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Recent Advances in Melanoma Staging and Therapy

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Background: Recent advances in the staging and treatment of melanoma were reviewed.
Methods: A literature-based review was performed.
Results: The current American Joint Committee on Cancer (AJCC) Staging system for melanoma has several drawbacks. Proposed changes in the staging system to take into account simplified tumor thickness categories, tumor ulceration, and the number (rather than size) of nodal metastases will allow stage groups with more uniform prognosis. The widespread application of sentinel lymph node biopsy for nodal staging allows accurate nodal staging with minimal morbidity. Reverse transcriptase-polymerase chain reaction (RT-PCR) is a very sensitive molecular staging test that may prove useful for identifying early metastatic disease. There is finally an effective adjuvant therapy for melanoma—interferon alfa-2b. Other adjuvant therapies, including melanoma vaccines, may provide effective and less toxic alternatives. New immunotherapy and gene therapy strategies are under investigation.
Conclusions: Ongoing and future adjuvant therapy trials will benefit from improved melanoma staging by accrual of homogeneous groups of patients. New approaches for adjuvant therapy await completion of clinical trials. Innovative new therapies offer hope for patients with advanced disease.
Key Words: Melanoma—Sentinel lymph node—Adjuvant therapy—Immunotherapy—Gene therapy.

The rapid increase in the incidence of melanoma has been paralleled by expanded research efforts to improve the outcome for patients with this disease. As a result, advances have been made in our ability to accurately determine the stage of disease, effective adjuvant therapy has been developed, and promising innovative treatment strategies are under investigation.

ADVANCES IN THE STAGING OF MELANOMA

Advances in the treatment of cancer often result from prospective, randomized clinical trials. To test new therapies, it is imperative to identify the proper population of patients to study. Staging systems allow us to group patients of similar prognosis to test new therapies, or to determine who is most likely to benefit from existing treatments. There are problems inherent in studying either a population with a very good prognosis, in whom it is difficult to demonstrate small differences in outcome, or a population with a very poor prognosis, in whom additional therapy is unlikely to provide any benefit. Furthermore, studies that include extremely heterogeneous populations of patients with both good and poor prognoses can be difficult to interpret. One key to successful clinical studies is proper identification of the groups of patients that are most likely to benefit from the therapy under investigation.

Proposed Changes to the AJCC Staging System

The current American Joint Committee on Cancer (AJCC) staging system for melanoma, established in 1992, has several drawbacks (Table 1). Improvements to the staging system have been suggested by Buzaid and colleagues, based on an updated analysis of the University of Alabama at Birmingham (UAB) and Sydney Melanoma Unit (SMU) databases.[1]

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TABLE 1. *The 1992 American Joint Committee on Cancer staging system for cutaneous melanoma*

Definitions			
Primary tumor (pT)*			
pTX	Primary tumor cannot be assessed		
pT0	No evidence of primary tumor		
pTis	Melanoma in situ (atypical melanotic hyperplasia, severe melanotic dysplasia), not an invasive lesion (Clark's level I)		
pT1	Tumor ≤0.75 mm in thickness and invades the papillary dermis (Clark's level II)		
pT2	Tumor more than 0.75 mm but not more than 1.5 mm in thickness and/or invades the papillary reticular-dermal interface (Clark's level III)		
pT3	Tumor more than 1.5 mm but not more than 4 mm in thickness and/or invades the reticular dermis (Clark's level IV)		
pT3a	Tumor more than 1.5 mm but not more than 3 mm in thickness		
pT3b	Tumor more than 3 mm but not more than 4 mm in thickness		
pT4	Tumor more than 4 mm in thickness and/or invades the subcutaneous tissue (Clark's level V) and/or satellite(s) within 2 cm of the primary tumor		
pT4a	Tumor more than 4 mm in thickness and/or invades the subcutaneous tissue		
pT4b	Satellite(s) within 2 cm of primary tumor		
Lymph node (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis ≤3 cm in greatest dimension in any regional lymph node(s)		
N2	Metastasis more than 3 cm in greatest dimension in any regional lymph node(s) and/or in-transit metastasis		
N2a	Metastasis more than 3 cm in greatest dimension in any regional lymph node(s)		
N2b	In-transit metastasis		
N2c	Both (N2a and N2b)		
Distant metastasis (M)			
MX	Presence of distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Metastasis in skin or subcutaneous tissue or lymph node(s) beyond the regional lymph nodes		
M1b	Visceral metastasis		
Stage grouping			
I	pT1	N0	M0
	pT2	N0	M0
II	pT3	N0	M0
	pT4	N0	M0
III	Any pT	N1	M0
	Any pT	N2	M0
IV	Any pT	Any N	M1

