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COMMENTARY

State of the Science 60th Anniversary Review

60 Years of Advances in Cutaneous Melanoma Epidemiology, Diagnosis, and Treatment, as Reported in the Journal Cancer

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Enormous advances in melanoma epidemiology, diagnosis, and treatment have occurred in the past 60 years. Before the 1960s, 60% of patients diagnosed with melanoma died, whereas today only 11% have a fatal outcome.[1] These advances have been the result of greater understanding of risk factors, improvement in early detection, and a worldwide increase in education and public awareness, far more so than any advances in treatment. Nonetheless, significant treatment advances have taken place over this time as well. A large number of important scientific and clinical contributions to melanoma have been published in *Cancer* in the 60 years of its existence. Many are highlighted in this review, along with other pertinent references from the rest of the medical literature that built on, substantiated, or foreshadowed these key contributions. The authors of this review conducted the most reviews of melanoma manuscripts submitted to *Cancer* in 2006, a fitting acknowledgment of the critical role peer reviewers play in the process of disseminating medical knowledge. Although only a few individuals could be selected to write this review, it is dedicated to all of the peer reviewers of melanoma manuscripts submitted to *Cancer* over the past 60 years.

Dr. Sondak has acted as a consultant for Schering-Plough, Pfizer, Bayer, Bristol-Myers-Squibb and Synta, and as a member of the Speakers' Bureau for Schering-Plough.

We wish to thank all of the hundreds of individuals who have given so freely of their time and effort to review the many melanoma submissions to *Cancer* over the past 60 years.

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EPIDEMIOLOGY, DIAGNOSIS, SCREENING, AND PROGNOSIS

The detailed clinicopathologic criteria for melanoma diagnosis and prognosis, published in *Cancer* by Drs Allen and Spitz in 1953, provided a foundation on which our current melanoma knowledge is based.[2] They noted the adverse prognostic impact of ulceration or an elevated mitotic rate. Indeed, ulceration became an established independent prognostic factor in primary melanoma in the revised 2001 American Joint Commission on Cancer staging system.[3] The prognostic relevance of mitotic rate has been confirmed,[4] and subsequently extended to predicting sentinel lymph node status.[5,6] Another early observation of Drs. Allen and Spitz, that of a better survival for women with melanoma,[2] has stood the test of time.[7] During the period from 1969 to 1999, overall melanoma mortality increased approximately 50%, from 2 deaths per 100,000 to 3 deaths per 100,000, but the increase was disproportionately greater in men aged $\geq$65 years (an increase of 157%, 3-fold greater than the rate for women of the same age).[8] Furthermore, thick tumors of $\geq$4 mm have increased significantly only in men aged $\geq$60 years,[9] and older men are more often diagnosed with the nodular subtype of melanoma.[10] Although several hypotheses have been advanced, including sex differences in skin awareness, none have yet fully explained why men have a disproportionate risk of developing thick melanomas.

Many others contributed critical observations to melanoma diagnosis, risk factors, and early detection. Drs. Mihm and Fitzpatrick emphasized early on that the most important tool for the early detection of melanoma was a careful complete skin examination from scalp to toe.[11] Moreover, greater than 25 years ago, members of the Melanoma Clinical Cooperative Group reported on the clinical characteristics of early cutaneous melanoma: increase in pigmented lesion size and presence of color change.[12] These features were subsequently incorporated in the ABCD mnemonic, and more recently in the revised ABCDE criteria for early melanoma diagnosis.[13] The addition of the E criterion, standing for "evolution," has been an important addition to melanoma early detection. Among others items, it captures the symptom of itching that appears to be relevant for the detection of a subset of thin melanomas,[14] and is commonly reported among patients presenting with invasive melanomas.[15]

Although today risk factors for melanoma are well known, it is worth noting that several were highlighted by scientific contributions in *Cancer*. The importance of regular follow-up of patients with dysplastic nevi[16] and the occurrence of dysplasia in nonfamilial melanoma[17] were both first described in *Cancer*. Grob et al confirmed that the total number of melanocytic nevi was also a major indicator of risk of nonfamilial melanoma.[18] Recognition of the importance of following patients with basal cell or squamous cell carcinoma emphasized how these patients were at risk for melanoma and described the magnitude of the risk.[19] Goggins and Tsao showed that melanoma survivors' risk of a second melanoma was highest in the first few months, but that this risk remained substantially higher than the risk of a first melanoma in the general population over a >20-year period of observation.[20] More recently, the report of an increased incidence of melanoma in renal transplant recipients has brought to light this group of at-risk patients who now live longer, more active lives.[21]

Certain groups, such as children and pregnant women, developing melanoma were also discussed early on in *Cancer* publications. Among the early reports of melanoma in children, many were in *Cancer*.[2,22-25] Barnhill et al called attention to the challenges involved in discriminating childhood melanoma from Spitz nevi and provided criteria defining atypical Spitz tumors.[26] Su et al examined the role of sentinel lymph node biopsy in atypical Spitz tumors.[27] More recently, Livestro et al conducted a case–control study comparing outcomes for childhood and adult melanomas, showing an equal or better outcome for children despite a higher rate of sentinel lymph node positivity.[28] Several reports of melanoma in pregnancy were published early in the history of *Cancer*.[29-31] In 1 population–based cancer registry of melanoma in pregnancy, the data suggested that melanoma during pregnancy carried a poor prognosis, although once the diagnosis was made, the course was not worse than expected for the stage.[32] Another study suggested that having a subsequent pregnancy had no effects on recurrence rate or survival.[33] More recently, a study from Germany highlighted that pregnancy did not appear to have an adverse long-term effect on survival in patients with clinically localized melanoma.[34] Currently, there is broad agreement that prognosis for women with melanoma during pregnancy, just as for nonpregnant women and for men, is primarily dependent on tumor thickness and ulceration.

