State of the Science

An Overview of NEW AND EXISTING THERAPIES for Metastatic Melanoma

by Sanjiv S. Agarwala, MD

In 2006, an estimated 62,190 Americans developed melanoma and 7,910 deaths were attributed to the disease.[1] Survival in melanoma is almost completely influenced by stage. Options for treatment of American Joint Committee on Cancer (AJCC) stage IV melanoma (distant metastases) are of limited therapeutic value as evidenced by the close association between the number of new stage IV patients diagnosed annually (8,000) and the death rate for the disease. Long-term remissions with standard chemotherapy agents are virtually unknown and aggressive immunotherapy options can cure only a handful of highly selected patients. Clearly the therapy of advanced melanoma represents an area of major unmet need.

Chemotherapy

The only chemotherapy agent approved by the Food and Drug Administration (FDA) for metastatic melanoma is dacarbazine (DTIC), an alkylating agent. Response rates with DTIC, historically reported to be as high as 20 percent, are now confirmed to be only 7.2-7.5 percent in two large recent randomized trials.[2,3] Median time-to-progression in these trials was less than two months with most patients progressing at the time of their first scan assessment for response. Complete responses and long-term remissions with DTIC chemotherapy are extremely rare.

Temozolomide (TMZ), also an alkylating agent, is an imidazotetrazine derivative that is converted to the same active metabolite as DTIC. TMZ has some potential advantages over DTIC in that it is orally administered, almost 100 percent bioavailable, and penetrates the central nervous system (unlike DTIC). A randomized trial of TMZ vs. DTIC conducted in Europe showed similar response rates and survival for both agents.[4] TMZ has modest activity in brain metastases from melanoma[5] and is approved for use in certain malignancies of the central nervous system. Although not FDA-approved for metastatic melanoma, TMZ is widely used, particularly in the community setting.

Other chemotherapeutic agents that have been tested in melanoma include:[6]

- The nitrosoureas (carmustine, lomustine)
- Fotemustine (not available in the U.S.)
- Vinca alkaloids
- Platinum analogues (cisplatin, carboplatin)
- The taxanes (paclitaxel, docetaxel).

Response rates with these agents are not superior to those with DTIC. They are not often used as single agents in the treatment of this disease but have been components of combination regimens.

The poor response rates obtained with single-agent chemotherapy led to the exploration of several combination chemotherapy regimens. Historically the regimen most widely used in the U.S. has been the "Dartmouth Regimen," a four-drug combination of dacarbazine, cisplatin, carmustine, and tamoxifen. Initial reported results with this regimen showed high response rates of >40 percent and led to speculation that tamoxifen was a critical component of this regimen.[7] However, subsequent studies not only showed that tamoxifen was ineffective in the treatment of melanoma,[8,9] but also that the Dartmouth Regimen was not superior to single-agent dacarbazine in an important randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG).[10] This and other trials have conclusively shown that there is no benefit for combination chemotherapy over single agents in the treatment of metastatic melanoma and this approach can no longer be recommended.

Immune Therapy

The unique relationship between melanoma and the immune system has been exploited with the development of several immunotherapeutic agents. The most extensively investigated agents in this class are the cytokines, of which Interleukin-2 (IL-2) is the most widely used in AJCC stage IV melanoma.

IL-2 plays a central role in the immune system by modulating the immunological effects of key cells: it stimulates cytotoxicity in T lymphocytes and natural killer (NK) cells and activates B-cells and macrophages.[11] IL-2 has been administered in various doses and schedules—low, intermediate, and high. The technique of administering high doses of IL-2 as an intravenous bolus once every eight hours (HDB IL-2) was developed by the National Cancer Institute based on animal models indicating that antitumor activity with this agent was dose-dependent.[12] Doses utilized were 600,000-720,000 units/kg every 8 hours from days 1-5 (cycle 1) and 15-19 (cycle 2) with a maximum of 14 doses per cycle or 28 doses per course (1 course = 2 cycles). In eight clinical trials involving 270 patients at several institutions, an objective response rate of 16 percent was noted, with a durable response rate of 4 percent.[13] The median response duration was 8.9 months (range 4 to 106+ months). Furthermore, 28 percent of responding patients, including 59 percent of those patients who achieved a complete response remained progression free at a median follow-up of 62 months, suggesting the possibility that these patients may be "cured." Based on these data, HDB IL-2 received approval by the FDA for the

treatment of metastatic melanoma in 1998. Efforts to improve the results of HDB IL-2 with the use of adoptive immunotherapy such as simultaneous administration of lymphokine activated killer (LAK) cells have not been successful.[14]

The administration of HDB IL-2 is associated with major toxicities, including a capillary leak syndrome leading to hypotension, renal insufficiency, and hypoxia, and these toxicities have precluded the drug's widespread application. The use of high-dose IL-2 is currently limited to specialized programs with experienced personnel, and is only appropriate for patients with good performance status and organ function.[15]

Low dose, subcutaneously administered regimens of IL-2 either as a single agent or in combination with other agents have not produced durable responses[16] and are no longer recommended for use in clinical practice.