* In case of discrepancy between tumor thickness and level, the pT category is based on the less favorable finding.

The Breslow thickness categories used in the present staging system (≤ 0.75, 0.76–1.50, 1.51–4.0, and > 4.0 mm) are cumbersome and not as predictive of survival as the simplified categories based on whole integers (≤1.0, 1.01–2.0, 2.01–4.0, and > 4.0 mm). Tumor ulceration, long known to be an important prognostic factor, is not taken into account in the current AJCC staging system. Finally, it is clear that the most important factor for nodal staging is the number—not the size—of nodal metastases.

Proposed changes improve the staging system by defining stage groupings according to more similar prognosis (Table 2). One thing the proposed changes do not

TABLE 2. *Suggested definitions for a new staging system*

Definitions	
Primary tumor (T)	
TX	Primary tumor cannot be assessed
TO	No evidence of primary tumor (unknown primary)
Tis	Melanoma in situ (atypical melanotic hyperplasia, severe melanotic dysplasia), not an invasive lesion
T1	Tumor ≤1 mm in thickness
T1a	no ulceration
T1b	with ulceration
T2	Tumor more than 1 mm but not more than 2 mm in thickness
T2a	no ulceration
T2b	with ulceration
T3	Tumor more than 2 mm but not more than 4 mm in thickness
T3a	no ulceration
T3b	with ulceration
T4	Tumor more than 4 mm in thickness
T4a	no ulceration
T4b	with ulceration
Regional lymph node (N)	
cN+	Regional node(s) are clinically shown to be involved
pN+	Regional node(s) are pathologically shown to be involved, but the number of positive nodes is not available
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis (clarify "c" or "p")
N1	Metastasis to only one regional node
N2	Metastasis to two but no more than four regional nodes
N3	Metastases to more than four regional nodes or presence of extranodal extension, regardless of the number of positive nodes, or bilateral regional nodal metastases for primary lesions with ambiguous drainage
Regional skin/subcutaneous (S)	
SX	Presence of regional skin metastases cannot be assessed
S0	No regional skin/subcutaneous metastasis
cS+	Regional skin/subcutaneous metastases detected by physical examination
pS+	Regional skin/subcutaneous metastases (including microsatellites) pathologically confirmed
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis in skin or subcutaneous tissue or lymph node(s) beyond the regional lymph nodes
M1b	Visceral metastasis

Note: Patients with local recurrence, in-transit, or satellite lesions in the head and neck region or trunk have a worse prognosis than patients with lesions of an extremity.

accomplish very well, however, is simplicity. It is hoped that the AJCC will adopt many of these proposed changes, perhaps in a simplified version that accurately reflects patient outcome.

Elective Lymph Node Dissection

For many years, proponents of elective lymph node dissection (ELND) have argued that early removal of regional lymph nodes imparts a survival advantage. However, four prospective, randomized trials have failed to show an overall survival benefit for ELND.[2–5]

A recent update of the Intergroup Melanoma Surgical Trial of ELND vs. observation of clinically negative regional lymph node basins for patients with intermediate-thickness melanoma again demonstrated no overall survival benefit for ELND. However, subgroup analysis identified some patients who did appear to benefit from ELND.