The appropriate diagnosis of cutaneous melanoma and the need for prevention and early detection were emphasized by the many contributions of Drs. Sober and Kopf.[35-38] The early diagnosis of melanoma has allowed the US and Australia to improve their 5-year survival rates (currently >90%).[1] There remains much work to be done, because early detec-

tion and screening methods have remained underused in many parts of the world, in particular in several Eastern European countries and Northern Ireland, in which 5-year survival rates are notably lower (53%-60%).[39]

It is worth noting that Koh et al were the first to bring an evaluation component into our approach to melanoma screening.[40] They demonstrated that the sensitivity of the visual examination by a dermatologist was 89% to 97%, with a positive predictive value of 35% to 75%, confirming its appropriateness as a cancer screening tool. McDonald subsequently summarized US melanoma screening efforts.[41] In the same context, Rhodes comprehensively emphasized public and professional education for the primary and secondary prevention of melanoma, and recommended personal responsibility in this process to ultimately reduce morbidity and mortality.[42] Koh et al subsequently provided a framework in which to evaluate screening of melanoma.[43] Geller et al took this challenge and carefully evaluated the American Academy of Dermatology screening program.[44] The authors showed that middle-aged and older men (aged $\geq$50 years) accounted for only 25% of screenees, but comprised 44% of those with a confirmed diagnosis of melanoma. They suggested that mass screening for melanoma could be improved by outreach to middle-aged and older men. Researchers in Australia planned and began a randomized controlled trial of a community-based intervention of screening for melanoma. Although the lack of governmental funding did not allow completion of the study, data from 18 of 44 communities enrolled in Queensland demonstrated that the intervention program had successfully motivated men aged $>$50 years to undergo screening for skin cancer, resulting in the highest yield of skin cancer within this subgroup.[45] Data regarding melanoma mortality have consistently shown that older men have higher disease-specific mortality. These recent studies confirm the relevance of targeting our screening efforts to older men.[46]

Ascertaining whether a patient has a family history of melanoma is an important aspect of history taking, but also provides opportunities for patient and family education. Geller et al demonstrated in a randomized control trial that siblings of melanoma patients who had received an intervention were more likely to examine all their moles 12 months later, including the ones on their backs.[47] Skin self-examination has a role in reducing melanoma mortality; as Berwick et al demonstrated, it could potentially reduce mortality related to melanoma by 63%.[48] Indeed, in a study in New York, skin self-examination was found to be a key predictor of presentation with a melanoma $<$1 mm in thickness.[49] Several groups have reported on multiple primary melanomas (MPM).[50-52] Blackwood et al examined the frequency of family history of melanoma in cases with MPM and found close to half had a positive family history.[53] Families of MPM patients also had a high incidence of dysplastic nevi and basal cell carcinoma, suggesting that they would benefit from screening, skin self-examination, and regular skin surveillance. Thus, the families of MPM patients should be screened as well.

Although we generally think of the principal melanoma subtypes as superficial spreading, nodular, lentigo maligna, and acral lentiginous melanoma, one should not forget the desmoplastic type. To our knowledge, the first ever description of desmoplastic melanoma was in *Cancer*, by Conley et al in 1971: "a rare variant of spindle cell melanoma."[54] Since 1971, several works, including many published in *Cancer*, have contributed to our knowledge of desmoplastic melanoma, including the higher local recurrence associated with the propensity for neurotropism, the lower incidence of lymph node metastases, especially in the pure histological variant, and the possible role of radiation.[55-61] Desmoplastic melanomas are more common on the head and neck, may look innocuous, and are frequently amelanotic; a high index of suspicion is needed to allow timely biopsy.

Throughout the history of *Cancer*, articles have highlighted the metastatic potential of thin melanomas.[62-64] In particular, the presence of regression has attracted attention and provoked debate as a potential factor affecting prognosis.[62,65] The presence of regression has not been consistently shown to impact prognosis of thin melanomas, although those thin melanomas with extensive regression appear to be over-represented among patients developing metastases.[46,66] The jury is still out, but increasingly data show that regression does not adversely impact either prognosis or the likelihood of finding a positive sentinel lymph node.[6,67,68] Although the debate continues as to whether either regression or Clark level should be used to select patients with melanomas thinner than 1 mm for sentinel lymph node biopsy,[68,69] data continue to accumulate supporting a potential role for mitotic rate in this decision-making process.[5,70]