Chemo-immunotherapy (Biochemotherapy)

Although at first glance counterintuitive, the combination of chemotherapy and immunotherapy in melanoma has not been antagonistic and results with these regimens were promising in Phase II studies. Broadly, two approaches have been tested: sequential chemotherapy (cisplatin, vinblastine, and dacarbazine, CVD) followed by immunotherapy (IL-2 given by continuous infusion at 9 MIU/m^2 and IFN-α) or concurrent chemo-immunotherapy. Both approaches showed similar results in Phase II trials with overall response rates between 40-60 percent and a long-term remission rate of about 9 percent. The concurrent approach was found to be more practical, less expensive, and less toxic with apparently equal efficacy.[17, 18] The sequential approach was recently compared to chemotherapy alone in a randomized trial conducted at the M.D. Andersen Cancer Center and, although response rate and time-to-progression were improved for the sequential biochemotherapy group, the survival difference was only of borderline significance, and toxicity was significantly worse.[19]

The concurrent CVD/IL-2/IFN-alfa regimen (BCT) was therefore adopted by the U.S. Intergroup as the experimental arm of an important randomized Phase III trial (ECOG 3695) and compared to CVD alone. This trial was stopped early after interim analysis revealed failure of the BCT arm to produce significantly better response rates, progression-free survival (PFS), overall survival (OS), or durable complete responses relative to chemotherapy alone. As expected, toxicity was greater for BCT.[20] Two other recent, randomized Phase III trials comparing BCT to chemotherapy conducted in Europe were also negative.[21,22] Based on these data, biochemotherapy for metastatic melanoma can no longer be recommended outside the context of a clinical trial.

It is clear from the preceding discussion that the currently known therapies for metastatic melanoma leave much to be desired. Efforts are now underway to approach the disease from a biological perspective and to seek out novel targets for therapy. Several potential targets for novel therapies now exist, including immunologic approaches, apoptotic therapies, and antiangiogenic therapies.

Novel Immunologic Approaches

Cytotoxic T-lymphocyte Antigen 4 (CTLA-4). A better understanding of the mechanisms of T-cell activation and regulation has identified the importance of the CTLA-4 antigen on T-cells. Essentially, for T-cell activation to occur, engagement of the T-cell receptor by antigen alone is insufficient; a second co-stimulatory signal is essential. This signal is provided by interaction between CD28 present on T-cells with members of the B7 family of antigens that exist on the antigen presenting cell. Subsequent to this process, the T-cell is activated and expresses CTLA-4. The latter acts as a negative feedback "brake" by competing with CD28 and itself binding to B7. This action reduces the T-cell response. It is logical therefore, that an antibody that would bind to CTLA-4 (anti-CTLA-4) would reduce or eliminate this negative signal and potentially lead to an active T-cell response.

Two human anti-CTLA-4 monoclonal antibodies have been developed and have entered clinical trials: MDX-010 (ipilumimab) and CP-675,206. Phase I and II studies have been conducted with antibody alone[23, 24] or in combination with peptide vaccines and chemotherapy.[25] Encouraging response rates of 15-20 percent have been observed and significant autoimmunity has been noted in some patients with a strong correlation between the two.[26, 27] Phase III trials with both of these exciting antibodies are ongoing and will determine if they are superior to currently available agents for metastatic melanoma.

Targeting Toll-like Receptor 9 (TLR9). TLRs are transmembrane proteins that serve as a "bridge" between innate and adoptive immune responses. Through interaction with TLR9, immunologically important cells such as dendritic cells and B-cells are activated. CpG 7909 is an oligodeoxynucleotide that binds to TLR9 and is undergoing evaluation in clinical trials alone or in combination with chemotherapy and vaccines.[28]

Targeting Signal Transduction Pathways

Signal transduction pathways are emerging as critical determinants of the malignant phenotype in many cancers. In melanoma, an important pathway is the RAS-MAPK signal transduction pathway. This pathway is highlighted by the discovery that activating mutations of B-RAF occur in up to 60-70 percent of melanomas.[29, 30] Mutations of B-RAF originally described in melanoma cell lines are usually missense mutations that lead to a valine for gluatamic acid substitution at an ATP-binding site (V600E). This mutation causes cells to become constitutionally activated.[29, 31]

Sorafenib is a small molecule that targets and inhibits B-RAF in addition to other tyrosine kinase receptors involved in angiogenesis such as vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3. A Phase I trial with sorafenib in solid tumors established the appropriate dose for Phase II trials as 400 mg PO bid.[32]

