VIEWPOINT

Adjuvant Immunotherapy in Stage II Melanoma—Further Risk Stratification is Needed

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Currently, most patients with stage IIB and IIC melanoma are treated with surgery and undergo subsequent routine surveillance for disease recurrence by dermatologists. However, the recent US Food and Drug Administration approval of immune checkpoint inhibitors (ICIs) as adjuvant therapy in this population is causing a paradigm shift in the management of patients with localized melanoma. Of the 91 000 invasive melanomas diagnosed annually in the US, 9.2% are stage IIB/IIC compared to 13% of stage III-IV disease (the setting previously approved for immunotherapy).[1-3] As a result, this expansion in indication for ICIs could nearly double the size of the ICI-eligible melanoma population, with more than 8000 additional patients meeting treatment criteria annually.[4] Dermatologists, who have historically managed patients with stage IIB/IIC melanoma with surgeons (typically surgical oncologists), will need to adapt to a new clinical framework where increasing numbers of patients with localized melanoma will also require involvement of medical oncologists. In this Viewpoint, we will review the evidence for ICI use in the adjuvant setting; discuss the individual and societal risks, benefits, and costs associated with ICIs; and highlight the need for more targeted patient selection approaches to mitigate risks of ICIs and improve outcomes in this population.

Evidence for ICI Use in the Adjuvant Setting

The melanoma mortality rate was stagnant until novel treatment arrived in 2011 in the form of ICIs. These agents, which include inhibiting antibodies against cytotoxic T-lymphocyte antigen-4, programmed death-1 (PD-1), programmed death ligand-1, and lymphocyte activation gene-3, have dramatically increased survival initially among patients with metastatic disease (stage IV) and later as adjuvant therapy for patients with stage III disease.[1]

In December 2021, following publication of the KEYNOTE-716 study,[5] the Food and Drug Administration approved the expansion of ICIs as adjuvant therapy in this population. In this study, patients with completely resected stage IIB/IIC melanoma were randomly assigned to pembrolizumab (a PD-1 inhibitor) or placebo for up to 17 cycles. Recurrence-free survival rates at the second interim analysis of 3 years were 76.2% with pembrolizumab and 63.4% with placebo (a number needed to treat of 7.8).[5]

ICI Benefits Few Patients With Stage IIB/IIC Melanoma and Harms Many Others

The aim of adjuvant therapy is to eradicate distant disease that may not yet be clinically detectable. However, this represents a relatively small population in stage IIB/IIC melanoma. Specifically, although recurrence is not uncommon among patients with stage IIB/IIC melanoma and is seen in up to 37% of patients,[4] only one-third of these first recurrences are distant in the combined stage IIB/IIC population (30% of stage IIB and 52% of stage IIC). This equates to 14% of the entire stage IIB/IIC population for whom systemic therapy may improve mortality and another 22% for whom systemic therapy may reduce morbidity from mitigating localized/regional recurrence risk.[4] This reality highlights a shortcoming of American Joint Committee on Cancer (AJCC) staging for melanoma in its limited ability to accurately discern which patients with stage II melanoma will progress.

Additionally, not all ICI recipients will develop a robust antitumor response. Durable responses are seen in only about 50% of all treated patients.[1] Combining this information with the recurrence rates suggests that 7% of patients with stage IIB/IIC melanoma may experience a mortality benefit from ICI therapy and another 11% may experience reduced morbidity from the mitigation of locoregional recurrence. In total, approximately 18% of the treated population would benefit from ICIs. Additionally, it is not yet known whether the improvement in recurrence-free survival among ICI-treated patients with stage IIB/IIC melanoma will ultimately translate into improvements in melanoma-specific survival or overall survival—the outcomes that matter most.

For dermatologists, the adoption of ICI therapy in stage IIB/IIC melanoma demands a nuanced understanding of its impact on patient outcomes as well as its contribution to more treatment-related toxicities. Up to 70% of patients with melanoma treated with anti–PD-1 monotherapy experience immune-related adverse events (irAEs), with over 40% experiencing chronic irAEs and at least 20% experiencing cutaneous irAEs.[6] These toxicities may result in lifelong treatment, hospitalization, and even death. Notably, 11% of patients treated with pembrolizumab in the KEYNOTE-716 trial[7] experienced high-grade irAEs and 16% discontinued treatment due to toxicity.

Public Health Implications: High Individual and Societal Costs of Therapy

Dermatologists, partnering clinicians, patients, and societal stakeholders must recognize that the expansion of ICI therapy carries considerable economic consequences. The direct costs of complete ICI therapy range from $115 560 (pembrolizumab) to $213 342 (nivolumab), not including the direct and indirect costs of managing irAEs.[2] Mean direct 30-day costs of an individual irAE, including inpatient and outpatient expenditures, range from $17 570 to $30 534, with many patients affected by toxicities of more than 1 organ system

(including cutaneous, respiratory, central nervous system/psychiatric, gastrointestinal, rheumatologic, ocular, cardiac, hepatic, hematologic, and endocrine toxicities).[1] As a conservative estimate, ICI treatment for all patients with stage IIB/IIC melanoma would contribute $1.3 billion of annual direct costs.[1,2]

Risk Stratification Tools to Identify Optimal Candidates for ICI

Although the new clinical standard of care is to consider ICIs in all patients with stage IIB/IIC melanoma, adjuvant therapy based on AJCC staging alone may result in considerable negative consequences for an uncertain melanoma-specific survival or overall survival benefit among a minority of treated patients. Improving our ability to identify patients who may benefit from ICI therapy will become increasingly important in the use of these potentially life-prolonging therapies while minimizing the harms for patients who would derive no benefit, a position in agreement with the American Society of Clinical Oncology.[5]

Several recent efforts have achieved more robust risk stratification than AJCC stage alone and may serve as the first steps in addressing this knowledge gap.[4,8] One of these leveraged machine learning approaches to develop prognostic models for melanoma recurrence using clinical and histopathologic features. Although the final models incorporated contributions from more than 30 distinct features, Breslow thickness, mitotic rate, and patient age were consistently ranked among the most predictive of recurrence.[8] However, validation of these tools is ongoing, with a need to incorporate additional features such as digital imaging, genomics, and novel tumor biomarkers (eg, tumor T-cell fraction and circulating cell-free DNA) to continue improving their performance.[5] These models will also need to be tested prospectively to ensure clinical utility.

Conclusions

The current landscape of stage IIB and IIC melanoma has markedly shifted with the approval of adjuvant ICI. As more patients begin systemic treatment for localized melanoma, dermatologists, surgical oncologists, and now medical oncologists will need to help patients navigate the benefits and harms of adjuvant ICI therapy. This new treatment paradigm may help some patients avoid disease recurrence, but it may also cause harm, especially among those patients whose disease would never have recurred without treatment. Dermatologists and oncologists must continue to work together in the development and validation of more accurate risk stratification tools to ensure optimal patient selection for adjuvant ICI therapy to maximize benefit and minimize harm.

ARTICLE INFORMATION

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