A provocative observation first made in *Cancer* was that there appeared to be no correlation between time to diagnosis and tumor thickness.[71] The authors observed highly variable rates of growth among different primary melanomas and speculated regarding heterogeneity in primary melanomas' inherent biology. Twenty-five years later we have overwhelming

evidence for the genetic heterogeneity of the entity we call cutaneous melanoma.[72-74] Several pathways may result in melanoma development, and understanding this heterogeneity may allow us to improve on our treatment of advanced disease. In this regard, the changing epidemiology of melanoma over the last decades seen in data from certain countries raises several questions. In Southern Sweden, a population-based study of histopathologically reviewed melanomas from 1965, 1975, and 1985 showed no significant decrease in mean tumor thickness over the time period, although survival had improved.[75] A recent update from the same group showed that none of the known prognostic factors such as age, sex, and ulceration explained the increased survival of melanoma patients for that period.[76] Similarly, Germany reported an improvement in overall survival of patients for the period 1990 to 2001 as compared with 1976 to 1989 that could not be entirely attributed to early diagnosis and more favorable primary tumors.[77] Although in an earlier analysis the median tumor thickness had decreased from 1.81 mm in 1976 to 0.53 mm in 2000,[78] when a multivariate analysis was performed, the more recent time period was an independent factor portending an improved prognosis.[77] One can only postulate as to the possible factors other than early detection that would contribute to this changing epidemiology. Have changing patterns of sun exposure altered the biology of melanoma, or the distribution of hitherto unappreciated biologic subtypes, impacting overall survival? Are there environmental factors other than sun exposure that have been altered? The prevalence of smoking has decreased in North America and in Europe. Smoking is known to influence melanoma prognosis,[79] and 1 study also suggests an impact on melanoma risk.[80] The contributing role of vitamin D, occupational exposures, redox-active metals, and smoking to melanoma incidence and survival are research questions that will need to be answered. Of all these possible factors, the role of vitamin D—and the suggestion that sun exposure is actually desirable from a health perspective—has received the most public attention. Melanoma clinicians have an obligation to understand the essential elements of the debate,[81] and recognize that even if vitamin D is important in some as yet undefined way in cancer incidence or outcome, oral supplementation rather than increasing solar exposure is the appropriate response.[82]

SURGICAL TREATMENT OF MELANOMA

Compared with most solid tumors, for which the past several decades have seen dramatic shifts from surgical to multidisciplinary management, the treatment of melanoma therapy has remained centered on resection. Surgery provides the best hope for long-term survival, not only for early-stage disease, but also for patients with regional and potentially distant disease. The nature of that surgery, however, has changed dramatically, resulting in significantly less morbidity, improved staging and identification of micrometastases, and enhanced survival.

One of the most dramatic changes in melanoma surgery over the past 60 years has been the extent of the primary excision for melanoma. On the basis of observations of local recurrence rates as high as 60% with surgeries designed solely to excise the visible primary tumor without a defined surrounding margin of normal tissue, the radical wide excision has been the cornerstone of melanoma surgery since it was first described by William Norris in 1857.[83] Very quickly, radical excisions of 3 to 5 cm beyond the primary became the standard of care. The morbidity of these surgeries was significant, with little data to support whether survival was improved. This led to the design and implementation of several randomized trials to answer whether such wide margins (3, 4, or 5 cm) were necessary, or whether more narrow (1 or 2 cm) margins were adequate.[84-86] Two of these important studies were published in *Cancer*. Cohn-Cedermark et al reported the results of the Swedish Melanoma Study Group trial, which evaluated 989 patients with primary melanomas between 0.8 and 2.0 mm thick.[87] Patients were randomly allocated to excision with a 2-cm or a 5-cm margin. There were no statistically significant differences in local recurrence rates or survival between the 2 arms. Similar results were published by Khayat et al, who randomly assigned 326 patients with melanomas $\leq$2 mm in thickness to 2-cm versus 5-cm margins.[88] This trial also demonstrated no differences in local recurrence or survival. Cumulatively, the results of all these trials established that 1-cm margins of excision were adequate for thin ($\leq$1 mm) melanomas, and that margins of excision greater than 2 cm beyond the primary melanoma were not necessary for most melanomas $>$1 mm in thickness.

Beyond the changing surgical margins, the most dramatic change in the surgical management of melanoma has clearly been the management of the clinically normal regional lymph node basin. Only approximately 10% of patients have clinical evidence of lymph node metastases at the time they initially present with melanoma (ie, palpably abnormal lymph nodes), but the approach to these patients remains basically unchanged. After confirming the presence of melanoma within the palpable lymph