Although sorafenib does not appear to have activity as a single agent in melanoma,[33] the drug may exhibit synergy with chemotherapeutic agents. Sorafenib has been combined with DTIC and with the

combination of paclitaxel and carboplatin. The latter combination was investigated in a Phase I/II study at the University of Pennsylvania. A promising response rate of 31 percent was noted along with a stable disease rate of 54 percent. The median time-to-progression was an impressive 8.8 months.[34] Based on these results, two important Phase III trials are being conducted in the U.S., Canada, Europe, and Australia. ECOG is coordinating Intergroup Trial E 2603 which randomized chemotherapy-naïve patients with metastatic melanoma to carboplatin and paclitaxel and either sorafenib or placebo in a double-blind fashion. The trial is expected to accrue 800 patients with overall survival as the primary endpoint. The PRISM trial was of similar design but tested this regimen in patients who had progressed on or following chemotherapy with dacarbazine or temozolomide. The primary end point of this trial was progression-free survival. Accrual was completed in 2006 and a preliminary analysis did not show an improvement in PFS for the sorafenib containing arm over paclitaxel and carboplatin alone. [Presented at ASCO 2007].

Apoptotic Therapy

Oblimersen Sodium (G3139, Genasense®). The balance between pro- and anti-apoptotic pathways in the cancer cell is a critical determinant of cell viability and survival. An imbalance in favor of anti-apoptotic signals occurs frequently in cancer and imparts a survival advantage to cancer cells and resistance to chemotherapeutic agents. One of the most important and clinically relevant anti-apoptotic proteins is bcl-2. Overexpression of bcl-2 protein occurs in approximately 90 percent of melanomas and prevents apoptosis by preventing release of cytochrome c from mitochondria.[35,36]

Oblimersen sodium is an antisense oligonucleotide that targets bcl-2 messenger RNA. In preclinical models, co-administration of oblimersen and dacarbazine down-regulated bcl-2 levels in melanoma cell lines, and a subsequent Phase I clinical trial showed encouraging responses in patients with metastatic melanoma.[37] A large randomized Phase III trial was conducted in 771 chemotherapy-naïve metastatic melanoma patients of dacarbazine (1000 mg/m^2 every 3 weeks) with or without oblimersen (7 mg/kg/day by continuous infusion for 5 days). Although significant increases in progression-free survival (2.6 vs. 1.6 months; $p < 0.001$) and response rate (13.5 percent vs. 7.5 percent; $p=0.007$) were noted, there was only a trend to a benefit for overall survival (9.0 vs. 7.8 months; $p=0.77$).[3] Interestingly, the baseline LDH (lactate dehydrogenase) level emerged as an important treatment interaction—oblimersen had a significant effect in survival for those patients whose baseline LDH was not elevated (11.4 vs. 9.7 months; $p=0.02$). This latter observation underscores the importance of LDH in melanoma prognosis as already exemplified by the revised AJCC staging system.[38]

In the last decade, the approach to treating advanced melanoma has undergone a paradigm shift

Antiangiogenic Therapy

Bevacizumab. The mechanism of action of antiangiogenic agents is based upon reduction of new vessel growth within tumors, regression of existing vasculature, and also improvement of delivery of chemotherapeutic agents into the tumor microenvironment. Bevacizumab is a recombinant humanized monoclonal antibody that targets VEGF. A small Phase II trial of bevacizumab (15mg/kg every 2 weeks) with and without low-dose subcutaneous IFN-alfa (1 MU daily) in 16 patients showed two responses.[39] Additional Phase II trials with bevacizumab are ongoing in combination with carboplatin and paclitaxel and the epidermal growth factor inhibitor, erlotinib.

The integrins. Specifically, αVβ3 and αVβ5 are targets for antiangiogenic therapy that is overexpressed in melanoma cells. MEDI-522 (Vitaxin®), a novel humanized monoclonal antibody, targets αVβ3 and was tested in a randomized Phase II trial of DTIC vs. MEDI-522 alone. A response of 13 percent was seen in the combination arm as compared to 0 percent in the MEDI-522 alone arm.[40] A Phase III trial with this agent is planned. Another monoclonal antibody that targets the integrins αVβ3 and αVβ5 is CNTO-95 and a Phase I/II trial with this agent is being conducted in the United States.

Thalidomide. This agent has re-emerged in cancer therapy due to its potential angiogenic effects. Combination trials of thalidomide in combination with temozolomide chemotherapy were initially promising,[41, 42] but more recent results with this regimen have been disappointing. Lenalidomide (CC-5013) is a newer analogue of thalidomide that also possesses immunomodulatory effects. It was tested in two randomized trials in metastatic melanoma, but both trials were stopped due to failure to achieve the primary interim therapeutic endpoint.

A Work in Progress

In the last decade, the approach to treating advanced melanoma has undergone a paradigm shift from a blind approach using chemotherapy and non-specific immunostimulants to a biologically driven strategy using targeted agents. Clearly, much work remains to be done, both in terms of clinical trials and the collection of biologically relevant tissue to understand mechanisms of resistance and response to these new and exciting therapeutic agents. It is still a "truism" that the standard of care for this disease remains a clinical trial and perhaps the best service we can offer

our patients is the encouragement to participate in this important effort.

Sanjiv S. Agarwala, MD, is chief of medical oncology at St. Luke's Hospital & Health Network in Bethlehem, Pa.

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