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ASO PERSPECTIVES

Perioperative Therapy in Melanoma: Several Questions Still Remain

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Surgical resection is the treatment of choice in the majority of patients with melanoma. Nevertheless, the prognosis of patients with the disease at stages IIB–IV after complete resection is heterogeneous, and recurrences occur in 30–70% of cases. Currently, systemic adjuvant therapy after complete surgery in patients with high-risk melanoma is the standard treatment administered with curative intent.[1–4] Molecularly targeted treatment with BRAF and MEK inhibitors (dabrafenib with trametinib in *BRAF*-mutated cases), and immunotherapy with immune checkpoint inhibitors (anti-PD-1: nivolumab or pembrolizumab, and anti-CTLA-4: ipilimumab) administered as adjuvant therapy, significantly decreased risk of relapse.

A new approach to the treatment of locoregional advanced melanomas is a systemic preoperative treatment to further reduce the risk of recurrence and increase the cure rate. However, there are still a lot of open questions in terms of the choice/sequence of therapy, correct staging, and follow-up.[5]

Recently published results of clinical trials raised even more issues regarding the puzzle surrounding perioperative therapy. New data from 2022 imply that the use of adjuvant therapy in earlier stages of high-risk melanomas, without nodal metastases (IIB–IIC), improves relapse-free survival (RFS) and distant metastasis-free survival (DMFS). In the KEYNOTE-716 phase III clinical trial, pembrolizumab was used postoperatively for up to 1 year in patients with stage IIB or IIC melanoma. This led to a significant reduction in the risk of disease recurrence or death versus placebo.[6,7] The RFS rate was improved after 24 months from 73 to 81% [hazard ratio (HR) 0.64], but the difference in DMFS was only 6% at this timepoint ($p = 0.006$).[7] Pembrolizumab has been approved for adjuvant therapy in fully resected stage IIB/IIC melanoma; however, its use may be controversial without additional predictive biomarkers for evaluation of proper risk–benefit for the individual patient, as the number needed to treat to achieve benefit is as high as 12–13 cases. Convergent data were presented for the nivolumab phase 3 CheckMate-76K trial, which showed a statistically significant improvement in RFS with an adjuvant treatment in patients with completely resected stage IIB/IIC melanoma, compared with placebo. Data presented at the 2022 Society for Melanoma Research (SMR) Annual Meeting demonstrated that nivolumab yielded a 58% reduction in risk of death or disease recurrence compared with placebo [HR 0.42; 95% confidence interval (CI) 0.30–0.59; $p < 0.0001$], with the 12 month RFS rates 89% for nivolumab arm and 79% with placebo, but the difference in DMFS rates after 1 year was again only 5%.[8] These differences may evolve with longer follow-up, as the kinetics of recurrences in stage II disease can be delayed compared with stage III disease.[7] On the other hand, the positive effect of adjuvant immunotherapy with anti-PD-1 drugs should be outweighed in terms of grade 3–4 treatment-related adverse events, which occurred in 17% of patients treated with adjuvant pembrolizumab.

The effect with adjuvant immunotherapy on disease systemic relapses is not so dramatic as could be expected, and even further escalation of this therapy with dual checkpoint immunotherapy (anti-PD-1 and anti-CTLA-4) failed in the improvement of RFS and DMFS (as demonstrated in the CheckMate 915 trial).[9] This might be related

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to a limited number of tumor-specific T cells that could be potentially activated by immunotherapy, the high toxicity of combined immunotherapy precluding administration of full systemic therapy to patients, and differences in dose and drug exposure used in this trial. Moreover, clinical trials of patients with high-risk stage II and stage III disease did not prove the overall survival benefit. These results should be taken into account when considering the possible use of neoadjuvant therapy, a strategy that seems to be especially attractive since immunotherapy administered preoperatively (when the tumor is not excised) could induce a stronger and broader tumor-specific T-cell response in a larger population of lymphocytes. Available data suggest that patients achieving complete remission after immunotherapy seem to have a durable response, and they may lead to omission of therapeutic lymph node dissection and a more individual approach to perioperative therapy, based on predictive factors related to the response to the preoperative treatment.[10] The first randomized clinical trial comparing adjuvant and neoadjuvant strategies in patients with stage III–IV melanoma was the SWOG S1801 trial, where 313 patients were randomized to an adjuvant arm with up to 18 cycles of pembrolizumab or a neo-/adjuvant arm with 3 cycles of pembrolizumab given preoperatively. Event-free survival (EFS) was significantly improved in the neoadjuvant arm compared with the adjuvant arm (HR 0.58, 95% CI 0.39–0.87; $p = 0.004$); the 2 year EFS rate was 72% in the neoadjuvant arm versus 49% in the adjuvant arm.[11] Currently, the phase III clinical trial NADINA, comparing neoadjuvant and adjuvant therapy in the stage III melanoma population, is ongoing.

The data from these trials and approval of systemic adjuvant immunotherapy lead to the reevaluation of the staging process in patients with thick melanoma. First, one can ask whether we still need sentinel lymph node (SLN) biopsy in this group of patients as, finally, we should use adjuvant therapy, and even in SLN-positive cases, the completion lymph node dissection is currently abandoned.[8] My answer is yes—we need SLN biopsy for better prognostication of individual patients, evaluation of the risk of locoregional and distant relapses, classification of patients into correct stage according to AJCC 8th edition of Melanoma Staging system, and better locoregional disease control. Moreover, adjuvant targeted therapy with BRAF/MEK inhibitors is currently approved only for stage III melanoma.[12] But still we are lacking personalized predictive factors for the choice of adjuvant therapy in patients who really need it, especially in stage II disease, where the magnitude of clinical benefit is low.

The recent large analysis based on the Surveillance, Epidemiology, and End Results database demonstrated that SLN biopsy status improves adjuvant therapy decision-making in patients with clinical stage IIB/C melanoma, and the model estimating 5-year melanoma-specific risk, which included SLN status, provided greater net benefit at treatment thresholds from 30 to 78% compared with the model without known SLN status.[13] The data from KEYNOTE-716 and ChekMate-76K trials strongly suggest that several patients with high-risk primary tumors without evidence of metastatic disease may have a systemic disease at the time of presentation,[14] so the SLN biopsy should be supplemented by detailed staging with computed tomography (CT) or positron emission tomography (PET)–CT after SLN biopsy and before initiation of adjuvant therapy, as is suggested by current National Comprehensive Cancer Network (NCCN) guidelines.[2] Specifically, positive SLN biopsy with diagnosis of stage IIIB disease may be related to occurrence of early distant metastases.[15]

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