nodes by fine-needle aspiration cytology (and not excisional biopsy unless the fine- needle aspiration is inconclusive), these patients should be staged to rule out the presence of asymptomatic distant disease. At a minimum, this should include a thorough history and physical examination, chest radiograph, and serum lactate dehydrogenase level, with any abnormalities prompting a more thorough search for metastases. Several investigators have shown that the use of computed tomography (CT) scans, (^{18}F)-fluoro-deoxyglucose positron emission tomography (PET), or fused PET-CT scans in this setting will upstage a significant percentage of patients to stage IV, which alters the treatment options. Tyler et al, publishing in *Cancer*, reported that PET scans of patients with stage III disease will change the management in 15% of cases, helping to establish the role of PET scanning in this setting.[89] For patients without evidence of distant metastases, radical lymphadenectomy (complete lymph node dissection) along with the primary melanoma excision is potentially curative, with 5-year survival rates ranging from 25% to 50% depending on the extent of lymph node involvement. Complete lymph node dissection is defined, in the case of palpable axillary metastases, as removal of level I, II, and III lymph nodes. For patients with cervical lymph node metastases, the gold standard has been radical neck dissection to remove the lymph nodes in levels I to V, although more recently several studies have demonstrated no difference in recurrence or survival with modified radical neck dissections. A more controversial question has been the extent of the inguinal dissection when the patient presents with palpable inguinal adenopathy. Some surgeons advocate routine excision of both the inguinal and the pelvic lymph nodes (so-called "superficial and deep groin dissection"). Others have advocated a more selective approach to the pelvic lymph nodes. Clearly, radiologic evidence of involvement of the pelvic lymph nodes on CT or PET is an indication for including the pelvic dissection. Another criteria that has been advocated has been the presence of disease in Cloquet lymph node, the lymph node situated between the inguinal and pelvic basins. However, Shen et al demonstrated that the absence of disease in Cloquet lymph node does not accurately predict the absence of involvement of the iliac lymph nodes.[90] Additional research is needed to understand the relative value of the deep dissection as well as its additional morbidity, for patients presenting with palpable lymph nodes. However, a pessimistic attitude that pelvic lymph node involvement is synonymous with incurable disease cannot be justified.[91]

The area in which the surgical management of melanoma has changed most dramatically is in the approach to patients who present with clinically negative regional lymph nodes. It is recognized that $\geq$20% of patients with melanomas $\geq$1 mm in thickness who present with clinically negative regional lymph nodes will eventually manifest clinically evident lymph node metastases. Historically, many surgeons advocated elective lymph node dissection (ELND), with the idea that early clearance of tumor deposits in the regional lymph node basin could prevent subsequent dissemination. However, given the significant morbidity of ELND, there was great interest in determining whether the procedure impacted overall survival. Four prospective trials evaluated the benefit of ELND for patients with melanoma, including 1 by Veronesi et al in *Cancer*.[92-95] All 4 trials failed to demonstrate a survival benefit for ELND, radically changing the paradigm for management of melanoma away from routine ELND to lymph node observation. However, the management paradigm would change even more dramatically with the introduction of lymphatic mapping and sentinel lymph node biopsy.

The landmark report by Morton et al in 1992 on the technique of lymphatic mapping and sentinel lymph node biopsy in the management of melanoma revolutionized the staging and management of melanoma.[96] Sentinel lymph node biopsy is a minimally invasive procedure for identifying patients with occult lymph node metastases. It is best performed at the time of wide excision of the primary, although it may still be performed in selected patients who already had a wide excision, as demonstrated by Gannon et al in *Cancer*.[97] The hypothesis underpinning the technique is that melanoma metastases within a lymph node basin evolve in an orderly fashion, with metastasis to the sentinel lymph node as the first step in the process. Identification and removal of the sentinel lymph node accurately stages that lymph node basin and, in turn, identifies those patients who would not be likely to benefit from a full lymph node dissection. The accuracy of the sentinel lymph node in reflecting the pathologic status of the entire regional basin has been confirmed in multiple studies.[98,99]

In addition to preventing unnecessary lymphadenectomies, sentinel lymph node biopsy also allows for more accurate staging than elective lymph node dissection. With significantly fewer lymph nodes to examine, the pathologist can serially step-section the lymph node (as opposed to simply bisecting it) for both routine hematoxylin and eosin staining and immunohistochemical staining for melanoma markers such as S-100, Melan-A, and HMB-45. The benefit of

this approach was clearly demonstrated by 2 studies in the pages of *Cancer*. Yu et al reported that examining sentinel lymph nodes with multiple sections and immunohistochemical staining detected metastases in 12% of cases that would otherwise have been reported as negative.[100] Abrahamsen et al also demonstrated that serial sectioning with immunohistochemical staining increased the detection of micrometastases.[101] These articles helped establish step-sectioning and immunohistochemical staining as the standard of care in the pathologic evaluation of the melanoma sentinel lymph node.

With sentinel lymph node biopsy established as the standard staging procedure for clinically negative regional lymph nodes, many investigators have sought to refine which patients should undergo the procedure. Sentinel lymph node biopsy is currently recommended routinely for all otherwise healthy patients with melanomas $\geq$1.0 mm thick, and used selectively by most surgeons for patients with thin melanomas ($<$1.0 mm). Two publications in *Cancer* demonstrated how factors beyond Breslow depth may help select patients with thin melanomas who should undergo sentinel lymph node biopsy, and ultimately perhaps define subsets of patients with melanomas $\geq$1.0 mm who may not need the procedure by virtue of a very low risk of occult lymph node metastasis. Kruper et al, using classification tree analysis, reported that variables such as vertical growth phase, lymphocytic infiltration, and mitotic rate could be used to identify patients at high and low risk for harboring sentinel lymph node metastases.[102] Paek et al provided additional evidence that patient age, mitotic rate, and primary tumor location could be used in addition to Breslow depth to determine the risk of a positive SLN.[6] With validation and additional data, these reports may ultimately lead to different selection criteria for SLN biopsy.

