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Adjuvant Immunotherapy and Radiation in the Management of High-risk Resected Melanoma

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ABSTRACT

Adjuvant therapy is widely used in melanoma cases because recurrence of disease after surgery is notoriously difficult to treat and usually results in the patient's death. Clinicians have a fundamental influence on the patient's decisions regarding adjuvant therapy, beginning with providing a clear understanding of the risk of specific types of recurrence based on features of the primary melanoma and status of the sentinel nodes and then explaining the morbidity of surgical treatment with and without adjuvant therapy. This review summarizes the role of adjuvant immunotherapy and radiation in the treatment of high-risk melanoma. We review the risks of specific types of recurrence as well as the potential oncologic benefits and relevant toxicities of available adjuvant therapies for high-risk melanoma.

INTRODUCTION

Adjuvant therapy is defined as treatment administered to patients who are rendered clinically and radiographically free of disease, often by surgical means, but at risk of recurrence if nothing further is done. The potential advantages to adjuvant therapy include a delay in the time to clinically evident recurrence, resulting in an increase in the time that patients perceive themselves to be disease free, a reduction in the risk of a specific form of and complications related to recurrence, and an increase in the cure rate by administration of therapy earlier in the course of disease when it is more effective, leading to improved overall survival. One potential benefit that patients derive from adjuvant therapy is the sense that they are combating their disease rather than awaiting recurrence. In exchange for a chance at these potential advantages, most patients accept the toxicities of adjuvant therapy, including those patients whose disease was controlled or even cured by the initial resection that rendered them disease free.

The intent of this review is to summarize recent updates and trends in the use of adjuvant therapy for high-risk melanoma. The main focus remains the debatable benefits of adjuvant interferon (IFN) therapy, vaccines, and granulocyte-macrophage colony-stimulating factor (GM-CSF). We discuss the use of adjuvant radiation for local control of melanoma that is at high risk for recurrence. Recurrent melanoma—whether in a regional nodal basin, confined to a single extremity (so-called in-transit metastases), or disseminated throughout the body—is notoriously difficult to effectively treat and usually results in the patient's death. Patients who perceive themselves at risk of recurrence, therefore, are often motivated to pursue adjuvant therapy with even a small chance of delaying or preventing recurrence.[1] Our role as clinicians is to provide appropriate and ethical counsel for our patients, explaining and defining the risk of recurrence, subtypes of recurrence, morbidity, and benefits of adjuvant treatment.

DEFINING HIGH-RISK MELANOMA

Clinicopathologic Factors Related to the Primary Lesion

Over the past several decades, volumes of work and data have accumulated to identify the characteristics of primary melanoma, which are used to stratify patients based on risk of recurrence and overall survival. Currently, Breslow thickness is the single most widely used clinicopathologic factor to individualize surgical management, with a difference of 0.01 mm in the thickness of 2 otherwise identical melanomas being enough to signal a difference in treatment. Clinical stage I melanomas (those with a primary melanoma ≤1 mm) are associated with a very low rate of distant metastasis and death from melanoma and with a low rate of local or regional recurrence.[2] Melanomas <0.76 mm in thickness are at particularly low risk for any type of recurrence or

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metastasis. There is considerable interest in further refining which ''thin'' melanomas are at sufficient risk of nodal metastasis to justify surgical staging of the regional nodes by sentinel lymph node biopsy.[3] Thin melanomas with ulceration (T1b) are very infrequent, but the available data suggest their risk of nodal metastasis is high enough to justify sentinel node biopsy. The 2010 version of the American Joint Committee on Cancer Melanoma Staging System replaces Clark level with mitotic rate, such that nonulcerated T1 melanomas with a mitotic rate of $\geq$1 mm^2 are considered T1b regardless of Clark level and T1a melanomas are those with a mitotic rate of zero.[4] At our center, we continue to advocate sentinel node biopsy for otherwise healthy patients whose melanomas are at least 0.76 mm in thickness, while we and others prospectively study the impact of mitotic rate on sentinel node positivity.[4]

