

Innovations and Challenges in Melanoma: Summary Statement from the First Cambridge Conference

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Abstract Innovations and Challenges in Melanoma, chaired by Michael Atkins and cochaired by Ulrich Keilholz, John Kirkwood, and Jeffrey Sosman, was held July 15 to 16, 2005, in Cambridge, Massachusetts. The conference brought together leading experts in the fields of cancer research, medical oncology, surgical oncology, anatomic pathology, dermatology, and immunotherapy who wished to advance the field of melanoma treatment by exchanging information and perspectives regarding recent advances and recommendations for further study. The conference proceedings published in this educational supplement to *Clinical Cancer Research* are intended to provide timely information and recommendations on how genetics, biology, and data information can enhance our understanding of melanoma biology and help inform the use of therapies for this disease.

Epidemiology, Biology, and Pathology

Although substantial efforts have been devoted to the improvement of melanoma treatment, the mainstay of treatment remains surgical excision. This treatment may be curative for patients with early disease and for some patients with regional lymph node metastases but has a less defined role in patients with distant metastases. Other treatments, including adjuvant therapy for resected regional disease or chemotherapy or immunotherapy for metastatic disease, provide only modest improvement in outcome. Therefore, it is essential that melanoma be detected early. Early detection is the major factor responsible for progress in melanoma treatment during the past 30 years and remains the most promising avenue for short-term and medium-term progress.

To improve our early detection activities, we must inspect and recognize the curable melanomas when they become visible on the skin (1). These early detection activities can be done by both clinicians and patients. Current efforts to encourage such activities include the ABCD method, the Basic Skin Cancer Triage, and the Check-It-Out Project.

For the past 20 years, early detection and screening for the public have focused on ABCD: A for asymmetry, B for irregular border, C for multiple colors, and D for diameter of >6 mm (2). This tool has been useful, but ambiguity exists regarding the threshold for action (presumably, the presence of just one of these features should precipitate a visit to the physician, but some may think that a lesion does not require action until two or more of these features are present). More importantly, melanomas do not necessarily manifest any of these signs. The Basic Skin Cancer Triage (3) is an eight-step algorithm that allows the clinician to triage patients and skin lesions into one of three categories: act (requires biopsy or referral), reassure (patient can be confidently reassured), and track (requires near-term surveillance to be sure it is stable). The Check-It-Out Project evaluated an intervention to increase thorough skin self-examination in a randomized trial. At baseline, the main predictors of thorough skin self-examination performance were (a) having been advised to do so by a physician, (b) availability of a partner (generally a spouse) to help, and (c) availability of a wall mirror (4). The intervention included cues, aids, a video, and brief in-person counseling by health educators. The result was a sustained increase in performance of thorough skin self-examination in the intervention group.

"Look and see" is the essence of reducing melanoma mortality. Both clinicians and patients need to be trained to look for and recognize melanomas on the skin. For clinicians, the current gold standard for diagnosing melanoma is the routine histopathologic examination. The purpose of pathologic

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examination of a lesion suspected of being a malignant melanoma is to provide an accurate diagnosis of melanoma and to provide prognostic information useful in the treatment of the patient. In the near future, pathologic attributes will also likely be used to predict responses to therapy and therefore serve as a guide in the selection of specific therapeutic agents, such as small-molecule inhibitors of signaling pathways. The pathologic examination will likely be supplemented by high-throughput or other molecular studies and techniques such as comparative genomic hybridization and gene expression profiling. In addition, mitogenicity and tumorigenicity should be added to the American Joint Committee on Cancer staging system as modifiers for stage I disease.

Effective diagnostic tools must be supplemented with successful therapeutic interventions. Future treatment should be based on an understanding of the genetic alterations found in melanoma. First, how melanoma genetics contribute to the inherited risk of melanoma predisposition must be explored. Second, the genetic changes in melanoma must be examined with regard to generating new markers or new patterns of gene expression, which will dovetail with our pathologic understanding of the disease, thereby allowing us to better prognosticate the disease course. Third, we have to understand how to exploit the genetic changes in signaling pathways, cell cycle control pathways, and apoptotic pathways to therapeutic effect. Understanding the role alterations in these pathways play in melanoma and understanding their interactions may provide key insights that will lead to effective therapeutic interventions.

