may help reduce the occurrence of more significant signs.

Depression, the most common mood disorder associated with IFN, affects 40% to 45% of patients with malignant melanoma undergoing high-dose IFN alfa-2b adjuvant therapy.[8,86,87] While depression is generally common in patients with cancer, studies suggest that IFN alfa therapy increases the likelihood of developing depressive symptoms.[8,85] The presence of depression or anxiety disorders near the time of treatment initiation is an important risk factor for the development of depression during IFN alfa-2b therapy. However, a past history of depression or psychiatric disorders does not appear to increase the risk of depression during treatment. Other risk factors for depression include the dose and duration of IFN alfa-2b therapy and lack of social support.[85]

Because of the risk posed by comorbid neuropsychiatric conditions, a psychiatric history should be obtained from each patient prior to IFN alfa-2b therapy, and patients should be closely evaluated for depressive symptoms during therapy. Specific questions concerning neuropsychiatric symptoms can be incorporated into routine evaluations or clinicians can utilize depression evaluation tools, such as the Beck Depression Inventory or the Minnesota Multiphasic Personality inventory, before treatment initiation and every 4 to 6 weeks during treatment.

Both prophylactic and symptomatic treatment of IFN alfa-2b-associated depression appear to be successful in reducing depressive symptoms.[85] The prophylactic use of paroxetine was assessed in a double-blind, placebo-controlled trial of patients with malignant melanoma treated with high-dose IFN alfa-2b adjuvant therapy.[86] Patients were randomized to receive either placebo (n = 20) or paroxetine (n = 18) beginning 2 weeks before IFN alfa-2b therapy and continuing for the first 12 weeks of therapy. The paroxetine-treated group had a significantly lower incidence of depression than the placebo group (11% vs 45%; P=.04). In addition, there were fewer discontinuations due to severe depression in the paroxetine group (1 patient) compared with the placebo group (7 patients).[86] A subsequent analysis of data from these studies found that in addition to depressive symptoms, anxiety, cognitive dysfunction, and pain were reduced in patients receiving paroxetine.[88]

These data indicate that pretreatment with paroxetine successfully reduces depression in patients receiving high-dose IFN alfa-2b therapy. However, because approximately half of patients undergoing IFN alfa-2b treatment do not experience depression, prophylactic therapy would expose many patients to unnecessary drugs. Symptomatic therapy with paroxetine or citalopram has been shown to be successful in patients with chronic hepatitis C receiving treatment with IFN alfa and ribavirin.[85,89] However, similar studies have not been conducted in patients with melanoma undergoing high-dose IFN alfa-2b therapy. Ocular toxicity has been reported in patients receiving selective serotonin-reuptake inhibitors in addition to IFN alfa,[90] and may be increased above the retinal toxicity that has been reported with IFN alfa-2b alone, so the possibility of this rare side effect should be considered. Due to its appetite stimulation, and sedative effects beyond antidepressant effects, mirtazepine may also be useful for supportive management of patients receiving IFN alfa-2b.

High-dose IFN alfa therapy has also been associated with an acute confusional state marked by disorientation, psychomotor retardation, lethargy, and psychotic symptoms. This state usually develops rapidly and generally resolves upon discontinuation of treatment. Case reports and small studies suggest that atypical antipsychotics such as olanzapine may be useful in the treatment of IFN alfa-induced confusional states.[75,85]

On rare occasions, mania has been reported in IFN alfa-2b-treated patients, typically in response to changes in IFN alfa-2b therapy (including dose reductions) or during treatment with antidepressants.[8,75] Manic symptoms may occur in conjunction with depression, irritability, and anxiety. One study found that gabapentin was an effective mood stabilizer in melanoma patients treated with adjuvant IFN alfa-2b and reduced both mania and anxiety symptoms.[91]