The following two questions get to the heart of the issue: (1) Does ELND provide a survival advantage for patients with clinically node-negative melanoma? and (2) Does lymph node dissection ever cure patients with nodal metastases?

Four randomized prospective trials have failed to demonstrate a statistically significant improvement in overall survival for patients undergoing ELND when all randomized patients are analyzed. However, a survival benefit has been demonstrated in some subgroups of patients.

Before effective adjuvant therapy for melanoma was available, some patients were cured by therapeutic resection of nodal metastases—even palpable nodal metastases. In fact, the 10-year survival rate for patients with a single positive lymph node (palpable or nonpalpable) is 40% to 60%, substantially better than that for patients with multiple positive nodes.[1]

Why It Has Been Difficult to Demonstrate an Overall Survival Advantage in Randomized Trials of ELND

This is a classic case of the drawbacks of studying a heterogeneous patient population. Most patients with intermediate-thickness melanomas do not develop nodal metastases. In fact, only about 20% of patients in the observation arm of the Intergroup Melanoma Surgical Trial developed nodal metastases. Therefore, only 20% of the patients who underwent ELND could potentially benefit from early removal of nodal micrometastases. If early removal of nodal micrometastases imparts a survival advantage similar to other forms of adjuvant therapy (i.e., 25% to 50%), then only 25% to 50% of the 20% of patients with nodal metastases, or 5% to 10% of patients overall, would enjoy a survival benefit. That is, in fact, the magnitude of the benefit actually demonstrated. When we examined the results of the Intergroup Trial, there was a 5% advantage overall for ELND.[6] Although this is not statistically significant, the sample size of this trial does not allow sufficient statistical power to detect a 5% difference in survival. Because of the heterogeneous population, inclusion of the node-negative patients causes a substantial dilution of survival benefit. Analysis of prospectively stratified subgroups, however, reveals more substantial differences in 10-year survival among selected groups that are in line with the above calculation. For example, there was a 29% reduction in mortality in patients with nonulcerated melanomas, a 27% reduction in mortality in patients with extremity melanomas, and a 35% reduction in mortality for patients with melanomas of Breslow thickness 1 to 2 mm. All of these were statistically significant. Although age was not a prospective stratification criterion, it appears that patients younger than 61 years of age benefit from ELND.

A convincing case therefore can be made for early removal of occult nodal metastases. This is supported by the results of the WHO Melanoma Program 14, in which the 5-year survival rate in patients with occult regional node metastases detected at ELND was 48.2%, versus 26.6% for patients in whom regional node dissection was delayed until the time of appearance of clinically evident nodal metastases.[5] Because the prognosis after therapeutic lymph node dissection alone is so much better for patients with a single positive lymph node compared to those with multiple positive nodes,[1] it makes sense that early therapeutic lymphadenectomy should save lives. It probably is better to perform lymphadenectomy for a single microscopically positive node than to wait until the nodal disease is palpable, by which time more than one node often is positive.

Most patients who currently undergo ELND suffer the morbidity of lymph node dissection without any possible therapeutic benefit. The optimal situation would be to identify those patients who actually have nodal micrometastases, and reserve regional lymphadenectomy for these patients. It is now possible to identify those patients using sentinel lymph node biopsy.

The Role of Sentinel Lymph Node Biopsy

Morton and colleagues first demonstrated the feasibility and accuracy of sentinel lymph node biopsy for nodal staging of patients with melanoma,[7] and other studies have documented the accuracy of the technique.[8–20] The procedure is performed on a outpatient basis, and can be done under local anesthesia. Sentinel lymph node biopsy

has the distinct advantage of providing accurate nodal staging information with a minimally invasive operation, which essentially involves the morbidity of a lymph node biopsy. Those patients who are found to have nodal metastases can then be selected for more aggressive treatment, including lymph node dissection and adjuvant therapy. Patients without nodal metastases suffer little morbidity from the procedure, and have a substantially better prognosis than do those with nodal metastases.