Staging and Local and Regional Therapy

Ideally, staging criteria for melanoma should be simple and based on factors that absolutely discriminate curable patients from patients destined to relapse and in the patients destined to relapse predict the pattern of failure and the most effective therapy. In reality, the variables currently used in melanoma staging are imperfect, and the process of modifying the staging criteria when more discriminating factors are identified is an enormous challenge. However, new adjuncts to the current staging system are needed for the risk assessment process to be effective.

The most likely new factor to change the complexion of the classification scheme for primary tumors (T stage) is mitotic rate. This factor may be more discriminating than ulceration in patients with stage I/II disease. Future multivariate analyses using sentinel lymph node biopsy are needed to investigate the effect of mitotic rate on patients with pathologically staged disease. In addition, prognostic modeling can be used as an adjunct to our framework of staging that can help us better discriminate patient risk factors. As new risk factors are discovered, our staging systems should evolve so that we can better determine surgical and systemic therapies.

Currently, minimally invasive intraoperative lymphatic mapping with sentinel node biopsy (LM/SNB) is the standard approach for staging the regional lymph nodes for early-stage melanoma. Three major studies are investigating the effectiveness of LM/SNB: the Multicenter Selective Lymphadenectomy Trials I and II (5, 6) and the Sunbelt Melanoma Trial (7). The Multicenter Selective Lymphadenectomy Trial I began in 1994

with the intent of determining the therapeutic benefit and true accuracy of LM/SNB. As of March 2002, a total of 2,001 patients had entered the study, and results from the third interim analysis (five planned) have validated the accuracy of this approach as a staging procedure (8). The initial SNB rate was 95.3% overall: 99% for the groin, 95% for the axilla, 84% for the neck, and 87% for the popliteal and other ectopic sites. The accuracy rates remained consistent throughout the study, showing the importance of preoperative lymphoscintigraphy, blue dye, and γ probe-directed sentinel node localization. A total of 19% of patients had tumor-positive sentinel nodes, and most of these patients underwent completion dissection. Of the 944 patients with tumor-negative sentinel nodes, 59 (6.3%) experienced disease recurrence in the regional basin after a median follow-up of 54 months. The rate of tumor-positive sentinel nodes essentially equals the incidence of lymph node recurrences (144 of 800, 18.1%) after wide excision alone, suggesting the biological significance of sentinel node metastases. The surgical complication rate related to LM/SLB was 10.1%, and there were no operative mortalities. Data showed a significantly ($P = 0.01$) higher 5-year disease-free survival (78%) for patients undergoing LM/SNB compared with those undergoing wide excision alone (73%). No difference was apparent in overall survival between the two treatment groups; yet, tumor status of the sentinel node remained the strongest predictor of outcome in these patients (9).

The Multicenter Selective Lymphadenectomy Trial II began in 2005 and was designed to determine if a therapeutic benefit exists for routine completion lymph node dissection in patients with microscopic or molecular involvement of the sentinel lymph node. Study accrual is ongoing. The Sunbelt Melanoma Trial is a prospective randomized study designed to examine the therapeutic value of completion lymphadenectomy and/or 1 month of adjuvant IFN- α in patients with molecularly involved sentinel lymph nodes based on reverse transcriptase-PCR evidence of melanoma-related mRNA. Although the trial did not complete its initial accrual goals due to slow enrollment, the organizers still anticipate that this trial should provide further insight into the therapeutic value of LM/SNB.

Although the role of SNB as a staging procedure has been shown, the therapeutic value of this technique is still in question. It is hoped that the results of these investigations will provide new insights into the therapeutic benefits of LM/SNB. Additional information obtained from more thorough evaluation of the sentinel lymph node, such as location of tumor deposits (subcapsular versus parenchymal), size of tumor deposits, functional capacity of immune cells, and presence of regulatory cells, may prove particularly useful in predicting distant relapse. Perhaps as we achieve a better understanding of the immunobiology of the sentinel node, the development of additional regional and systemic melanoma therapies will become possible.

