Evolving Therapies in the Clinical Management of Melanoma

PRESENTED BY LISA A. KOTTSCHADE, APRN, MSN, CNP, and SVETOMIR N. MARKOVIC, MD, PhD

From Mayo Clinic, Rochester, Minnesota

Presenters' disclosures of conflicts of interest are found at the end of this article.

https://doi.org/10.6004/jadpro.2019.10.3.9

Since 2011 there has been an explosion of drugs for the treatment of metastatic melanoma, including *BRAF* mutation–guided therapy with BRAF/MEK inhibitors—vemurafenib (Zelboraf) plus cobimetinib (Cotellic), dabrafenib (Tafinlar) plus trametinib (Mekinist), and encorafenib (Braftovi) plus binimetinib (Mektovi)—as well as the immunotherapies ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda). At JADPRO Live 2018, Lisa Kottschade, APRN, MSN, CNP, and Svetomir Markovic, MD, PhD, of Mayo Clinic, in Rochester, Minnesota, shared clinical data supporting emerging targeted therapies and immunotherapies used in the treatment of advanced/metastatic melanoma while detailing strategies to manage and mitigate potential adverse events of these agents.

CHANGES IN STAGING CRITERIA

With the release of the American Joint Committee on Cancer (AJCC) eighth edition cancer staging manual on January 1, 2018, significant changes were made to the criteria for T1 lesions and stage III disease, and new substage categories were added to stage III and stage IV. As Ms. Kottschade reported, T1a lesions are now defined as nonulcerative, and they are also thinner lesions (< 0.8 mm in thickness). A T1b lesion now is any melanoma with a thickness of 0.8 mm to 1.0 mm regardless of the ulceration status or any ulcerated melanoma less than 0.8 mm in thickness.

The big change in stage III, said Ms. Kottschade, is the addition of "in-transit/satellite/microsatellite" to each of the "N" subcategories along with the addition of a new stage IIID subcategory. There has also been a narrowing of patients considered stage IIIA, with upstaging of most stage III patients.

Finally, changes have also been made to the nomenclature for stage IV disease. A fourth "M" substage was added to account for the presence of any central nervous system (CNS) disease.

"I think this was a good move," said Ms. Kottschade. "Patients were previously all lumped together, but we know in melanoma that patients with CNS involvement really are in a category of their own."

UPDATES IN STAGE III MANAGEMENT: SURGERY

As Dr. Markovic reported, results of the MSLT-II trial, which random-

J Adv Pract Oncol 2019;10(3):252–255

ized nearly 2,000 patients with melanoma and sentinel-node metastases to either no further surgery following sentinel lymph node biopsy or completion of lymph node dissection, have changed practice (Faries et al., 2017). Although disease-free survival was better in the patients who underwent lymphadenectomy, overall survival at the 3-year time point did not show a difference.

"Patients with sentinel node–positive disease apparently do not benefit from complete lymph node dissection and should thus avoid the toxicities of further surgery," said Dr. Markovic.

However, Dr. Markovic added that "If you have a melanoma that is 5.0 mm, this result would probably not apply. This is still a multidisciplinary conversation we have to have with our surgeons."

UPDATES IN STAGE III MANAGEMENT: ADJUVANT THERAPY

As Ms. Kottschade reported, the past 5 years have seen improvements in the prevention of recurrence postsurgery for patients with melanoma with the approval of the checkpoint inhibitor ipilimumab and targeted therapies dabrafenib and trametinib. More recently, the results of CheckMate 238 demonstrated superior efficacy for nivolumab vs. high-dose ipilimumab for patients with stage IIIB, IIIC, or IV melanoma who were at high risk for recurrence (Weber et al., 2017). Nivolumab showed a statistically significant improvement in distant metastasis-free survival vs. ipilimumab, thus leading to the US Food and Drug Administration approval of nivolumab in the adjuvant setting, and investigators continue to look at the durable clinical benefit of this outcome, said Ms. Kottschade.

Another recent study, KEYNOTE-054, randomized high-risk, resected, stage III cutaneous melanoma patients to pembrolizumab or placebo and showed an improvement in recurrence-free survival for patients who received treatment (Eggermont et al., 2018). The study remains blinded for distant metastasis-free survival as well as overall survival, said Ms. Kottschade, but should lead to the regulatory approval of pembrolizumab.