In addition to the obvious advantage in terms of morbidity, sentinel lymph node biopsy probably is more accurate than ELND for determining nodal stage. ELND specimens undergo routine histology (1 or 2 histological sections from the center of each node), whereas examination of the sentinel node involves serial sections and immunohistochemical evaluation, which often detects tiny micrometastases not seen on routine histology. Data from the Intergroup Surgical Trial indicate that routine histology of ELND specimens underestimates the number of patients with nodal metastases (Table 3). Even with serial sectioning and immunohistochemistry of sentinel nodes, the number of patients who ultimately will develop nodal metastases probably is underestimated (Fig. 1).[21]

Molecular Staging of Melanoma

The reason for the discrepancy between estimated and actual numbers of patients who develop metastases may be that some patients have "submicroscopic" lymph node metastases that are not detected even with careful pathologic analysis. Reverse transcriptase polymerase chain reaction (RT-PCR) analysis of lymph nodes is a very sensitive test that can detect one melanoma cell in 1 million normal cells. RT-PCR detects specific mRNA expressed by melanoma cells.[22] It has been reported that RT-PCR detection of tyrosinase mRNA in histologically negative sentinel nodes correlates with decreased disease-free and overall survival.[23] Routine RT-PCR analysis of sentinel lymph nodes may improve our ability to predict those patients who are at higher risk for recurrence.

TABLE 3. *Incidence of regional node metastases (Intergroup Melanoma Surgical Trial)*

Group	Tumor thickness		
	1–2 mm	2–3 mm	3–4 mm
Wide local excision (based on first recurrence)	13%	27%	33%
ELND (based on pathology report)	5%	19%	38%

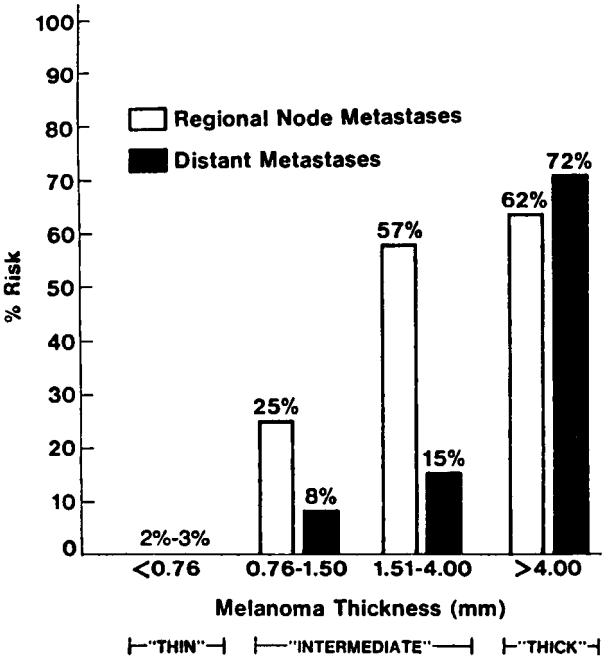

FIG. 1. Estimated risk of developing clinically evident (palpable) regional nodal metastases within 3 years or distant metastases within 5 years according to tumor thickness. (From Balch CM, Cascinelli N, Sim FH, et al. Elective lymph node dissection: results of prospective randomized trials. In: Balch CM, Houghton AN, Sober AJ, Soong S-J, eds. *Cutaneous Melanoma*. St. Louis: Quality Medical Publishing, 1998:405–18, with permission.)

It also has been demonstrated that RT-PCR analysis of tyrosinase mRNA in peripheral blood correlates with prognosis for patients with melanoma.[24] Although there are conflicting reports, RT-PCR analysis of peripheral blood samples may prove to be an important molecular staging test to determine the need for and effectiveness of adjuvant therapy, and for follow-up.