Cognitive dysfunction. Some patients undergoing cancer therapy experience cognitive dysfunction, popularly referred to as "chemobrain," marked by forgetfulness, absentmindedness, and an inability to focus on various tasks. The impact on cognitive function appears to be related to the type of cancer and the specific chemotherapeutic agents used. Cancer therapies may be associated with neurotoxicity, anemia, cytokine induction, altered hormonal status, and vascular injury, all of which may affect cognitive function. Psychosocial factors including the stress induced by a cancer diagnosis, anxiety, and depression may also contribute to cognitive changes.[92]

Some studies have documented changes in cognitive function in patients treated with IFN alfa.[93,94] Most involved patients with renal cell carcinoma, often in combination with other agents such as IL-2 or dexamethasone.[93] A study of patients with chronic hepatitis B or C who received 12 weeks of low-dose IFN alfa therapy found that treatment was associated with significant cognitive impairment.[94] Cognitive functions have not been well-studied in patients receiving high-dose IFN alfa adjuvant therapy. Capuron and associates noted significant increases in cognitive impairment within 8 weeks of the initiation of high-dose IFN alfa-2b therapy in patients with metastatic melanoma, while no changes were observed in patients receiving prophylactic paroxetine.[88] Another study of high-dose adjuvant IFN alfa-2b therapy in 6 patients with melanoma did not detect significant changes in cognitive function during the first 3 months of therapy, but did note deterioration in attention and mental flexibility over time.[95]

Dexmethylphenidate may be another treatment option for patients who experience significant cognitive symptoms during IFN alfa-2b therapy. In a placebo-controlled study of patients with breast or ovarian cancer treated with 4 or more cycles of cytotoxic chemotherapy, dexmethylphenidate was significantly more effective than placebo in improving fatigue and memory.[96] However, this observation has not been confirmed in patients receiving high-dose IFN alfa-2b therapy.

Conclusions

Most of the major side effects of IFN alfa-2b therapy can be successfully managed with proper support. Careful baseline assessments may help identify patients at high-risk for adverse events, and frequent monitoring helps detect any toxicities at an early stage. Proper support and aggressive management of side-effects by a multidisciplinary team may help patients complete the full course of treatment and potentially experience the benefits associated with high-dose IFN alfa-2b therapy.

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POSTTEST Interpreting Developments in Melanoma Treatment

For each question or incomplete statement below, please indicate your answer or completion in the space provided on the evaluation form on page 16.

1. At the molecular level, high-dose IFN alfa-2 therapy:
- A. Results in dephosphorylation of JAK
- B. Induces expression of phosphorylated STAT1
- C. Has the same effects on lymphoid and melanoma cells
- D. Does not cause detectable changes

2. In a recent study by the Hellenic Cooperative Oncology Group that compared conventional high-dose IFN alfa-2b therapy (induction plus maintenance) to the induction phase only:
- A. The induction phase only was associated with reduced survival compared with conventional therapy
- B. Conventional therapy was associated with reduced survival compared with the induction phase only
- C. The induction phase only was associated with similar survival outcomes but better tolerability than conventional therapy
- D. The induction phase was associated with similar survival outcomes but worse tolerability than conventional therapy

3. Which of the following is NOT a favorable prognostic factor in patients treated with IFN alfa?
- A. High baseline S100B levels
- B. Ulceration of the primary tumor
- C. Earlier disease stage
- D. High pretreatment levels of proinflammatory cytokines

4. Members of the RAS family transmit signals from receptor tyrosine kinases that:
- A. Directly activate the p53/RB pathway
- B. Activate the MAPK pathway, but not the PI3K pathway
- C. Activate the PI3K pathway, but not the MAPK pathway
- D. Activate both the MAPK and PI3K pathways

5. BRAF mutations:
- A. Are observed only in mucosal melanoma
- B. Are common in benign melanocytic nevi
- C. Are always associated with malignancy
- D. Act to block cellular growth