Finally, in the adjuvant setting for patients with a *BRAF* mutation, although the combination of dabrafenib and trametinib trended towards improved 3-year overall survival vs. placebo, it did not reach statistical significance as outlined by the study (p = .000019; Long et al., 2017). However, the combination did result in a significantly lower risk of recurrence.

According to Ms. Kottschade, these three trials raise important questions for clinicians.

"Although nivolumab was approved for all stage III patients regardless of their substage, we really have to ask ourselves, is this an appropriate therapy for patients who are stage IIIA according to AJCC edition 8?" she observed.

In addition, Ms. Kottschade highlighted the lack of tissue available for *BRAF* testing and the lack of a direct head-to-head comparison in *BRAF*-mutated patients between targeted therapy and immunotherapy in the adjuvant setting. Furthermore, she said, there is confusion about what to do with patients who relapse on adjuvant therapy. Finally, Ms. Kottschade underscored the risk of lifelong toxicity for patients on adjuvant immunotherapy.

"That's an important conversation we really need to be having with our patients up front."

ADVANCES IN SYSTEMIC THERAPY FOR METASTATIC DISEASE

As Dr. Markovic reported, over the past 12 months in this rapidly developing field, the COLUMBUS study introduced the third combinatorial regimen for $BRAF^{V600E}$ and/or $BRAF^{V600K}$ mutated melanomas: encorafenib and binimetinib (Dummer et al., 2018; The other two combinations are vemurafenib plus cobimetinib and dabrafenib plus trametinib.) Although this was a complicated study, said Dr. Markovic, the message was very simple: the combination of encorafenib plus binimetinib vs. vemurafenib showed an advantage of the dual inhibition with respect to progression-free survival. Although basically a recapitulation of the prior combinatorial trials of BRAF and MEK inhibitors, said Dr. Markovic, this third combination offers a potential improvement vis-à-vis toxicity. Outcomes were also improved relative to prior phase III clinical trials, Dr. Markovic added, but these are not head-to-head comparisons.

An IDO inhibitor, epacadostat, failed to deliver in combination with pembrolizumab in a phase III study over pembrolizumab alone.

"These disappointing negative results put some cold water on the field of IDO inhibitors of metabolism within the tumor," Dr. Markovic observed.

MANAGEMENT OF IMMUNE-RELATED TOXICITY

As Ms. Kottschade explained, the advent of immunotherapy and targeted therapy has so dramatically altered the landscape of melanoma that many people are actually starting to use the word "cure." While these drugs have greatly improved survival, however, there is also significant associated toxicity, and if not properly managed, patients must discontinue therapy.

"Adverse events that occur via the activation of a patient's immune system can occur in any tissue, organ, or system," said Ms. Kottschade, who emphasized that they can be severe and sometimes fatal.

With a single anti–PD-1 agent, the rate of immune-related adverse events has been shown to be between 70% and 73%. With combination therapy, however, 95% of patients experience some sort of immune-related adverse event.

"Although grade 3 to 4 toxicity is limited to about 15% to 20% of patients receiving single-agent therapy, with dual checkpoint inhibition, more than 50% of patients have a severe reaction," said Ms. Kottschade.

The clinical spectrum of immune-related adverse events includes gastrointestinal, hepatic, endocrine, and pulmonary toxicities, but dermatologic toxicities are the most commonly seen with ipilimumab and PD-1 blockades. Up to 60% of patients will experience a dermatologic adverse event, which often manifests as a diffuse maculopapular rash. In the absence of rash, patients may also have pruritus and can develop vitiligo. While not life-threatening, said Ms. Kottschade, the latter can be very psychologically damaging to the patient.

"Up to 30% of patients experience itching with no observable rash, which can actually be worse for some patients," she added.

For dermatologic events, Mayo Clinic manages patients based on the amount of body surface area involved. For patients with 20% or less involvement, Ms. Kottschade and colleagues manage these patients symptomatically: oral antihistamines, topical agents, and sometimes diphenhydramine at nighttime.

With more body-surface-area involvement, however, steroids are used. Patients are also referred to dermatologic colleagues and therapy can be withheld.

Gastrointestinal toxicities include both diarrhea and colitis, which are separate entities, even though they often occur together.