ADJUVANT THERAPY OF MELANOMA

Historical Perspective

The search for effective adjuvant therapy for patients with resected high-risk melanoma has resulted in many clinical trials conducted over the past three decades. Initial studies employed a series of nonspecific immunostimulants. Bacille Calmette-Guérin (BCG) induces regression in up to 80% of cutaneous melanoma metastases when injected intralesionally.[25,26] Up to 20% of uninjected lesions in the same patient also may regress. Interest in the adjuvant use of BCG arose following the suggestion of benefit in nonrandomized trials, but no benefit was demonstrated in nine subsequent prospective randomized trials.[26]

Adjuvant use of *Cryptosporidium parvum*, another nonspecific microbial immunostimulant, also looked promising based on retrospective studies. Again, prospective, randomized trials failed to substantiate the efficacy of this agent. Levamisole, yet another nonspecific immunostimulant, showed no benefit in three of four randomized trials. Other agents tested in randomized trials in the adjuvant setting but not found to be of benefit include dacarbazine (DTIC) chemotherapy alone or in combination with other cytotoxic drugs, DTIC plus immunostimulants, transfer factor, thymosin, isoprinosine, megestrol acetate, and retinoids.[26]

These studies demonstrate the critical importance of prospective randomized trials to ultimately prove or disprove the clinical efficacy of adjuvant therapies. Retrospective analyses repeatedly were found to be misleading. It also became clear that the next generation of clinical trials would require more powerful agents and large enough sample sizes to detect clinically relevant differences in disease-free and overall survival.

Melanoma Vaccines

Development and testing of melanoma vaccines for both adjuvant use and treatment of advanced disease have been ongoing for many years, but until recently, there have been few efforts to subject vaccines to the rigors of phase III randomized trials. Vaccines currently are being tested in the adjuvant therapy of resected stage II and III melanoma. A large Southwest Oncology Group (SWOG) trial involving over 670 patients has compared 2 years of treatment with an allogeneic melanoma cell lysate to observation in patients with stage IIA melanoma (primary tumor 1.5–4.0 mm and clinically negative nodes). Results are expected sometime in 1999. A new Intergroup trial comparing a ganglioside vaccine (GM2-KLH) to high-dose interferon alfa-2b currently is underway, and a large multicenter randomized trial of an allogeneic whole-cell melanoma vaccine (coordinated by the John Wayne Cancer Institute in Santa Monica, CA) recently began. In addition to allogeneic vaccines, autologous defined antigen vaccines—involving both peptide and ganglioside antigens—are entering clinical trials in the adjuvant therapy of melanoma.

Interferons

In the 1980s, attention turned to two very potent, well-defined immunostimulants, interferon-gamma and interferon-alpha. In 1986, the Southwest Oncology Group studied adjuvant interferon-gamma in high-risk patients in a randomized prospective trial. Patients receiving interferon-gamma on the SWOG trial had no clinical benefit—and may actually have done worse—compared to patients receiving no adjuvant therapy.[27] At about the same time, adjuvant interferon-alpha was studied in two trials conducted by the North Central Cancer Treatment Group (NCCTG) and the Eastern Cooperative Oncology Group (ECOG). The NCCTG trial employed a high dose of interferon alfa-2a three times per week for 3 months. Overall, the NCCTG results showed no significant benefit for disease-free or overall survival. For the subgroup of node-positive patients, however, a statistically significant improvement in disease-free survival was demonstrated, with 40% alive and disease-free at 5 years in the treatment group compared to 30% in the control group.[28]