One of the most important questions regarding sentinel lymph node biopsy is the impact that the early removal of microscopic regional disease has on overall survival. Interim results of the Multicenter Selective Lymphadenectomy Trial I, which randomized patients to wide excision alone or wide excision plus sentinel lymph node biopsy, with complete lymph node dissection for any patients with a positive lymph node, provided some crucial information. The 5-year survival for patients who had a complete lymph node dissection on the sentinel lymph node biopsy arm (including patients with positive sentinel lymph nodes as well as those patients who had a false-negative sentinel lymph node biopsy) was significantly better than for those patients undergoing complete lymph node dissection for a recurrence on the wide excision arm (66.2% vs 54.2%%; hazards ratio, 0.62 [$P<.02$]).[103] An unresolved question is how much the subsequent completion dissection benefits the patient over and above the sentinel lymph node biopsy, because in many cases the sentinel lymph node may be the only lymph node found histologically to contain disease. This has prompted several authors to try to identify patients at low risk of harboring additional microscopically evident disease in the nonsentinel lymph nodes.[104,105] The experience of Wagner et al, as published in *Cancer*, has been representative; most investigators have had difficulty reliably predicting which patients may safely avoid a lymph node dissection.[106] These reports have cemented the completion lymph node dissection as the standard of care when a patient has a positive sentinel lymph node, at least for now. This question is being prospectively addressed in the Multicenter Selective Lymphadenectomy Trial II, which randomizes patients with a positive sentinel lymph node to completion dissection or observation with serial ultrasonography of the regional basin.

In addition to lymph node dissections, the surgical management of regional disease includes the control of in-transit and satellite metastases. In-transit and satellite metastases develop in 5% to 8% of patients with melanomas $>$1.5 mm in thickness.[107] Initially, satellite lesions were defined as skin involvement within 2 cm of the primary tumor, whereas in-transit metastases were $>$2 cm from the primary tumor. Historically, these lesions were considered and treated separately. However, Singletary et al demonstrated in *Cancer* that classifying these lesions on the basis of distance from the primary tumor had no prognostic significance.[108] The current American Joint Committee on Cancer staging system for melanoma merges satellite metastases and in-transit disease into a single staging entity within stage III disease.[3,109]

The management of in-transit disease remains extremely challenging. Although surgery may be reasonable when the number of lesions is small, this occurs in only the minority of cases. When the disease is confined to an extremity, however, isolated limb perfusion consisting of regional administration of high-dose chemotherapy, usually melphalan, has been shown to be extremely useful in controlling disease. Minor et al, in *Cancer*, demonstrated how isolated limb perfusion allows for doses up to 15 to 25 times higher than could be obtained with systemic therapy,[110] and several articles published in *Cancer* have documented high complete and partial response rates.[110-112] The duration of response to isolated limb perfusion is typically 9 to 12 months, but

a subgroup (approximately 20% to 25% of the total patient population) can have sustained complete responses. Toxicities range from mild erythema and edema to extensive epidermolysis and functional impairment, and can rarely result in the need for amputation. For patients whose disease is still limited to the extremity on recurrence, reperfusion may be possible.[113,114]

A newer approach to in-transit disease is that of isolated limb infusion (ILI), a less invasive and less toxic approach.[115] Access is gained to the circulation of the affected limb by percutaneous radiologic techniques, and a tourniquet is inflated around the proximal limb. The chemotherapeutic agent is then infused into the isolated limb, albeit at lower doses than those used with isolated limb perfusion (ILP), because there will be some systemic leakage. In 1 series using melphalan and dactinomycin, the overall response in limbs treated by ILI was 85%, with a complete response of 41% and a partial response of 44%, and the median duration of response was 16 months, results that compare favorably with the more invasive and complex technique of ILP.[116] Currently, ILI is being further evaluated in phase 2 trials.

Finally, a role for surgery in the treatment of stage IV melanoma has emerged over the last decade. For most solid tumors, the development of distant metastases heralds the end of involvement by the surgeon. For melanoma, however, there is documented long-term survival among patients after complete resection of metastatic lesions.[117] Careful patient selection is required, taking into account the stage of the original melanoma, the disease-free interval, the number and site of the metastases, the patient's current health status, the feasibility of complete resection, and the morbidity of the planned operation, and most patients will not be candidates. The potential of surgical resection in stage IV disease and the importance of proper patient selection was nicely illustrated by Meyer et al in a retrospective review of 444 patients with stage IV melanoma.[118]

CYTOTOXIC CHEMOTHERAPY IN MELANOMA

Despite many studies, the results of cytotoxic chemotherapy for metastatic melanoma have remained disappointing. Median survival for newly diagnosed metastatic melanoma patients remains under 1 year even with the newest combination therapies. A comprehensive and critical review of the melanoma chemotherapy literature over the last 40 years has been published recently in *Cancer,*[119] but many of the original studies appeared there as well.