Several other factors merit discussion in terms of deciding which T1 melanomas should undergo sentinel node biopsy. When a tumor extends to the deep margin, it raises the concern that the primary may extend more deeply than is immediately evident. Some surgeons consider this an indication for sentinel node biopsy, but frequently no additional invasive tumor is seen and some patients are overtreated. Repeat biopsy and initial complete excision without sentinel node biopsy are both options, and our practice is to restrict sentinel node biopsy as part of the initial approach to patients in whom either the measured thickness is already very close to our 0.76 mm cutoff or a visible residual pigmented lesion is present. The presence of histologic evidence of regression has been used by many surgeons to select such tumors for sentinel node biopsy, with the rationale that the regression is a sign that the primary once extended more deeply into the dermis and hence might have a higher likelihood of metastasis. However, recent studies have failed to support this idea, and most studies show that regression in a primary melanoma is associated with the same or perhaps even less risk of nodal metastasis[5]; we do not employ this criterion to select patients for sentinel node biopsy. Finally, younger patients are more likely to have a positive sentinel node than older patients with melanomas of the same thickness,[6] although no agreement exists on the exact cutoff values for ''young'' and ''old'' in this context.[7] Because younger patients in general have fewer comorbidities and more years of potential life to manifest nodal and distant recurrence, we tend to be somewhat more likely to offer sentinel node biopsy to younger patients with T1 melanomas.

Although the previous discussion has focused on T1 melanomas, it is worth emphasizing that we do not set an upper limit on the performance of sentinel node biopsy: Patients with thick (>4 mm), clinically node-negative melanomas are offered sentinel node biopsy just as are patients with intermediate-thickness primaries.[8]

Lymph Node Status as a Predictor of Distant Metastasis

Sentinel node biopsy is a staging procedure designed to assess the risk of subsequent metastasis and death from melanoma. In a large, prospective randomized trial, patients with an intermediate-thickness melanoma and a positive sentinel node were far more likely to die than those with a negative sentinel node.[9] Extensive data from nonrandomized studies also document the independent prognostic significance of sentinel node status.[10] Patients with clinically or radiographically evident nodal metastasis, whether at the time of initial diagnosis or as a recurrence after prior wide excision of the primary, fare worse than those with positive sentinel nodes.[11-13] Regardless of how nodal metastases present, complete lymphadenectomy is associated with cure in 30% to 43% of patients after extensive follow-up (5-30 years), and thus aggressive surgical therapy is an important part of the management of any stage III melanoma.[11-13] In addition, as the number of lymph nodes involved increases, the risk of distant metastasis and death also increases. Interestingly, even after nodal metastasis has occurred, prognostic information can be gained by knowing the thickness and ulceration status of the primary tumor.[14]

At the present time, patients with stage III melanomas are considered appropriate candidates for lymphadenectomy and adjuvant therapy. Significant interest exists in trying to identify a subset of node-positive patients who may be at very low risk for regional or distant recurrence, presumably those with very small tumor deposits in the regional nodes.[15] To date, however, a threshold below which the risk of further recurrence in the regional basin and beyond is low enough to safely allow observation of the patient without either lymphadenectomy or adjuvant therapy has not been defined, but prospective trials are ongoing.[16]

Lymph Node Status as a Predictor of Regional Recurrence

Theoretically, a subset of patients with stage III melanoma may be defined as low risk and as such do not require lymphadenectomy; currently, there is recurrence in the nodal basin of many patients with stage III disease despite lymphadenectomy. Furthermore, recent large epidemiologic studies designed to determine national trends in completion lymphadenectomy have described a surprisingly low number of

patients who proceed to lymphadenectomy after sentinel node biopsy.[17,18] Others have reported similar survival outcomes from comparing single-institution data of patients who were observed after a positive sentinel node biopsy with those who later had completion lymphadenectomy.[19] Such studies should be interpreted with caution as the groups are often small in number; dissimilar with regard to tumor thickness, age, and comorbidities; and highly selected.[20] Finally, several issues arise from observing the nodal basin after a positive sentinel node biopsy outside the context of a clinical trial: (1) the potential for surgical cure may be lost in some patients, (2) patients would risk increased morbidity (lymphedema) after completion lymphadenectomy for microscopic disease versus therapeutic lymphadenectomy for palpable disease, and (3) the use of adjuvant radiation for bulky disease would add to this long-term morbidity.[19,20]

