Ten Years of Progress in Melanoma

The surge in new cases and deaths from melanoma began a few decades ago and continues unabated (Table 1). In the United States, melanoma is increasing in men more rapidly than any other malignancy and in women more rapidly than any other malignancy except lung cancer. The lifetime risk of developing melanoma in the United States is now estimated to be 1 in 36 men and 1 in 55 women.

Although these trends are daunting, the past decade brought important advances, including a better understanding of risk and prognostic factors, discovery of aberrant signaling pathways driving melanoma, and FDA approval of targeted immunotargeted and molecularly targeted therapies. This article details these areas of progress.

### Epidemiology

In 2006, the International Agency for Research on Cancer Working Group moved tanning devices to group 1 (carcinogenic in humans). The WHO recommends a ban on indoor tanning for children younger than 18 years. These authoritative studies document the health risks of artificial tanning devices, particularly the risk of developing melanoma. Marketing efforts by the indoor tanning industry target teenage and young adult women; far more young women undergo indoor tanning than young men. This highlights the need for better education and broad societal change with respect to unnecessary ultraviolet irradiation, particularly in this segment of the population. On January 1, 2012, California became the first state to ban use of indoor tanning beds in all children younger than 18 years, and other states are considering similar restrictions.

### Staging

The sixth edition of the AJCC staging system (2002) defined Breslow thickness and ulceration but not level of invasion to determine T stage. The most recent analysis of the AJCC melanoma staging database for stage I and II patients indicates that mitotic index is a powerful and independent predictor of survival. In a multifactorial analysis, mitotic index was the second most powerful predictor of survival after tumor thickness. In the current version of the AJCC guidelines (2010), mitotic index replaces Clark level as a criterion for upstaging patients with a melanoma of 1 mm or less from stage IA to IB.

### Workup

A common scenario observed in NCCN melanoma clinics is the arrival of newly diagnosed asymptomatic patients with stage I and IIA disease who have undergone staging PET/CTs, MRIs, or both. Although a workup to establish the extent of disease before surgery has value, current imaging techniques have a very low yield in...
asymptomatic patients with stage I and II melanoma, and the risks for false-positives (with attendant invasive biopsies) often outweigh the low yield of true-positives. The NCCN Melanoma Panel recommends that no 3-dimensional imaging be performed for asymptomatic patients with stage I and IIA melanoma; this imaging is only recommended to evaluate specific signs and symptoms of disease. Adoption of this guideline by physicians across the United States will reduce patient anxiety and the risks of overtreatment, and may save substantial health care resources.

In the stage III melanoma setting, the yield of 3-dimensional imaging is also low, estimated to be 5% or less in asymptomatic patients with microscopic nodal metastases. Patients with ulcerated primaries or palpable nodal metastases have a somewhat higher rate of detection of metastases on imaging, but concerns remain regarding false-positives. PET/CT may be more useful than conventional CT in the workup of patients who have relatively high pretest probabilities of occult metastatic disease (eg, patients with stage IIIB and IIIC melanoma).

Treatment

Adjuvant Therapy

High-dose interferon α-2b (HD IFN α-2b) was approved by the FDA in 1995 for adjuvant therapy of resected stage IIB and III melanoma based on the results of ECOG E1684. Results of E1690 were presented in 2000 and confirmed an improvement in relapse-free survival (RFS) with HD IFN α-2b but no effect on overall survival (OS). Longer follow-up of 713 patients treated with HD IFN α-2b versus observation on E1684 and E1690 were published in 2004 and confirmed a statistically significant improvement in RFS but found no statistically significant improvement in OS. Subsequent studies by the EORTC of pegylated interferon versus observation in patients with resected stage III melanoma also showed an improvement in RFS but no effect on OS. Crossover to interferon after nodal relapse in patients in the observation groups may have confounded the ability to detect an OS effect of adjuvant interferon.

For the past decade, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Melanoma have included interferon (either HD IFN α-2b or, more recently, pegylated interferon) as an option for adjuvant therapy of resected high-risk melanoma, based on the randomized trial evidence cited earlier (to view the most recent version of these guidelines, visit NCCN.org). This recommendation is designated category 2B by the NCCN Melanoma Panel, reflecting differences of opinion among committee members concerning the therapeutic index of interferon in the adjuvant setting. The committee continues to strongly support consideration of a clinical trial in the adjuvant setting (eg, E1609, a randomized phase III trial of HD IFN α-2b vs. ipilimumab, 3 mg/kg, vs. ipilimumab, 10 mg/kg; ClinicalTrials.gov identifier: NCT01274338).