Interferon Alfa-2b

The ECOG trial, E1684, was the first study to demonstrate a survival benefit for any form of adjuvant therapy for melanoma. This study used high-dose intravenous interferon alfa-2b (20 million international units/m^2 5 days per week) for 1 month, followed by subcutaneous injections (10 million IU/m^2 3 times per week) for 48 weeks. Patients entered into this study had thick (>4 mm) primary lesions with pathologically negative nodes (AJCC Stage IIB) or any thickness primary with pathologically positive nodes (Stage III). Prognostic factors were well balanced between the treatment and control group, with two important exceptions: (1) the number of positive nodes in the Stage III patients was not recorded, so it is unknown if the groups were balanced with regard to this critical prognostic factor; and (2) the Stage IIB patients (those with node-negative thick primary lesions) randomized to interferon had more ulcerated lesions, a poor prognostic factor, than did those in the observation group.[29]

For all eligible patients in this trial, interferon therapy resulted in an improvement in 5-year disease-free survival from 36% to 37%. The 5-year survival rate improved from 37% to 46% with interferon therapy. These results were statistically significant ($P = .02$) and represent the first evidence of overall survival benefit for any adjuvant therapy in patients with high-risk melanoma. The benefit was greatest for node-positive patients: the 5-year risk of relapse improved 66%, and the 5-year risk of mortality improved 40%.[29]

The ECOG trial deliberately chose to assess an interferon dose at or near the maximum tolerable dose. Toxicity with this regimen was significant, and 2 of the 143 patients in the treatment group died as a result of therapy. Adverse constitutional and neuropsychiatric symptoms (e.g., headache, depression) and laboratory findings of myelosuppression and hepatotoxicity occurred often. Still, with appropriate monitoring and dose modification

when necessary, 74% of the patients were able to complete a full course of therapy.

An interim analysis of ECOG Trial 1690, a follow-up study that included patients similar to those included in ECOG Trial 1684, recently has been reported.[30] This three-arm trial randomized patients to observation, low-dose interferon alfa-2b, or high-dose interferon alfa-2b. With 52 months median follow-up, high-dose interferon alfa-2b was found to significantly improve relapse-free, but not overall, survival. The overall survival of the observation group, however, was substantially better than that seen in ECOG Trial 1684. It seems that adjuvant interferon alfa-2b therapy of high-risk melanoma patients imparts a reproducible relapse-free survival advantage. The magnitude of benefit in terms of overall survival has been brought into question. Further analysis and follow-up of patients in ECOG Trial 1690 are necessary. For example, many of the patients who recurred in the observation group may have been treated subsequently with interferon alfa-2b, which could confound the results.

Low-dose interferon alfa-2b had no effect on either disease-free or overall survival in ECOG 1690. A World Health Organization study of low-dose interferon alfa-2a (3 million IU 3 times per week over 3 years) in patients with resected, node-positive melanoma recently was reported as a negative trial as well.[31] These results indicate that low-dose interferons are not effective as is adjuvant therapy for melanoma.

Interferons in Stage II Melanoma

Preliminary results of three European studies have suggested a disease-free survival advantage (but, as yet, no overall survival advantage) from 12 to 36 months of low-dose (3 million IU three times a week) interferon-alpha in patients with clinical stage II melanoma.[31–34] Follow-up of these studies is required to determine if these results hold up over time and translate into an overall survival advantage. These studies have been criticized because surgical staging of regional lymph nodes was not performed.[35] Many patients with clinically negative nodes (20% to 25%) actually have microscopic nodal metastases that are not palpable. Many of the recurrences are in the regional lymph nodes; however, the most effective therapy for prevention of nodal recurrence is lymph node dissection, not interferon, for positive nodes.

Because of the substantial difference in prognosis for patients with intermediate-thickness melanomas with metastases versus those without nodal metastases, adjuvant therapy trials involving such heterogeneous groups of patients are difficult to interpret. With the availability of sentinel lymph node biopsy for accurate nodal staging, the indiscriminate use of adjuvant therapy based on clinical staging of regional lymph nodes is not likely to gain wide acceptance.