The very first trial of dacarbazine (DTIC) in melanoma was reported in *Cancer* in 1971.[120] In this trial at the "University of Sydney Professorial Surgical Unit," DTIC was given at a dose of 4.5 mg/kg daily for 10 days. Four of 20 patients had an objective response after a single cycle of treatment, and the authors observed that "intravenous DTIC therapy was easy to administer and not distressing to the patient." Many different schedules and combinations of DTIC in melanoma have been explored over the last 36 years, and the drug was ultimately approved by the US Food and Drug Administration for use in melanoma. A prescient review by Luce appeared the next year in *Cancer*, summarizing the response rates to chemotherapy: 5%-28% for single agents and up to 50% for the combination of dactinomycin and vincristine.[121] Luce also attempted to correlate clinical response with responses observed in murine model systems, and found no correlation for 11 chemotherapy drugs then under investigation. This endeavor continues to beguile investigators: predicting response in human cancer remains very difficult to this day.

A serious toxicity of DTIC, hepatic veno-occlusive disease, was first reported in *Cancer.*[122] A much more common toxicity of DTIC, nausea and vomiting, is today much less problematic thanks to the common use of highly effective 5HT-3 receptor antagonists such as ondansetron and granisetron. Indeed, use of ondansetron to prevent DTIC-induced nausea was first reported in *Cancer* in a trial by Legha et al.[123]

Multiple DTIC-containing combinations have been tested over the years, many demonstrating higher response rates than DTIC alone. Three DTIC-containing regimens were compared by Wittes et al in 1978, showing no marked superiority for any regimen in response rates or survival.[124] This was just 1 harbinger of many failures of combination chemotherapy to demonstrate a clear advantage over DTIC alone. The widely used 4-drug "Dartmouth regimen" (DTIC, cisplatin, carmustine, and tamoxifen)[125] was prospectively compared with DTIC alone in a cooperative group study. Although the combination regimen had a slightly higher response rate (18.5% vs 10.2% for DTIC alone), overall survival was not impacted.[126] This disappointing result, along with equally unimpressive results from a large phase 2 cooperative group trial,[127] led to the demise of this regimen.

The combination of cisplatin, vinblastine, and DTIC (CVD), still used in some settings today, was published in *Cancer* as a neoadjuvant (preoperative) regimen.[128] The reported response rate was high;

48% of patients had either a complete or a partial response, and the bone marrow suppression was not as severe as with the Dartmouth regimen. Subsequently, CVD was tested in metastatic melanoma.[129] This regimen rapidly became a standard approach, and was subsequently used as the backbone of several "biochemotherapy" regimens that included interleukin (IL)-2 and interferon-α. These regimens generated tremendous enthusiasm for their very high response rates (up to or exceeding 50%.).[130] Unfortunately, when a randomized Eastern Cooperative Oncology Group/intergroup trial compared CVD/IL-2/interferon biochemotherapy to CVD chemotherapy alone, no significant benefit in overall survival was seen.[131] This lack of overall survival benefit for biochemotherapy over chemotherapy alone has now been confirmed in a large meta-analysis.[132]

Given the disappointments with DTIC-based regimens, many other agents have been tested in metastatic melanoma patients over the years, with several of these trials reported in *Cancer*. Legha et al reported on the then novel drug paclitaxel in melanoma.[133] Paclitaxel at a dose of 250 mg/m^2 given over 24 hours produced objective responses in 12% of previously untreated patients. The nitrosourea fotemustine, which crosses the blood–brain barrier, was tested in a French multicenter phase 2 trial. A response rate of 24.2% was reported, and patients with brain metastases experienced an impressive 25% objective response rate.[134] Subsequently, a major randomized phase 3 trial compared fotemustine to DTIC; although fotemustine significantly delayed brain metastasis and doubled response rates (15.5% vs 6.8%), overall survival was not significantly increased (7.3 months vs 5.6 months, $P = .067$).[135] A major limitation of fotemustine, as with other nitrosoureas, is the high incidence of severe bone marrow suppression, which could be predicted by a multifactorial scoring system.[136]

High-dose chemotherapy was explored in melanoma, as it was in other solid tumor and hematological malignancies. In a study published in *Cancer*, Thatcher et al reported an extremely high 81% response rate for a combination of DTIC with melphalan or ifosfamide followed by autologous bone marrow rescue.[137] Unfortunately, a high incidence of adverse effects, including toxic deaths, was reported as well. Two further studies in *Cancer* examined high-dose cisplatin in combination with DTIC in melanoma.[138,139] Both studies had disappointing response rates (12% and 17%) and severe toxicity. High-dose chemotherapy has continued to be tested intermittently, but overall this approach has not been successful in melanoma.

A novel method of introducing large molecular weight chemotherapy agents into cancer cells, potentially overcoming drug resistance mechanisms, is to use transient electric pulses. Electrochemotherapy with bleomycin was highly effective in a phase 1/2 trial in causing regression of superficial melanoma lesions.[140] This method of introducing large molecular weight molecules has been adapted to transfer DNA and is actively being explored.