Adjuvant Therapy, Vaccines, and Immune Monitoring

Adjuvant therapy of melanoma has not made significant progress for the past decade. Nearly every agent that has shown any clinical evidence of antitumor efficacy in advanced melanoma has been evaluated in the adjuvant setting, and

several agents that have shown no measurable antitumor effects in advanced disease have been explored as well. Currently, the only effective and Food and Drug Administration–approved adjuvant therapy for patients with high-risk melanoma is high-dose IFN- α 2b. In the setting of high-risk melanoma, adjuvant therapy with high-dose IFN- α 2b has shown improved overall survival in two multicenter cooperative group or intergroup trials. Consequently, efforts at identifying the population of patients who benefit most from adjuvant therapy may be most useful in the context of IFN therapy. Immunologically, there is evidence that the adjuvant setting may be qualitatively different than the advanced disease setting, and factors that seem to impede progress in advanced disease therapy, such as profound levels of immunologic tolerance, with a bias of immune responses toward T_H2 rather than T_H1 cytokine expression, may be less an issue in the adjuvant setting. Recent use of IFN in the neoadjuvant setting has shown surprising single-agent antitumor activity and also creates an opportunity to directly examine the mechanisms responsible for its clinical benefit. Furthermore, these results highlight the potential value of neoadjuvant studies to explore mechanisms of action of other agents to be considered for testing in the adjuvant setting.

Vaccine therapy, including autologous, allogeneic, and peptide vaccines, has been widely studied in the management of melanoma. However, despite the extensive effort to develop melanoma vaccines, none are currently available as approved therapy. Only a handful of vaccines have been evaluated in phase 3 clinical trials, and to date, none of these phase 3 trials has had an overall positive result. Moreover, virtually all of the vaccines that have progressed to phase 3 trials have faced significant hurdles in terms of manufacturing, distribution, and quality assurance, which has affected both the likelihood of obtaining regulatory approval and the ability to commercialize the agent should clinical efficacy be shown and regulatory approval be granted (10).

Although autologous vaccines have numerous theoretical advantages, including the possession of unique or rare tumor antigens that develop through mutational events and appropriate HLA matching for optimum antigen presentation to T cells, few patients have sufficient tumor available for most autologous vaccine strategies. In addition, no consensus exists on how the autologous tumor should be processed, preserved, modified, and delivered to serve as an effective vaccine. The amount of autologous tumor available is rarely enough to produce more than two or three vaccination doses, and the interval between initial tumor harvest and ultimate availability of the clinical vaccine may result in interval tumor progression that diminishes the likelihood of vaccine efficacy.

A phase 3 clinical trial using autologous tumor processed with a heat shock protein mixture (Oncophage) to facilitate tumor antigen presentation has completed accrual. As we await the results of this phase 3 trial, the limitations of this approach remain apparent: only a percentage of melanoma patients have accessible tumor from which the heat shock protein autologous vaccine can be generated, the randomized clinical trial is being conducted in patients with advanced metastatic disease who may have associated immunosuppression that may reduce vaccine effect, and the vaccine is being compared with a variety of therapies of varying, albeit limited, efficacy. Whether the advantages of this particular autologous vaccine formulation will be sufficient to allow it to show

clinical efficacy in a setting where so many other vaccines have failed remains to be seen.

Allogeneic vaccines have significant advantages over autologous tumor vaccines in terms of availability for patients in all stages of the disease and ability to be administered repeatedly over a protracted period. They may also be more inherently recognizable to the patient's immune system than an autologous cell preparation, although they may lack unique or rare antigens that could be important antigenic targets. Although allogeneic vaccines are amenable to a degree of standardization and can be manufactured in sufficiently large quantities to allow large-scale randomized trials in multiple institutions, significant issues in the manufacture and standardization of the final vaccine product remain.