Available evidence suggests that radiation decreases the risk of recurrence after lymphadenectomy,[21] but controversy remains regarding which patients are at sufficient risk of regional recurrence. To date, the presence of multiple involved lymph nodes, the finding of invasion of melanoma through the lymph node capsule into the surrounding tissue [extracapsular extension (ECE)], and lymph nodes >3 cm are the best established indicators of increased risk of regional recurrence after lymphadenectomy and are the most commonly employed criteria used to select patients for adjuvant radiation therapy to the nodal basin.[22]

ADJUVANT RADIOTHERAPY TO THE PRIMARY SITE

Surgical resection remains the primary initial treatment for cutaneous malignant melanoma. Local recurrences, once adequate margins have been obtained, are infrequent and have been consistently reported as <5%.[23,24] However, certain circumstances may arise in which local recurrence at the primary site may be substantially higher, and radiation therapy may be considered to improve local control. In some instances, anatomic restrictions may cause difficulties in obtaining widely negative margins. Thus, radiotherapy has been effectively used in the setting of either positive or close margins. Other risk factors for subsequent local recurrence are the presence of satellitosis and recurrent disease at the primary site. In these settings, the patient typically undergoes repeat resection followed by postoperative radiation therapy. Additional risk factors for local failure following surgery include thick tumors (Breslow >4 mm), particularly those arising in the head and neck. These lesions often present difficulties in obtaining adequate margins, and patients are frequently offered adjuvant radiotherapy.

An additional risk factor for local recurrence appears to be related to the particular histologic classification of melanoma. Desmoplastic melanoma is a rare subtype, accounting for approximately 1% of all melanomas; it is characterized by variably pleomorphic, spindle-shaped cells with associated collagen production. This subset is frequently associated with perineural spread, so-called neurotropism, and has been associated with local failure rates of up to 20% to 50%.[25,26] Although prospective data regarding the role of radiotherapy in desmoplastic melanoma are lacking, we tend to offer radiation postoperatively to those patients who exhibit perineural spread and/or thick lesions, based on retrospective reports demonstrating an improvement in local control with this use of postoperative radiation.[25,26] Additionally, radiotherapy should be considered in desmoplastic melanoma that is not resected with wide margins and in locally recurrent lesions.[27]

ADJUVANT RADIOTHERAPY TO THE REGIONAL LYMPH NODE BASIN

Multiple retrospective series have reported improvements in regional control to the resected nodal basin at high risk for subsequent failure following postoperative radiotherapy. These studies have consistently shown risk factors to include multiple positive nodes (>3 nodes), large nodal size (>3 cm), ECE, and/or recurrent disease, with combinations of these factors conferring the greatest risk.[28] Recently, prospective data have been reported from Australia that demonstrate improved regional control with adjuvant radiation therapy in patients with positive nodes, large nodes, and/or ECE.[29] This study was recently presented at the 2009 annual meeting of the American Society for Radiation Oncology as a plenary session. Inclusion criteria for this trial included any of 1 or more parotid, 2 or more cervical or axillary, or 3 or more positive groin nodes; ECE; at least a 3-cm node positive in the head and neck or axilla; or a 4-cm node in the axilla. After lymphadenectomy, patients were randomized to receive either radiation therapy (48 Gy in 20 fractions) to the regional nodal field or observation. Regional relapse as a first relapse was the primary end point. Patients ($N = 250$; 123 in the radiation arm and 127 in the observation arm) from 2002 to 2007 were randomized from 16 centers. Although overall survival was not different, this study showed a statistically significant improvement in lymph node field control with the addition of radiotherapy: 20 patients in the radiation arm versus 34 patients in the observation arm ($P = 0.041$). Although these emerging data help confirm the role of

radiotherapy in the adjuvant setting, particular issues germane to the resected site (ie, the cervical, axillary, or inguinal nodes) are worth discussing.