The challenge of dealing with the common terminal event in advanced melanoma, central nervous system metastasis, was laid out by Gottleib, Frei, and Luce in a 1972 review.[141] Recently, the drug temozolomide has shown activity in melanoma.[142] This drug has some advantages over DTIC. It is an orally bioavailable drug that is converted nonenzymatically to 5-(3-methyl-1-triazeno)imidazole-4-carboxamide, the same active metabolite of DTIC. It also crosses the blood-brain barrier, which DTIC does not. The combination of temozolomide with thalidomide was reported to have high levels of activity in a phase 2 single center trial.[143] Unfortunately, this was not corroborated in a cooperative group phase 2 trial, where this regimen appeared to be only modestly active in melanoma patients with brain metastases, but had an unacceptably high incidence of thromboembolism,[144] a toxicity also reported when thalidomide was combined with interferon-α.[145]

IMMUNOLOGIC THERAPIES IN MELANOMA

The field of clinical tumor immunology began over 100 years ago with observations by William Halsted of a favorable association between lymphocytic infiltration of the tumor and the clinical outcome of breast cancer. The therapeutic use of inflammatory mediators in the treatment of cancer also began in the 1890s, with the work of William Coley, a surgeon who injected large tumors with viable Gram-positive microorganisms. The resulting inflammatory process sometimes resulted in tumor regression, but was associated with significant systemic toxicity and even mortality. The material, known as Coley toxin, has come back under discussion in parallel with today's more detailed understanding of the cells and molecules involved in the innate and adaptive immune systems. It was not until much later, in the 1960s and 1970s, that the foundations of the most successful form of immunotherapy to date, allogeneic bone marrow transplantation, were established.[146] The canine models that provided the basis for early human investigation were a rich source of knowledge regarding histocompatibility and the basis of cellular immunotherapy. Later, it turned out that much of

the insight into histocompatibility genes and related genes that control the allo-immune response was also relevant to the immune response against tumor antigens, forming the basis for much of contemporary tumor immunotherapy research.

Melanoma has long been a focus of research and clinical trials of immunotherapy because of its innate resistance to other therapies as well as the occasional observation of spontaneous or postinflammatory tumor regression. Many early immunotherapy reports for melanoma appeared in *Cancer*. It is possible to chart the course of the field by reviewing these articles, which in the tradition of the journal include both therapeutic trials and clinicopathologic observations. To review these papers is not only to witness a glimpse of how the field began, but also to be reminded of the steady and substantial improvements in study design, statistical analysis, correlative science, and human subjects protection that have occurred during the past 6 decades.

Reports began to appear in *Cancer* in 1973, starting with a large therapeutic trial using autologous tumor coupled to xenogeneic serum gamma globulin, with the authors reporting activity in 2 patients and possible immune responses 4 additional patients (a clinical benefit rate of 12%).[147] The first description of bacillus Calmette–Guerin (BCG) in the adjuvant setting was the subject of a small trial consisting of 2 different doses of BCG administered by scarification to patients with resected high-risk melanoma.[148] Although no conclusions regarding the clinical activity of this therapy could be made on the basis of this 13-patient trial, the correlative immunologic studies demonstrated a phenomenon that remains 1 of the recurring themes in melanoma immunotherapy: the association between immune responsiveness and favorable outcome.[149] Whereas immunotherapy approaches (and clinical trial design, conduct, and reporting) have evolved to far more sophisticated levels, the ability to distinguish response to therapy from general immune responsiveness as a predictor of favorable outcome remains a formidable obstacle. As an example, the recent report by Gogas et al showed a strong association between development of autoimmunity during adjuvant interferon-α, and disease-free and overall survival.[150] This provided evidence that we may be able to identify host protection from melanoma *after* the therapeutic intervention, but as yet we have not identified predictive factors for matching patients to therapies, nor have we developed highly effective treatments that break tolerance and overcome the immune resistance and escape that protect the melanoma from the host.

Attempts to focus on tumor-associated antigens in melanoma also began in the early 1970s, and the results from a large series reported from Duke University provided insight into aspects of melanoma immunology—in particular, the antigenic specificity of response to vaccination and the impact of exposure to tumor on cytotoxic lymphocyte responses—that continue to be addressed by today's researchers.[151] These investigators also made the observation, as have others, that patients with visceral metastatic disease rarely if ever benefited from immunotherapy and stated that their future trials of vaccine therapy would be limited to patients with skin and soft tissue metastasis, "using chemotherapy in those with more extensive disease" (no wonder chemotherapy got off to such a poor start).

In a similar approach, the group at Jefferson reported the use of a mixture of irradiated autologous melanoma cells plus BCG injected intradermally in patients with advanced melanoma, observing 4 responses among 18 patients, but noting that responses were of short duration and occurred only in those with nonvisceral metastatic sites.[152] Although the same group of investigators had previously reported in *Cancer* the regression of a lung metastasis after the intratumoral injection of multiple cutaneous metastases with BCG,[153] their conclusion in this 1977 article was that the BCG/autologous tumor vaccine approach they used did not have general applicability because of its low overall activity. Although the predominant limitation of BCG therapy for melanoma is indeed its low activity, the 1975 report in *Cancer* of deaths from BCG injections into subcutaneous nodules points out that even relatively mild immunotherapies can have profound toxicities, an observation that further supports the crucial need for a thorough understanding of the mechanisms of action and of toxicity for all of our therapeutic agents or regimens.[154]

Studies using BCG by various routes continued throughout the late 1970s and early 1980s,[155-158] but the use of any form of intralesional therapy, including the purportedly less toxic methanol-extracted residue of BCG, became less compelling as the data regarding its low activity and occasionally severe toxicity became established.[159] However, BCG and related preparations such as DETOX (consisting of mycobacterial cell wall plus *Salmonella* phospholipids) continued to be used in phase 3 trials with allogeneic melanoma vaccines.[160,161] These vaccines, just as with BCG alone, have not shown sufficient activity to warrant their routine use for high-risk melanoma patients.[162,163]

