Treatment Options Expanding for Advanced Melanoma

Presented by John A. Thompson, MD

Abstract

Immunotherapies and BRAF and MEK inhibitors have dramatically improved outcomes in advanced melanoma. The availability of these novel approaches has necessitated changes to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). The NCCN Guidelines feature algorithms that aid clinicians in selecting initial therapy, which now includes anti-programmed death protein receptor-1 PD-1 inhibitors among the recommended systemic therapy options for patients with metastatic or unresectable disease. (J Natl Compr Canc Netw 2015;13:673–675)

"The NCCN Guidelines for melanoma have come a long way," said John A. Thompson, MD, Co-Director of the Melanoma Clinic at the Seattle Cancer Care Alliance, member of the Clinical Research Division of the Fred Hutchinson Cancer Research Center, Professor of Medical Oncology at the University of Washington School of Medicine, and Vice-Chair of the NCCN Melanoma Panel. A more refined treatment approach is now possible by classifying patients with metastatic or unresectable disease according to *BRAFV600E* mutation status, bulk and tempo of disease, and performance status, Dr. Thompson continued. Considering the relevant patient and disease characteristics, he added, "We can put the patient on the appropriate pathway for treatment, including suggested frontline and second-line therapies."

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Dr. Thompson has disclosed that he has received consultant fees or honoraria from Amgen, Inc.

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In the 2015 update to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Melanoma, the systemic therapy section was significantly revised by converting the "Preferred Regimens" and "Other Active Regimens" lists into algorithms for the treatment of patients with metastatic or unresectable disease according to *BRAFV600* mutation status. In addition, a new "Principles of Immunotherapy and Targeted Therapy" section discusses the effectiveness of these novel treatments, with recommendations for managing related toxicities.

Importantly, the recommended systemic treatment options for metastatic or unresectable melanoma now include (depending on patient and disease characteristics) ipilimumab, dabrafenib plus trametinib, pembrolizumab, and nivolumab. The updated NCCN Guidelines for Melanoma elevate the anti-programmed death protein receptor-1 (PD-1) agents to the frontline setting for metastatic or unresectable disease. Anti-PD-1 antibodies are now suggested as options for frontline therapy, because the panel assessed that response rates are higher and toxicity is lower than with ipilimumab.

Immunotherapy Options for Patients With Unresectable or Metastatic Disease

In selecting treatment for a patient with metastatic or unresectable disease, key factors include *BRAF* mutation status, tumor bulk, and tempo. An important consideration is whether the patient "has time for an immune response to develop," he noted.

Using Ipilimumab

The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor ipilimumab has showed an overall survival advantage compared with active controls in 2

major trials in patients with metastatic melanoma.[1,2] In a recent pooled analysis of long-term survival data from phase II and III trials in advanced melanoma, 3-year survival rates were 26% for treatment-naïve patients and 20% for previously treated patients.[3]

Response to ipilimumab can be delayed, and some patients may appear to progress before their tumors regress. "Don't abandon treatment prematurely," he advised.

Clinicians must also become familiar with immune-related adverse effects, especially gastrointestinal toxicity. Algorithms for managing toxicity related to ipilimumab are found at hcp.yervoy.com. For moderate toxicity (4–6 stools per day, abdominal pain, blood or mucus in stool), withhold ipilimumab and if symptoms persist beyond 1 week, prescribe a steroid, he told attendees. For severe toxicity (≥ 7 stools/day over baseline, peritoneal signs consistent with perforation, ileus, fever), permanently discontinue ipilimumab, evaluate for bowel perforation, consider endoscopy, and give steroids until improvement, then taper over 1 month.

Incorporating PD1 Inhibitors

Pembrolizumab and nivolumab are currently FDA-approved for the treatment of metastatic or unresectable melanoma with disease progression following ipilimumab and, if with *BRAF*600 mutation positive, a BRAF inhibitor. The NCCN Guidelines for Melanoma now include the PD-1 inhibitors as front-line treatment options for metastatic or unresectable disease.