6. Therapeutic agents that target molecules involved in signal transduction pathways in patients with melanoma:
- A. Are likely to be successful as single agents
- B. Should not be combined with conventional chemotherapeutic agents
- C. Are mostly in phase 3 clinical trials
- D. Will probably need to be used in treatment regimens tailored to genetic defects in the patient's melanoma

7. Therapeutic strategies being tested in metastatic melanoma include:
- A. Inhibition of the MAPK pathway
- B. Inhibition of angiogenesis
- C. Induction of apoptosis
- D. All of the above

8. Which of the following IFN alfa-2b-associated side effects usually occurs early in the course of therapy?
- A. Flu-like symptoms
- B. Depression
- C. Fatigue
- D. Anorexia

9. The most common dose-limiting chronic toxicity of IFN alfa-2b therapy is:
- A. Cognitive dysfunction
- B. Sexual dysfunction
- C. Fatigue
- D. Depression

10. Risk factors for the development of depression in patients treated with IFN alfa-2b do NOT include:
- A. Depression or anxiety disorders near the time of therapy initiation
- B. Lack of social support
- C. Dose and duration of IFN alfa-2b therapy
- D. A history of depression

EVALUATION FORM Interpreting Developments in Melanoma Treatment

Please use the scale below in answering these questions. Fill in the circle completely. You may use pen or pencil.

Very low Low Moderate High Very High

1. To what degree will you apply the following objectives of the educational activity in your practice and/or professional responsibilities?

A. Interpret the latest data on various adjuvant interferon alfa-2b regimens and extrapolate these findings to clinical practice

❍ ❍ ❍ ❍ ❍

B. Summarize defects and alterations in signal transduction pathways that contribute to the progression of melanoma

❍ ❍ ❍ ❍ ❍

C. Evaluate strategies of molecularly-targeted therapy for melanoma

❍ ❍ ❍ ❍ ❍

D. Identify side effects of interferon alfa-2b therapy and assess approaches to management that may improve patient comfort and adherence

❍ ❍ ❍ ❍ ❍

2. To what extent were you satisfied with the overall quality of the educational activity?

❍ ❍ ❍ ❍ ❍

Very low Low Moderate High Very High

3. To what extent was the content of the activity relevant to your practice or professional responsibilities?

❍ ❍ ❍ ❍ ❍

4. To what extent did the program enhance your knowledge of the subject area?

❍ ❍ ❍ ❍ ❍

5. To what extent did the program change the way you think about clinical care and/or professional responsibilities?

❍ ❍ ❍ ❍ ❍

6. To what extent will you make a change in your practice and/or professional responsibilities as a result of your participation in this educational activity?

❍ ❍ ❍ ❍ ❍

7. To what extent did the activity present scientifically rigorous, unbiased, and balanced information?

❍ ❍ ❍ ❍ ❍

8. To what extent was the activity free of commercial bias?

❍ ❍ ❍ ❍ ❍

Posttest Answer Sheet

1. ❑ 2. ❑ 3. ❑ 4. ❑ 5. ❑ 6. ❑ 7. ❑ 8. ❑ 9. ❑ 10 ❑

If you wish to receive credit for this activity, please complete the form below and:

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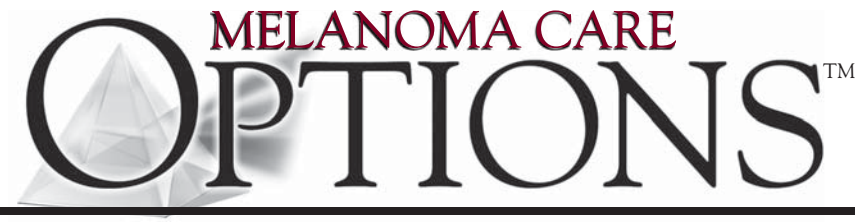
Name: Degree:

Address: City, State, ZIP:

Organization: Specialty: Last 5 Digits of SSN (required):

Telephone Number: Fax: E-mail:



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Issue 3: Interpreting Developments in Melanoma Treatment

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