The later 1970s saw the evolution of other forms of melanoma vaccination, including the use of oncolysates prepared from surgically excised autologous melanoma infected with the Newcastle disease virus or vaccinia virus.[164,165] By that time, it had been

reported that this and other viruses could induce the production of interferon,[166] so the stage was set for the advent of interferon in melanoma therapy. In *Cancer* in 1983, Retsas et al reported a single response among 17 pretreated melanoma patients receiving human lymphoblastoid interferon,[167] and the next year Creagan et al reported a 31-patient trial of high-dose recombinant interferon-α, given intramuscularly 3 times weekly, with 7 objective responses but substantial toxicity, predominantly constitutional.[168] The authors' conclusions that interferon "has some antitumor activity accompanied by difficult side effects" were corroborated by several other reports, including a larger series by the same group.[169,170] They continue to be valid today; interferon's use is limited for the most part to the adjuvant therapy of stage III disease and to biochemotherapy regimens that contain interferon-α and IL-2 added to combination chemotherapy, both controversial therapies.[171,172] Use of those 2 cytokines without chemotherapy was investigated by Keilholz et al, who observed promising activity (objective response rate 41%) with acceptable tolerability using a regimen of moderate-dose intermittent subcutaneous interferon-α plus a "decrescendo" dose schedule of intravenous infusional IL-2.[173] However, enthusiasm for this combination was dampened by subsequent reports that yielded objective response rates under 10% despite substantial toxicity.[174,175] Meanwhile, the more promising data with biochemotherapy combinations, detailed in the earlier section of this review, supported the continued development of such combinations over double-cytokine regimens.

The investigation, characterization, and therapeutic manipulation of tumor antigens in melanoma has also been well represented by reports appearing in *Cancer* over the last 25 years. One of the first and most comprehensive reports was that of Hollinshead et al, who performed a series of studies in a multicenter collaboration.[176] In this report, the authors started by defining tumor-associated antigens from membrane preparations of primary or metastatic melanomas that induced delayed-type hypersensitivity reactions in patients with various stages of disease. They observed a positive reaction in nearly 90% of patients with early-stage melanoma who were disease-free at the time of testing, whereas only 1 of 3 of patients with advanced disease responded. The tumor-associated antigen, identified as a glycolipoprotein, was then used as a vaccine in a trial that featured decreasing doses of antigen in response to local inflammatory reactions occurring at the starting doses. These authors went on to describe the use of DTIC chemotherapy (and in 1 case, an intensive course of plasmapheresis that induced a second remission in a patient who had initially responded and later progressed) to "reduce circulating inhibitory substances" to the vaccine. They reported a low response rate to chemotherapy and a very high response rate to "chemoimmunotherapy" (including a majority of patients who crossed over from the chemotherapy to the chemoimmunotherapy treatment) as well as the presence of inflammatory infiltrates in tumors that were biopsied during regression.[176] Further studies to identify tumor-associated antigens included efforts of the Memorial-Sloan Kettering group, which extensively investigated the immunogenicity of gangliosides found predominantly on melanoma by using antibodies[177] or ganglioside vaccinations.[178] Gene therapy as a component of immunotherapy for melanoma has appeared in the design of vaccines based on melanoma cells transduced to express a gene that renders them immunogenic, such as interferon-γ.[179]

Other current approaches to immunotherapy of melanoma are reflected in several recent *Cancer* publications describing the use of defined-sequence peptide fragments of melanoma antigens with known histocompatibility antigen restrictions,[180] and in some cases chemical modification of the amino acid sequence to enhance peptide binding to class I molecules and/or recognition by the T cell receptor.[181] Novel delivery methods have also been reported, including the intranodal delivery of a plasmid encoding an important melanoma tumor antigen.[182] Furthermore, 1 of the pioneering reports describing the use of a fully human antibody against the CTLA4 molecule that dampens T cell responses and appears to mediate some of the activity of regulatory T cells appeared in *Cancer* in 2006.[183]

Adoptive immunotherapy, the prototype of which is allogeneic hematopoietic cell transplant for hematologic malignancy, has been applied to melanoma and other solid tumors since the 1980s. Whereas allogeneic transplants have rarely provided sufficient activity to be worthy of further pursuit,[184,185] manipulations of autologous cell products may provide a level of antitumor cytotoxicity not achieved with any of the other immunotherapy strategies detailed above.[186-190] Ironically, as investigators came to believe that high-dose IL-2 appeared to provide most or all of the therapeutic activity attributed to IL-2 plus lymphokine-activated killer cells, the addition of cells was largely abandoned.[191-193]

Conclusions

In the 60 years of existence of *Cancer*, great strides in understanding and treatment of melanoma have been made. Although treating advanced disease has

remains challenging, the road to further advances has already begun to be mapped with discoveries in the genetic heterogeneity of melanoma, knowledge of pathways that can be targeted, and a growing understanding of the tumor microenvironment and the host's immunological responses. We look forward to *Cancer*'s continuing contributions to our knowledge of melanoma.

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