One allogeneic vaccine that has overcome such manufacturing challenges is Canvaxin (11, 12). This vaccine has been studied in two multi-institutional randomized phase 3 trials in patients with resected stage III and resected stage IV melanoma. Unfortunately, both trials were discontinued, and the blind was broken when the Data Safety Monitoring Board review determined that based on preliminary data, the vaccine was unlikely to show superiority to the control treatment.

Cancer vaccines using defined peptide antigens may have a place in the future of melanoma therapy. However, currently, peptide vaccines are valuable for dissecting the host-tumor relationship. Questions of the current era have included too great an emphasis on comparing the efficacy of various strategies. For example, "Are dendritic cell vaccines, whole melanoma cell vaccines, peptide vaccines, or viral vaccines most effective?" The answer thus far is that all have some promise, but all fall far short of our goals. Thus, the goals of the next generation of cancer vaccines should be to attempt to dissect out the host-tumor relationship and identify targets for immune interventions that can enhance the efficacy of vaccines just as we attempt to identify targets at a molecular level for cell signaling in melanoma.

Future vaccine investigations need to determine whether the currently available vaccines are best suited to use in the metastatic disease setting, where the evaluation of clinical activity is clear but the tumor and even the immune response are harder to achieve, or in the adjuvant setting, where the evaluation of immune response may be more easily achieved, but the evaluation of efficacy is more complicated. It is critical that we discover what immune monitoring can teach us so that we can decide whether we are moving in the right direction in vaccine therapy.

The primary objective of immune monitoring is to determine the efficacy of a vaccine to induce or augment a specific T-cell response. Suitable animal models for immune monitoring are lacking, because preclinical vaccine development in small rodents does not allow serial immune monitoring of peripheral blood, as is commonly used in patients. The current situation is characterized by a lack of gold standards for T-cell assessment, uncertainty about the association between immune monitoring assay results and clinical end points, and lack of knowledge regarding the contribution of different aspects of T-cell function to clinical efficacy. It is acknowledged that T-cell monitoring will have to be validated in large trials with clinically active vaccines, but this necessity should not discourage the current application of novel assays within clinical trials of all stages.

Immunotherapy for Advanced Disease

Few, if any, effective therapies exist for patients with unresectable stage IV melanoma. High-dose interleukin-2 is the only approach that produces reproducible durable complete responses in the stage IV patient population, but it comes at a significant cost in terms of toxic effects and expense and is observed in only 5% to 8% of patients. Although cytokine-based immunotherapy is currently of limited benefit, it is likely to be a critical component to any curative strategy for the treatment of melanoma. Opportunities for enhancing cytokine-based therapy include better patient selection, elimination of immunosuppressive effects, and targeting cytokines directly to the tumor sites. Recent data suggest that cancer patients may have increased numbers of regulatory T cells, and that in some patients, cytokine therapy may actually lead to enhanced immunoregulation (suppression) rather than immune activation. The long-observed association between autoimmunity and the response to immunotherapy suggests that the immunoregulatory response to cytokine-based immunotherapy may be predetermined by host genetic factors. However, other data suggest that the tumor itself may influence the function of immune cells within the tumor microenvironment. Given the critical need to enhance our understanding of the mechanisms underlying response and resistance to cytokine-based immunotherapy and to discern factors predictive of response to such treatment, whenever possible, patients should be considered for enrollment in research protocols that address these issues. In particular, the opportunity exists for potentially shifting the immune response to cytokine therapy toward effective anti-tumor immunity by combining cytokines with lymphodepletion, ONTAK, or CTLA4 antibodies.