As Dr. Thompson explained, "Clinicians questioned why they had to give a new metastatic patient ipilimumab when there are other immune checkpoint inhibitors that have a lower risk of serious toxicity and a higher response rate. The melanoma panel evaluated the multiple new publications concerning checkpoint inhibitors, and we moved up the 2 PD-1 inhibitors. I believe they belong in the frontline category."

More than one fourth of patients with melanoma refractory to ipilimumab have shown response to pembrolizumab, with many ongoing responses.[4] In previously untreated patients with *BRAF* wild-type metastatic disease, nivolumab was shown to significantly improve progression-free and overall survival, with a 1-year overall survival rate of 72.9% compared with 42.1% in the control (dacarbazine monotherapy) arm (hazard ratio [HR], 0.42; $P<.001$), and median progression-free survival of 5.1 versus 2.2 months, respectively (HR, 0.43; $P<.001$).[5] Whether PD-L1 expression will be a useful biomarker in patients treated with anti-PD-1 therapy is still unclear, as positive staining does correlate with higher rates of response; however, responses are also observed in PD-L1–negative patients.

Immunotherapies in Development

Although not currently recommended by the NCCN Guidelines for Melanoma and not approved by the FDA, combinations of PD-1 inhibitors and ipilimumab are under active investigation. The combination of ipilimumab and nivolumab was recently reported to induce an objective response rate of 59% and complete response rate of 22% in patients with metastatic melanoma. This combination immunotherapy was also associated with a rate of serious (grade 3 or 4) toxicity of 54%, underscoring the importance of early recognition and treatment of immune-related toxicities.[6]

An exciting immunotherapy approach in development is adoptive T cell transfer. In a pooled analysis of 3 trials in patients with progressive metastatic melanoma, investigators evaluated the ability of adoptive cell transfer using autologous tumor-infiltrating lymphocytes (TILs) to mediate durable complete regressions in heavily pretreated patients who underwent lympho-depleting preparative regimens. Objective response rates were 49% to 72%, with 22% of the 93 patients showing complete tumor regression. The actuarial 3- and 5-year survival rates for the entire group were 36% and 29%, respectively, but for the 20 patients with complete response, rates were 100% and 93%.[7]

Ongoing research in the area of T-cell transfer "are telling us about the antigens that the immune system recognizes," he said.

These strategies are "just the beginning" of harnessing the immune system in melanoma, Dr. Thompson indicated. Other immunotherapy approaches include involvement of cytokines (IL-15, IL-21), immune agonist antibodies (OX-40, 41BB), vaccines, and receptor-directed cytokines.

Molecularly Targeted Agents

Among all cancers, melanoma shows the most somatic mutations,[8] many consistent with damage

from ultraviolet light.[9] Some of these are driver mutations (eg, *BRAF*, *nRAS*, *cKIT*) but many are silent.[9] Nonetheless, these silent mutations may be encoding abnormal proteins expressed by the melanoma cell, which means that the immune system might someday be directed toward recognizing these acquired mutated proteins, Dr. Thompson suggested.

Meanwhile, targeted drugs blocking *BRAF* and *MEK* signaling are important components of the treatment armamentarium for *BRAF*-mutated tumors and have better efficacy when used in combination. An interim analysis of the COMBI-d study presented at the 2014 ASCO Annual Meeting showed a 25% reduction in risk of progression (P=.035) and a 37% reduction in risk of death (P=.023) with dabrafenib plus trametinib compared with dabrafenib alone in patients with unresectable stage IIIC or IV, *BRAF* V600E/K mutant melanoma.[10]

Dermatologic toxicities are also reduced with the combination of dabrafenib and trametinib, "but other toxicities emerge," Dr. Thompson acknowledged. These may include pyrexia and chills, which can be managed with dose interruptions or reductions, or by the addition of low to moderate dose corticosteroids. The updated NCCN Guidelines for Melanoma provide some useful recommendations for managing toxicities.

Acquired resistance to targeted agents remains a treatment challenge. The mechanisms underlying this are being explored, with the hope of having a means of delaying or eliminating the development of resistance.

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