Surgery

Sentinel lymph node biopsy (SLNB) allows detection of subclinical nodal metastases, enhances pathologic staging, and identifies patients at higher risk of relapse who may be candidates for additional surgery or adjuvant therapy. The international, prospective, randomized MSLT-I trial evaluated the efficacy and safety of the procedure. An improvement in 5-year disease-free survival was seen in patients with intermediate-thickness melanoma who underwent SLNB. However, no significant improvement in melanoma-specific survival was seen in these patients compared with those who underwent initial wide local excision followed by lymphadenectomy if necessary. The NCCN Melanoma Panel recommends SLNB for patients with stage IB through IIC
melanoma; the committee has refined algorithms to identify patients with stage IA melanoma who may be candidates for SLNB. In patients found to have a positive sentinel node, the role of completion lymphadenectomy remains undefined. MSLT-II is currently enrolling patients randomized to completion lymphadenectomy versus close observation (ClinicalTrials.gov identifier: NCT00297895).

**Systemic Therapy**

After struggling for decades with limited success, the melanoma community recently ushered in a new era of hope for patients with metastatic/unresectable melanoma. Ipilimumab is a human monoclonal antibody that binds to the cytotoxic T-lymphocyte antigen-4 (CTLA-4), blocks the corresponding immune checkpoint signal, and results in lymphocyte proliferation and immune stimulation. The FDA approved ipilimumab monotherapy (3 mg/kg every 3 weeks for 4 cycles) for unresectable and/or metastatic melanoma, based on results of a phase III randomized trial. HLA-A*0201–positive patients who had experienced progression despite previous therapy were randomized to a peptide vaccine (gp-100), ipilimumab plus gp-100 vaccine, or ipilimumab monotherapy. OS was longer in the ipilimumab-containing arms (10.4 months) compared with the gp-100 vaccine arm (6.4 months). Although the response rate in the ipilimumab monotherapy group was only 11%, most responses were durable, with 60% of responses continuing longer than 2 years. A second randomized phase III trial comparing dacarbazine and ipilimumab (10 mg/kg) versus dacarbazine and placebo showed longer median OS with ipilimumab and dacarbazine (11.2 months) versus dacarbazine alone (9.1 months); corresponding results for 3-year survival were 21% vs. 12%.

Treatment with ipilimumab may be associated with immune-related adverse events (irAEs), ranging from mild to life-threatening severity, and including rash, colitis, hepatitis, and hypophysitis. The NCCN Guidelines for Melanoma address the selection of patients who are appropriate candidates for this therapy. With prompt diagnosis and proper treatment, these irAEs can be successfully managed in most cases. Remaining questions include 1) the optimal dose (3 vs. 10 mg/kg), 2) the role of ipilimumab as adjuvant therapy, and 3) the role of combinations of ipilimumab with adoptive T-cell transfer protocols, molecularly targeted agents, or other immunomodulators. Clinical trials to address these questions are underway or in development.

Advances during the past decade in understanding the molecular pathways that drive melanoma led to another major area of progress in systemic therapy. Activating mutations in *BRAF* (a part of the RAS-RAF-MEK-ERK-MAP kinase pathway) are found in approximately half of patients with metastatic cutaneous melanoma. Vemurafenib is a potent and selective inhibitor of oncogenic *BRAF*. In a phase III trial, 675 patients with metastatic melanoma and *BRAF* mutation (as detected with the COBAS 4800 V600E mutation test) were randomized to vemurafenib (960 mg orally, twice daily) versus dacarbazine (1000 mg/kg every 3 weeks). The hazard ratio for death in the vemurafenib group was 0.37 (P < .001). Approximately 80% of patients treated with vemurafenib had some degree of tumor regression; the response rate was 48%. Despite the high level of antitumor activity, the development of resistance to vemurafenib remains a problem. Issues to address include strategies to block *BRAF*-driven growth for a longer time (eg, MEK inhibitors sequentially following *BRAF* inhibitors or in combination with *BRAF* inhibitors) and combinations of vemurafenib with immunotherapies such as ipilimumab.

Substantial progress has been made during this decade in understanding the biology of adoptive T-cell therapy of melanoma, including the incorporation of more effective immune conditioning regimens, identification of the role of central memory
phenotype T cells, and the development of T cells genetically engineered to recognize targets that are specific to melanoma or its related vasculature.\textsuperscript{13,14} Novel agents under clinical development (anti–PD-1 and anti–PDL-1), molecularly targeted agents (MEK inhibitors), novel cytokines (IL-15, IL-21), and other agents suggest that the prospects for successful treatment of metastatic melanoma are likely to improve significantly in the next 10 years.\textsuperscript{15}

References