Previous studies have shown a role for several types of tumor cells in immunity, including CD4⁺CD25⁺ T-regulatory cells, type 1 regulatory cells, natural killer T cells, and immature myeloid cells. The best characterized of the immunoregulatory cells are the T-regulatory cells. The exact mechanism of action and the nature of the antigen recognition of T-regulatory cells are still under debate, but recent studies suggest that T-regulatory cells can recognize self-antigens, including tumor-associated antigens, with high avidity and, when stimulated, suppress autoimmunity, tumor immunity, and graft rejection (13–15). The type 1 regulatory cells comprise a subset of CD4⁺ T cells that are induced by antigen-specific activation in the presence of interleukin-10 (16). Such type 1 regulatory cells can induce T-cell anergy and suppression of immune responses, primarily via the production of high levels of cytokines interleukin-10 and transforming growth factor- β (17). The broadly immunosuppressive role of cytokines produced by type 1 regulatory cells suggests that these cells could play a significant role in shaping the tumor microenvironment to favor the growth of tumor cells. Invariant natural killer T cells from both humans (expressing the V α 24 TCR chain) and mice (V α 14 chain) are strongly activated by the marine sponge-derived glycolipid, α -galactosylceramide, leading to the rapid secretion of both T_H1 and T_H2 cytokines (18–21). In addition to a diminished ability to proliferate in response to α -galactosylceramide, invariant natural killer T cells produce little IFN- γ while still maintaining functional interleukin-4 production (22–25). This defect seems to be reversible *in vitro* by stimulation with α -galactosylceramide-loaded dendritic cells,

suggesting a possible therapeutic means to relieve invariant natural killer T-induced immune suppression in cancer patients (24). Finally, there is accumulating evidence that progressive tumor growth is associated with an increased frequency of immature myeloid cells that can inhibit tumor-specific T lymphocytes (26, 27). Although the precise mechanism of action on T cells has yet to be fully elucidated, there is some indication that immature myeloid cells act in part through down-regulation of the CD3 ζ chain on responding CD8⁺ T cells (28, 29). As evidence mounts to suggest that the balance of immature and mature myeloid cells *in vivo* can have a significant effect on both naturally occurring and vaccine-induced antitumor T-cell responses, it is becoming increasingly apparent that effective cancer immunotherapy may require correction of aberrant myeloid cell differentiation frequently observed in tumor-bearing hosts.

Several membrane-associated factors expressed by tumor cells have also been shown to inhibit T-cell function. Arguably, the most important of these is PD-L1/B7-H1, which engages the inhibitory receptor on activated T cells called PD-1 (30). A study of the function of PD-L1 in a preclinical setting discovered that most tumor cells up-regulate PD-L1 expression on IFN- γ treatment, including B16 melanoma (31). Using TCR transgenic/PD-1-deficient T cells, absence of PD-1 was associated with markedly improved tumor rejection *in vivo*, under conditions in which even CTLA-4-deficient T cells did not reject. In addition, administration of a polyclonal antibody against PD-L1 has been shown to promote tumor rejection in other models (32). Together, these results support the development of reagents to block PD-1/PD-L1 interactions for clinical investigation. Other gene expression profiling experiments have revealed that transcripts that encode metabolic factors that limit T-cell function also are commonly expressed in metastatic melanoma lesions. The molecule furthest along in exploration is indoleamine-2,3-dioxygenase. The availability of a straightforward inhibitor of indoleamine-2,3-dioxygenase activity makes it possible to consider clinical investigation of this strategy.

There are a number of multiple redundant mechanisms that inhibit the immune response. Future goals should be to identify which ones are the most important for particular tumors and to determine reagents that will be able to inhibit those regulatory mechanisms. Future challenges in this area include the identification of unique regulatory cell markers that can be used to more specifically target these cells *in vivo* and a more accurate characterization of the molecular nature of immune suppression. In addition, gene expression profiling of metastatic tumors before and after therapy should be done to use an unbiased approach toward identifying factors that predict clinical response.

Molecularly Targeted Approaches in Advanced Disease

Clinical trials of chemotherapy in melanoma have failed to show superiority of one regimen over another. Currently, the only standard cytotoxic agent used in melanoma treatment is dacarbazine. Additional pharmacologic agents are urgently needed. An increasing number of potential targeted therapeutic agents have been identified, including sorafenib, farnesyltransferase inhibitors, and imatinib mesylate. In addition, the

potential of antiangiogenic agents in the treatment of patients with melanoma, either as single agents or in combination, has yet to be fully explored. It is more likely that combinations of antiangiogenic agents with either chemotherapy or other targeted therapy will be needed to produce significant clinical benefit.