Some suggest that the head and neck region is particularly prone to regional recurrence after surgical resection for metastatic melanoma. The addition of radiotherapy has consistently improved regional control to upward of 90% in resected basins with high-risk features.[28] However, the cost for treatment includes a 10% rate of complications at 5 years, including possible hearing loss, wound breakdown, bone exposure, and ear pain. In the axilla, recurrences up to 50% have been reported after resection in patients with ECE and/or ≥2 involved nodes; this may be reduced by at least 50% with the addition of radiotherapy.[28] For patients offered postoperative radiotherapy for high-risk pathologic features, side effects may be seen in up to 30% of patients at 5 years, with the most significant being lymphedema. The inguinal region provides the anatomic site at greatest risk for lymphedema and other complications after surgical dissection and radiotherapy. Also, some suggest that patients with a body mass index >30 kg/m^2 are at even higher risk for treatment-related complications after radiotherapy (up to 80%).[28]

In each lymphatic region—the cervical, axillary, or inguinal nodal—the entire clinical picture needs to be carefully considered prior to offering adjuvant radiotherapy. Prospective data have now confirmed an improvement in regional control in patients with resected regional disease and high-risk features.[29] However, the risks of regional and distant failure need to be weighed before offering adjuvant therapy. Clinical judgment may steer a patient toward being offered systemic therapy if this risk and its consequences outweigh the risk of regional failure. Additionally, the potential for long-term morbidity needs to be evaluated. Patients with significant postoperative complications and those with a body mass index >30 kg/m^2 with inguinal metastases are at particular risk for morbidity with postoperative radiotherapy and must be treated cautiously.

RADIOTHERAPY WITH CONCURRENT IFN TO THE REGIONAL LYMPH NODE BASIN

The use of radiotherapy with concurrent IFN has been prospectively evaluated at our center; the results were reported at the 2008 annual meeting of the American Society for Radiation Oncology as an oral presentation.[30] Inclusion criteria included stage III nodal disease involving axilla, neck, or groin with ≥4 positive nodes; a single node ≥4 cm; a node with microscopic extracapsular disease involving >10% of capsule circumference. Induction interferon-alfa-2b (IFNα-2b), 20 MU/m^2 per day, was administered intravenously for 5 consecutive days every week for 4 weeks. Subsequently, radiation (30 Gy in 5 fractions) was given with concurrent IFNα-2b, 10 MU/m^2 subcutaneously 3 times per week, on days alternating with radiation. The next maintenance therapy was delivered with adjuvant IFN-α-2b, 10 MU/m^2 subcutaneously 3 times per week, to a total of 1 year. A total of 29 consenting patients were enrolled between August 1997 and March 2000. The maximum (worst) grade of acute nonhematologic toxicity during concurrent treatment was grade 3 skin toxicity noted in 2 patients (9%). Late effects were limited. Of the evaluable patients, the probability of regional control (in the regional nodal basin) was 78% at 12 months, and the median follow-up was 80 months among 10 survivors (43%). The median overall survival was 35 months, and the median failure-free survival was 20 months. These data may be useful in developing new radiation and bioimmunotherapy trials.

RADIOTHERAPY DOSE AND FRACTIONATION

The MD Anderson Cancer Center has had excellent experience with hypofractionated radiotherapy.[31] This regimen has advantages such as the ability to complete the treatment course quickly (ie, 3 weeks) and possible radiobiological advantages of high dose per fraction treatment to relatively radioresistant cells. Doses of 30 Gy in 5 fractions are delivered, with no more than 2 fractions given per week, separated by 72 hours. On the other hand, the University of Florida has reported their results with the MD Anderson Cancer Center regimen and a more conventionally fractionated radiotherapy schedule to a median dose of 60 Gy at 2 Gy per fraction.[32] Results were reported as equivalent with conventional fractionation and hypofractionation. It is critically important that hot spots are kept to a minimum with the hypofractionation approach and that the spinal cord, brain, and bowel maximum dose are kept <24 Gy to prevent significant injury. Although each case is individualized, we tend to prefer conventionally fractionated therapy because of concerns for late morbidity that may be seen with the hypofractionation approach. As mentioned previously, the Australian regimen of 48 Gy in 20 fractions has now been validated prospectively, although late morbidity has yet to be reported.