THE SUNBELT MELANOMA TRIAL: COMBINING ACCURATE STAGING AND ADJUVANT THERAPY

The Sunbelt Melanoma Trial is a multi-institutional, prospective, randomized trial that integrates the advances in melanoma staging and adjuvant therapy. The principal goal is to use ultra-staging to identify those patients who are most likely to benefit from adjuvant therapy. The central hypothesis is that adjuvant interferon alfa-2b therapy plus regional lymph node dissection is more effective than lymph node dissection alone at prolonging disease-free and overall survival for patients with early nodal metastasis. Early nodal metastasis is defined as a single microscopically positive sentinel node only, or RT-PCR-positive—only positive sentinel nodes.

All patients who are younger than 71 years old with melanoma $\geq$1.0 mm Breslow thickness, have no palpable lymph nodes, have no evidence of distant metastasis, and who are otherwise fit to receive interferon alfa-2b therapy are eligible (Fig. 2). At the time of lymphatic mapping and sentinel lymph node biopsy, a portion of each sentinel node is frozen and stored at -70°C for possible RT-PCR analysis at a later time. The remaining lymph node is examined by routine histology, serial sectioning, and immunohistochemical staining for S-100 protein. With a median Breslow thickness of 2.3 mm, 25% of patients have had a positive sentinel node by histology or immunohistochemistry. This attests to the sensitivity of the pathological analysis of the sentinel nodes.

Patients with histologically or immunohistochemically positive sentinel nodes are eligible for Protocol A. All patients undergo regional lymph node dissection. Patients with one histologically or immunohistochemically positive sentinel node as the only nodal metastasis are randomized to either observation or high-dose adjuvant interferon alfa-2b therapy, with stratification by Breslow thickness (1.0–2.0 mm, $>$2.0 to 4.0 mm, or $>$4.0 mm).

Patients with more than one histologically or immunohistochemically positive sentinel node, any evidence of extracapsular extension of the tumor, or any non-sentinel node that contains metastatic melanoma, are not randomized but are treated with standard high-dose interferon alfa-2b. These patients are followed to determine the predictive value of prospective peripheral blood PCR analysis for survival and recurrence. In this way,

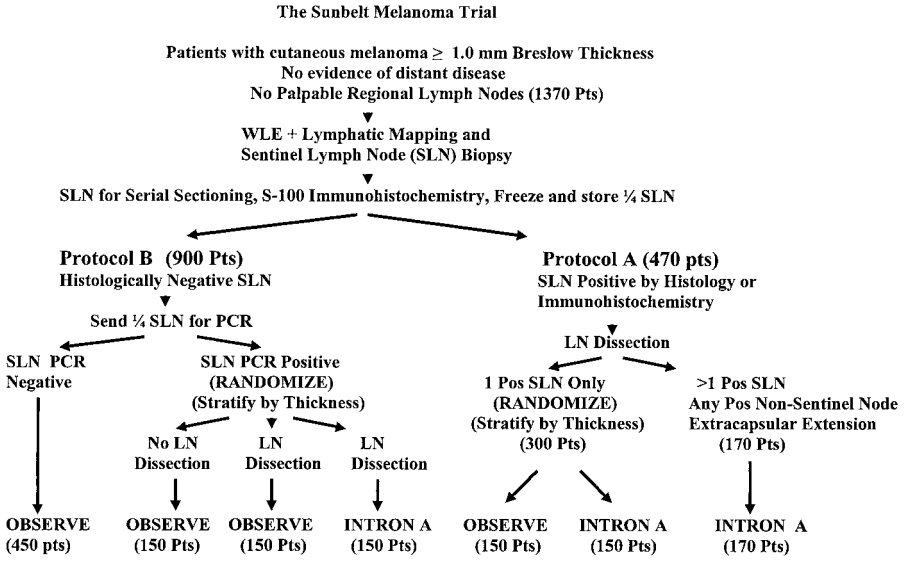

FIG. 2. Schematic describing Protocols A and B in the Sunbelt Melanoma Trial.

valuable molecular staging information will be obtained from this group of patients who receive standard adjuvant therapy. This group of patients also will be eligible to go off study and participate in other protocols, if desired, so as not to limit the therapeutic options of patients with multiple positive lymph nodes.