Single-agent sorafenib, an inhibitor of mutant and wild-type BRAF as well as the vascular endothelial growth factor and platelet-derived growth factor receptors, is associated with few objective responses and a modest degree of tumor stabilization (33). Two clinical trials combining sorafenib with chemotherapy are completed or in progress. The most extensively evaluated combination has been sorafenib with carboplatin and paclitaxel (34). These two chemotherapy agents have long been known to synergize, and enhancement of each agent by sorafenib has been observed in nonmelanoma models. In a single-arm phase 2 trial, this regimen was associated with an objective response rate and progression-free survival that exceeded results previously obtained with this chemotherapy combination alone in patients with melanoma. Considering that prior systemic therapy for metastatic disease had failed in many patients in this trial, the results are encouraging.

The only clinical agents that affect RAS activity are the farnesyltransferase inhibitors. In melanoma, where a small subpopulation of tumors is promoted by NRAS mutations, the therapeutic value of farnesyltransferase inhibitors is currently being evaluated in a phase 2 trial. It has yet to be determined if a positive interaction with chemotherapy might exist with farnesyltransferase inhibitors in melanoma, but such studies in an NRAS mutant population seem justified by preclinical data (35).

Imatinib mesylate is an agent that is potent against both c-kit and platelet-derived growth factor receptor- β , potential therapeutic targets in patients with melanoma based on preclinical evidence (36, 37). Imatinib is not associated with significant single-agent activity in phase 2 trials (38), but the value of this agent in specific subsets of patients or in combination with chemotherapy is unknown.

Although the number of therapeutic targets in melanoma is increasing, the order of importance of those targets is debatable. Obviously, the mitogen-activated protein kinase pathway deserves much study because of its frequent perturbation in melanoma. The critical role played by the mitogen-activated protein kinase pathway in cell survival is further supported by multiple studies with small interfering RNAs and pharmacologic inhibitors, showing the adverse consequences of raf or mitogen-activated protein/extracellular signal-regulat-

ed kinase blockade. Despite our increasing knowledge of the regulation of the mitogen-activated protein kinase pathway, it remains unclear how its inhibition results in melanoma cell death. Ongoing laboratory and clinical studies need to clarify this, so that this emerging class of novel therapeutic agents can be most effectively used.

Summary Statement

Early detection is currently a major, but perhaps underemphasized, aspect of melanoma treatment. Efforts need to be focused in the advocacy community and the medical education community to encourage early detection practices. Patients need to realize that melanoma is treatable in 90% of cases, and that it is their responsibility to discover the lesions and seek treatment. In addition, if more physicians were trained to perform an effective biopsy as part of the standard physical examination, this would probably do more to cure melanoma than any pharmacologic agent. Although melanoma is a curable disease, as more and earlier-stage melanomas are detected, an increasing fraction of all melanoma deaths will come from patients whose lesions were initially considered low risk. Additional study of this group of patients is needed to identify prognostic factors.

In addition, staging systems need to evolve as new important risk factors become evident based on multicenter evaluations of prognosis. Prognostic modeling can be an adjunct to the framework of staging to aid in the better discrimination of patient risk and better selection of surgical and systemic therapies. Also needed is a universal and standardized approach for tissue banking of primary and lymph node samples and blood samples for future genetic analysis. This should be a standard protocol in all institutions where melanoma research is conducted and requires the active participation of clinicians and pathologists.

Although some promising leads have developed in the treatment of metastatic melanoma, it is unlikely that in the near future, a higher percentage of patients with metastatic disease will be cured. For the foreseeable future, the best chance to affect the natural history of the disease remains early detection and adjuvant therapy for those patients at high risk. Although current adjuvant therapy comes with significant toxic effects, opportunities exist for identifying mechanisms of action and predictive markers that might limit therapy to those most likely to benefit in addition to facilitating the development of more effective alternative regimens.

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