ADJUVANT SYSTEMIC THERAPY TO REDUCE DISEASE RECURRENCE AND DEATH

Lack of Efficacy of Chemotherapy and Nonspecific Immunotherapies

Over the past 4 decades, well over 100 randomized clinical trials have investigated cytotoxic chemotherapeutic agents and nonspecific immunostimulants such as bacille Calmette-Guèrin (BCG),

Corynebacterium parvum, or levamisole.[33] Despite the fact that at an alpha level of statistical significance of 0.05 one would expect one clinical trial in 20 to yield a falsely positive result despite ineffective therapy being tested, none of these trials had positive results, and none of these agents are currently indicated for adjuvant therapy of melanoma outside of controlled clinical trials. Interest in nonspecific immunotherapy has declined as more active immunostimulatory cytokines—in particular, IFN—came into clinical practice.

Adjuvant Immunotherapy With IFN

IFNα-2b is the only US Food and Drug Administration (FDA)-approved adjuvant regimen for patients with stage IIB and stage III melanoma and is considered the standard of care for these patients in the United States. We will review clinical trials addressing the benefit of adjuvant IFN and discuss the controversies of these trials.

The Eastern Cooperative Oncology Group (ECOG) trial E1684 was the first randomized, placebo-controlled study of high-dose IFNα-2b (HDI) in 287 patients with stage IIb (n = 31) or stage III melanoma. HDI is administered at 20 MU/m^2 per day intravenously 5 days per week for 1 month and 10 MU/m^2 subcutaneously 3 times per week for 48 weeks. At initial publication after a median follow-up time of 6.9 years, relapse-free survival (RFS) increased from 1.0 to 1.7 years, and overall survival (OS) increased from 2.8 to 3.8 years, both of which were statistically significant.[34] Updated results after a very long median follow-up of 12.6 years showed the RFS benefit to have been maintained, but the statistical significance of the survival benefit had been lost.[35] The diminished survival benefit after longer follow-up was of uncertain cause but led many physicians to question whether HDI was worth the significant side effects.[36]

The next cooperative group trial of IFN only increased the uncertainty about adjuvant therapy in melanoma. ECOG trial E1690 accrued 642 patients to a 3-arm study comparing HDI (n = 215) to low-dose interferon (LDI; 3 MU/m^2 3 times per week for 2 years, n = 215) to observation (n = 212). HDI showed an improvement in RFS (44% relapse-free at 5 years) compared to LDI and observation (40% and 35%, respectively). However, unlike ECOG trial E1684, no OS benefit was seen with either HDI or LDI compared to observation.[37] Since HDI was approved by the FDA during this trial and patients with thick melanomas were allowed to enter the trial without any nodal staging or dissection, crossover of observation-arm patients to HDI after nodal relapse was a confounding factor that may have affected the survival results. This emphasizes the important role surgical staging can play in adjuvant therapy trials and clinical decisions.

A third study, ECOG E1694, accrued 880 patients and compared an investigational ganglioside vaccine with HDI. HDI demonstrated a statistically significant benefit compared to the vaccine in terms of RFS and OS.[38] This raised the question of whether HDI led to benefit or the vaccine caused harm, a question that has gained additional credence after a randomized trial of the same vaccine compared to observation in patients with stage II melanoma was stopped early because of a possible decrease in survival for vaccine-treated patients in the face of definite evidence of no impact on RFS.[39]

With more than 2,000 patients treated on clinical trials of adjuvant HDI, we are left with a number of questions and controversies. After reviewing these trials and combining the data into a meta-analysis, it is clear that HDI delays recurrences and improves disease-free survival.[40] Mocellin et al[41] recently published a meta-analysis that included 14 randomized controlled trials and more than 8,000 patients. In this analysis was a statistically significant improvement in disease-free survival (hazard ratio, 0.82) in 10 of the 17 comparison trials (IFN-alfa vs comparator) and improved OS in 4 of the 14 comparison trials. The OS benefit of HDI, if any, is small; in the meta-analysis, all IFN-treated patients regardless of dose and schedule experienced a 10% relative decrease in the risk of death, which translated into a 2.8% increase in 5-year survival. To further complicate matters, it is unclear whether the whole year of treatment with HDI is needed to obtain these benefits from IFN. Pectasides et al[42] reported no observed differences in RFS and OS with 1 month versus 1 year of adjuvant HDI. However, concerns about this study have been raised in regard to the statistical methods used as well as the lower dose of HDI used by the trial compared with conventional dosing. Therefore, when counseling patients regarding treatment with adjuvant HDI, several issues must be discussed at length: (1) How important is RFS for this individual patient? Patients and physicians often have differing opinions on this matter, with patients often placing more emphasis on RFS than physicians. (2) What is the toxicity of HDI? Clearly, with a relatively small overall benefit, one is less likely to give adjuvant IFN to patients with an increased risk of toxicities, such as those with already underlying severe psychiatric disorder, autoimmune disease, or poor cardiac, liver, or renal function. (3) What is the risk of relapse in any given patient? (4) If pursuing HDI, what is the appropriate length of treatment needed?