Patients with histologically and immunohistochemically negative sentinel nodes are eligible for Protocol B. After informed consent is obtained, the stored portion of the sentinel node is evaluated by RT-PCR analysis. Markers analyzed include tyrosinase, MART1, Mage3, and gp100. A positive PCR test is defined as detection of tyrosinase plus at least one other marker. If the sentinel node is negative by RT-PCR analysis, the patients are observed. If the sentinel node is positive by RT-PCR analysis, the patients are stratified by tumor thickness and randomized to one of three arms: observation, lymph node dissection, or lymph node dissection plus interferon alfa-2b. Protocol B not only will define in a prospective fashion the natural history of patients with PCR-only–positive sentinel nodes, but also will determine if adjuvant interferon alfa-2b therapy plus lymphadenectomy is superior to lymphadenectomy alone in terms of disease-free and overall survival. All patients also will undergo prospective analysis of peripheral blood by RT-PCR to determine the value of this molecular staging test.

The Sunbelt Melanoma Trial involves over 50 centers nationwide; over 700 patients have been enrolled in the study in just over 18 months. This study offers a unique opportunity to use the advances in melanoma staging to determine the need for adjuvant therapy. The importance of the Sunbelt Melanoma Trial is amplified by the interim results of ECOG Trial 1690, because it is essential to define precisely the subgroups of patients who benefit from adjuvant therapy. This ongoing study promises to yield important information that will be helpful in the treatment of melanoma patients in years to come.

PROSPECTS FOR THE FUTURE

New therapies for patients with advanced melanoma offer hope where once there was none. Patients with unresectable systemic metastases have several options for treatment, including chemotherapy, immunotherapy, or gene therapy. Conventional chemotherapy offers some hope of tumor response, but little chance for long-term survival.[36] New agents with activity against melanoma are being developed. One such drug, temozolomide, is an oral agent that has been shown to have acceptable toxicity and promising response rates in patients with metastatic melanoma.[37]

Durable complete responses have been achieved with high-dose interleukin-2 (IL-2) alone.[38,39] Biochemotherapy regimens include an aggressive combination of IL-2, interferon alpha, and chemotherapy, and have demonstrated response rates of up to 60%, with complete response rates often in excess of 10%. Some of these complete responses with IL-2–based therapy have been observed for years. The demonstration of long-term complete responses to immunotherapy or biochemotherapy offers promise that refinements of such therapies may lead to actual cure of patients with systemic metastases. Further research is necessary to limit the toxicity of the regimens and increase the complete response rate.

Various approaches to stimulating specific immune responses against metastatic melanoma are under inves-

tigation. Dendritic cell therapy is a particularly interesting approach. Dendritic cells are the most effective antigen-presenting cells for primary immune responses, and can be programmed to stimulate a vigorous immune response against melanoma cells. Gene therapy using dendritic cells is under investigation.[40]

Other gene therapy approaches also are being studied. Gene therapy strategies have been designed to stimulate anti-tumor immune responses, to express prodrug/suicide genes, and to induce programmed cell death (apoptosis) of melanoma cells.

CONCLUSIONS

Advances in the staging of melanoma promise to focus adjuvant therapy on patients who are most likely to benefit from it, and make interpretation of the results of clinical trials easier. Sentinel lymph node biopsy has made it possible to obtain accurate nodal staging information with a minimally invasive operation. RT-PCR analysis may be an important molecular staging test to detect those patients at risk for recurrence. Interferon alfa-2b has been established as the first Food and Drug Administration–approved adjuvant therapy for melanoma. Melanoma vaccines offer the hope of less toxic adjuvant therapy in the future. New immunotherapy and gene therapy approaches to the treatment of advanced disease offer the hope of long-term survival. These advances may usher in a new era of melanoma therapy in which surgery is no longer the only effective weapon against this malignancy.

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