"Colitis is usually associated with diarrhea but includes abdominal pain and imaging or endoscopic findings consistent with inflammation," said Ms. Kottschade, who noted that colitis appears more commonly with ipilimumab than with PD-1 inhibitors. "There have actually been fatal bowel perforations with patients treated with ipilimumab."

With respect to liver toxicities, these are mostly in the form of asymptomatic transaminitis. Hyperbilirubinemia can also occur with combination therapy, said Ms. Kottschade, but less than 15% are grade 3 to 4. Again, these toxicities are more common with the anti–CTLA-4 agent ipilimumab than PD-1 checkpoint inhibitors, and there have been a few cases of hepatic failure. For patients unresponsive to steroids, mycophenolate is sometimes used.

According to Ms. Kottschade, endocrine adverse events, including thyroiditis and hypophysitis, are probably the most difficult to diagnose and the easiest to treat, but these are events that usually last a lifetime.

"We see thyroid dysfunction in about 15% of patients, and I think this is a very underreported number," said Ms. Kottschade. "I tend to see it in about 30% to 40% of my patients."

Pneumonitis has also become a challenge and is occurring with greater frequency, said Ms. Kottschade. Most of the time, these patients can present asymptomatically, but can also decompensate very quickly.

Finally, multiple studies have been published on patients who develop rheumatologic immune-related adverse events. "These are very real and scary side effects that we can see in the clinic," said Ms. Kottschade.

MANAGEMENT OF ADVERSE EVENTS IN TARGETED THERAPY

As Ms. Kottschade reported, between 40% and 60% of patients with melanoma have a somatic mutation of *BRAF*^{V600}, and combination therapies with BRAF and MEK inhibitors have demonstrat-

ed significant improvement in progression-free and overall survival. However, one of the most common and frustrating side effects is pyrexia.

"With the combination of dabrafenib and trametinib, pyrexia occurs in approximately 50% of patients, with 5% being grade 3 to 4," said Ms. Kottschade. "These patients can experience severe chills, hypotension, dehydration, and even renal failure with severe pyrexia."

Dermatologic adverse events include various types of rash presentation and secondary cutaneous malignancies. Hepatotoxicity, cardiac toxicity, and other rare, serious adverse events, including rhabdomyolysis, uveitis, pneumonitis, hyperglycemia, hemorrhage, and panniculitis, can also occur in patients receiving targeted therapy.

"One advantage of targeted agents over immune checkpoint inhibitors is that the side effects will dissipate within a few days of stopping the drugs," said Ms. Kottschade. "However, advanced practitioners should be very cautious when switching patients back and forth between therapies."

Disclosure

Ms. Kottschade has acted as a consultant for Array BioPharma and Bristol-Myers Squibb and has received research funding from Bristol-Myers Squibb. Dr. Markovic has nothing to disclose.

References

Dummer, R., Ascierto, P. A., Gogas, H. J., Arance, A., Mandala, M., Liszkay, G.,...Flaherty, K. T. (2018). Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): A multicentre, open-label, randomised, phase 3 trial. *Lancet, 19*(10), 1315–1327. https://doi.org/10.1016/S1470-2045(18)30497-2

Eggermont, A. M. M., Blank, C. U., Mandala, M., Long, G. V., Atkinson, V., Dalle, S.,...Robert, C. (2018). Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *New England Journal of Medicine, 378*, 1789–1801. https://doi.org/10.1056/NEJMoa1802357

Faries, M. B., Thompson, J. F., Cochran, A. J., Andtbacka, R. H., Mozzillo, N., Zager, J. S.,...Elashoff, R. M. (2017). Completion dissection or observation for sentinel-node metastasis in melanoma. *New England Journal of Medicine, 376*(23), 2211–2222. https://doi.org/10.1056/NEJMoa1613210

Long, G. V., Hauschild, A., Santinami, M., Atkinson, V., Mandalà, M., Chiarion-Sileni, V.,...Kirkwood, J. M. (2017). Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *New England Journal of Medicine, 377*(19), 1813–1823. https://doi.org/10.1056/NEJMoa1708539

Weber, J., Mandala, M., Del Vecchio, M., Gogas, H. J., Arance, A. M., Cowey, C. L.,... Ascierto, P. A. (2017). Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *New England Journal of Medicine, 377*(19), 1824–1835. https://doi.org/10.1056/NEJMoa1709030