Overall, most patients with stage III melanoma should be counseled about adjuvant IFN, and a lengthy discussion of its risks and benefits should be undertaken, with active patient participation.

Table. Summary of Current US Adjuvant Clinical Trials[a]

Title	Agent	Sponsor
A Phase I Study of Poly IC:LC and NY-ESO-1/gp100/MART-1 Peptides Emulsified With Montanide ISA 51 With Escalating Doses of CP 870,893 in the Treatment of Subjects With Resected Stage III or Stage IV Melanoma	Biological: CP 870,893 with Hiltonol poly IC:LC and NY-ESO-1/gp100/ MART-1 peptides emulsified with Montanide ISA 51 VG	Moffitt Cancer Center/Jeffrey Weber, MD, PhD
Determine Toxicity and Antibody Responses With a KLH Conjugated Bivalent Vaccine Containing GD2 Lactone, GD3 Lactone With Immunological Adjuvant QS-DG or OPT-821 in Patients With Disease Free AJCC Stage III or IV Cutaneous Melanoma	Biological: KLH conjugates with GD2L and GD3L	Memorial Sloan Kettering Cancer Center
Efficacy Study of Ipilimumab Versus Placebo to Prevent Recurrence After Complete Resection of High Risk Stage III Melanoma	Drug: ipilimumab	Bristol-Meyers Squibb
Novel Adjuvants for Peptide-Based Melanoma Vaccines	Biological: MDX-CTLA4 antibody Tyrosinase/gp100/MART-1 peptides melanoma vaccine	FDA Office of Orphan Products Development
Sorafenib, Tamoxifen, and Cisplatin in Treating Patients With High-Risk Stage III Melanoma	Drug: cisplatin Drug: sorafenib tosylate Drug: tamoxifen citrate	San Diego Pacific Oncology & Hematology Associates
Standard High-Dose Alpha Interferon Versus Intermittent High-Dose Alpha Interferon	Drug: interferon-alpha-2b	Dermatologic Cooperative Oncology Group
Adjuvant Therapy of Pegylated Interferon-2b Plus Melanoma Peptide Vaccine	Drug: pegylated interferon-alfa 2b (PEG Intron) Drug: GP-100 peptide vaccine	MD Anderson Cancer Center Schering-Plough
A Phase III Study to Test the Benefit of a New Kind of Anti-cancer Treatment in Patients With Melanoma, After Surgical Removal of Their Tumor	Drug: GSK 2132231A Drug: placebo	GlaxoSmithKline
Gene-Modified T Lymphocytes With or Without Vaccine Therapy and/or Aldesleukin in Treating Patients With High-Risk Melanoma	Biological: ALVAC-MART-1 vaccine Biological: MART-1:26-35(27L) peptide vaccine; Biological: aldesleukin Biological: autologous anti-MART-1 F5 T-cell receptor gene-engineered peripheral blood lymphocytes Biological: incomplete Freund's adjuvant	National Cancer Institute
Stage IV Surgery Versus Best Medical Therapy	Procedure: surgery Procedure: surgery plus 2 adjuvant doses of BCG Other: best medical therapy	John Wayne Cancer Institute Melanoma Research Alliance

AJCC: American Joint Committee on Cancer; FDA: Food and Drug Administration.

[a] Adapted from www.clinicaltrials.gov. For a complete list of ongoing clinical trials, please refer to http://clinicaltrials.gov.

Observation alone and experimental trials are also valid choices to offer patients with stage III disease. High-risk stage II patients were included in all of the mentioned trials; even though the benefit of adjuvant IFN in this subgroup of patients is even less clear than in stage III, some such patients will choose to pursue adjuvant treatment.

Pegylated IFN as an Alternative to Standard IFN

The many questions around the benefits of HDI, combined with the significant challenges patients face in undertaking this therapy (not the least of which are a month of daily visits to a hospital or clinic for intravenous infusions followed by thrice-weekly injec-

tions), have led to many clinical trials seeking alternatives. Pegylated IFN is widely used in the treatment of hepatitis, where available evidence suggests that it is more effective and possibly less toxic than regular IFN. Pegylated IFN also has a much longer half-life, allowing once a week injections to provide continuous drug exposure without the high peaks and long troughs associated with HDI. In Europe, where HDI has not been widely adopted, a large randomized trial compared pegylated IFNα-2b (Peg-IFN) administered for 5 years to observation. RFS was statistically significantly increased for patients randomized to Peg-IFN, but OS was not. Of particular interest, however, was the observation that patients with clinically occult nodal metastases diagnosed by sentinel node biopsy appeared to fare particularly well with Peg-IFN adjuvant therapy: Both relapse-free and distant metastasis-free survival were significantly increased, and a trend toward improved survival was seen as well.[42] Peg-IFN in this dose and schedule shares many of the substantial toxicities of HDI, but some patients will find it more convenient; with appropriate and aggressive dose-reduction to keep toxicities to a minimum level, many patients will find it possible to stay on therapy long term with little or no impact on daily function.[43] Just recently, the Oncology Drug Advisory Committee voted to recommend that the FDA approve Peg-IFN as an alternative adjuvant approach for melanoma patients, but a final FDA decision on this point is still pending.

Investigational Approaches With Vaccines and New Immunotherapies

Even if Peg-IFN is approved as an additional option for adjuvant therapy, it represents at best a small advance over existing approaches.[43,44] Numerous other approaches have been tested, particularly vaccines designed to stimulate an immune response against any remaining melanoma cells in the body. Although some have shown promise in subsets of patients,[45] none have reached the stage of FDA approval or widespread use. Indeed, the recent finding that some treated patients in several vaccine studies (including the ganglioside vaccine trial referred to previously) have fared worse than patients on observation or placebo has caused considerable consternation in the melanoma community.[46] Even if long-term follow-up shows no actual adverse impact of melanoma vaccines, the failure of these trials to demonstrate an advantage for vaccination requires a rethinking of our approach to immunotherapy of melanoma in general. Another immunomodulatory cytokine besides IFN that has been evaluated as an adjuvant therapy in melanoma is GM-CSF, alone or with vaccines. Nonrandomized trial data spurred interest in this agent,[46,47] but unless the currently ongoing ECOG E4697 trial shows that GM-CSF alone or with a peptide vaccine improves RFS or OS, the current evidence is not sufficient to support its use outside the research setting. New agents with greater immunomodulatory effects (and much greater toxicity), such as ipilimumab,[48] are beginning to undergo testing in randomized adjuvant trials in patients with a risk of relapse high enough to justify the significant toxicity potentially associated with treatment.

FUTURE PROSPECTS FOR MORE EFFECTIVE ADJUVANT THERAPIES

Reason clearly exists to be optimistic about the future of adjuvant therapy for melanoma. Improvements in our ability to determine prognosis, fueled by the development of new genomic or other biomarkers to identify and quantitate metastatic potential and/or the presence of residual tumor cells after surgery, will allow us to eliminate treatment toxicity for patients who are cured by surgery alone and focus attention on the patients who stand to gain most from therapy. Biomarkers can also help identify those patients who are most likely to respond (or be resistant) to therapy, allowing those who will not respond to standard treatment to be entered directly into clinical trials (Table).[49] The potential value of such an approach has been shown by the recent identification of single nucleotide polymorphisms in the interleukin-28 gene that may predict IFN sensitivity or resistance in hepatitis.[50] Finally, emerging targeted therapies that can eliminate cells bearing specific mutations may find an increasingly important role in adjuvant therapy, before multiple other mutations that allow resistant clones to emerge can take place.[51] Regardless of which approach or combination of approaches one pursues, effective adjuvant therapy begins with complete resection of the primary tumor and any clinically evident metastases, combined with a thorough staging evaluation and assessment of the risk of subsequent recurrence or metastasis.

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