Adjuvant Therapy for Cutaneous Melanoma

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KEYWORDS

• Melanoma • Adjuvant therapy • Immunotherapy • Targeted therapy • BRAF • MEK

KEY POINTS

- Immunotherapy (in the form of ipilimumab, nivolumab, and pembrolizumab) in the adjuvant setting for node-positive melanoma has been shown to improve recurrence-free survival.
- Adjuvant radiation therapy can be considered for patients at high risk of regional nodal recurrence; however, its utility in the era of immunotherapy is uncertain.
- Approximately half of patients with metastatic cutaneous melanoma have an activating mutation in the BRAF gene, most commonly located on the V600 residue (90% V600E).
- Adjuvant BRAF/MEK inhibition for patients with activating BRAF mutations has been shown to improve recurrence-free survival as well as reduce the risk of distant metastasis compared with placebo.
- Development of resistance to BRAF inhibitors is common; however, there are emerging data to suggest that BRAF inhibitor resistance may not be permanent, and there may be value to rechallenging select patients with BRAF/MEK inhibition.

INTRODUCTION

Per the National Cancer Institute Web site, adjuvant therapy is defined as any chemotherapy, radiation, targeted, hormone, or biologic therapy given after the primary treatment in order to decrease the risk of disease recurrence.[1] In the setting of residual disease burden or recurrent disease, additional therapy is not considered adjuvant, and discussion of therapy in these situations will not be covered in this review. The current National Comprehensive Cancer Network guidelines recommend consideration of adjuvant therapy for patients with stage III melanoma.[2] However, the benefit of adjuvant therapy needs to be compared with the potential adverse events (AEs) as well as the baseline probability of locoregional disease recurrence and development of metastatic disease. The decision for or against treatment needs to be individually tailored.

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Surg Oncol Clin N Am 29 (2020) 455–465
https://doi.org/10.1016/j.soc.2020.02.009
surgonc.theclinics.com

The single most important prognostic factor for patients with cutaneous melanoma remains their sentinel node status.[3] However, the extent of nodal disease, thickness of the primary tumor, as well as whether there is ulceration present have significant prognostic value and need to be taken into consideration.[4,5] This combination of factors determines the current staging system described by The American Joint Committee on Cancer (AJCC). In the AJCC Eighth Edition, the 5-year melanoma-specific survival (MSS) of patients with stage II disease is 90% compared with 77% for stage III disease.[4] However, within these stage groupings there is wide variation with 5-year MSS of stage IIC (ulcerated primary >4 mm thick) being 82%, which is comparable to that of stage IIIC (5-year MSS 83%) and worse than stage IIIA disease (5-year MSS 93%). Currently, clinical trials are underway to determine the efficacy of checkpoint immunotherapy in these high-risk stage II patients.[6,7] Furthermore, in the era of the second Multicenter Selective Lymphadenectomy Trial and the DeCOG trial, which demonstrated that completion lymph node dissection (CLND) for sentinel lymph node–positive disease did not improve MSS, observation of nodal basins is being performed more routinely in lieu of CLND.[8,9] Because MSS for patients with stage III disease varies depending on the extent of nodal involvement, without CLND it may not be possible to as precisely risk-stratify stage III patients. Furthermore, existing clinical trials that support the use of adjuvant therapy in advanced melanoma primarily included stage III patients with completely resected disease.

The current options for adjuvant therapy for melanoma have changed drastically since the development of modern immunotherapy and targeted therapies. Adjuvant therapy can be thought of as falling under 4 broad categories: immunotherapy, targeted therapy, radiation therapy (RT), and chemotherapy.

ADJUVANT IMMUNOTHERAPY IN ADVANCED MELANOMA

Interferon-Alpha

Historically, adjuvant therapy options for melanoma were limited. Interferon-alpha (INF-α) was the first immunotherapeutic agent approved as adjuvant therapy for high-risk melanoma by the Food and Drug Administration (FDA) in 1995.[10] INF-α was shown to have modest benefit, while harboring unfavorable side-effect profiles.[10–18] Grade 3 and 4 toxicities were reported in up to two-thirds[19,20] of patients, and a 2017 meta-analysis including 15 trials showed an improvement in 5-year overall survival (OS) of 3%, with this benefit seemingly limited to patients with ulcerated primary lesions.[21] INF-α has fallen out of favor with the introduction of other immunotherapy agents.

Ipilimumab

Ipilimumab, a monoclonal antibody targeting CTLA-4, has been FDA approved for adjuvant therapy in stage III melanoma since October 2015. The initial study that demonstrated the efficacy of adjuvant ipilimumab was EORTC 18071, a phase 3 clinical trial comparing high-dose ipilimumab, 10 mg/kg, versus placebo every 3 weeks for 4 doses and then every 3 months for up to 3 years.[22,23] The trial showed significant improvements in 5-year recurrence-free survival (RFS; 40.8 vs 30.3%), OS (65.4% vs 54.4%), and distant metastasis–free survival (48.3 vs 38.9%).[23] Immune-related grade 3 or 4 AEs occurred in 41.6% of the patients in the ipilimumab group with 5 patients dying secondary to immune-related AEs.[22,23]

Until recently there were no data directly comparing the efficacy of INF-α to ipilimumab or other immunotherapy. The results of the Intergroup E1609, a phase 3 randomized study comparing high- and low-dose ipilimumab to INF-α, were recently released

in abstract form.[24] The results showed a statistically significant improvement in OS with low-dose ipilimumab (3 mg/kg) compared with high-dose IFN (hazard ratio [HR] 0.78, $P = .044$) and a trend toward improved RFS (HR 0.85, 99.4% confidence interval [CI; 0.66, 1.09], $P = .065$). There was no significant difference in either OS or RFS for patients who received high-dose ipilimumab (10 mg/kg) compared with high-dose INF-α. Grade 3 or 4 AEs were noted in 37% of patients treated with 3 mg/kg ipilimumab compared with 58% with 10 mg/kg ipilimumab and 79% with high-dose INF-α with AEs leading to discontinuation of treatment in 35%, 54%, and 20% of patients, respectively.[24]

Nivolumab

Nivolumab, a monoclonal antibody targeting the programmed cell death protein 1 (PD-1), was first approved by the FDA for use as adjuvant therapy for resected stage III and stage IV patients in December 2017.[25] This approval was a result of published data from the CheckMate 238 Trial, a randomized, double-blind, phase 3 trial of patients with completely resected stage IIIB, IIIC, or IV melanoma. Patients were randomized to receive nivolumab (3 mg/kg) every 2 weeks or ipilimumab (10 mg/kg) every 3 weeks for 4 doses and then every 12 weeks for up to 1 year. The 1-year RFS was 70.5% versus 60.8% (HR 0.65, $P<.001$) favoring the nivolumab group. Furthermore, there was less grade 3 or 4 toxicity noted in the nivolumab group (14.4% vs 45.9%) and a lower rate of treatment discontinuation because of AEs (9.7% vs 42.6%).[26] Updated results from this trial continued to show improved RFS with nivolumab over ipilimumab, with minimum follow-up extended to 24 months.[27]

Pembrolizumab

More recently, another checkpoint inhibitor, pembrolizumab, a monoclonal antibody targeting PD-1, was approved by the FDA for adjuvant therapy in patients with completely resected node-positive disease.[28] This approval was based on data from KEYNOTE-054, which randomized patients with completely resected stage III disease to receive either pembrolizumab or placebo.[29] Patients received 200 mg of pembrolizumab or placebo intravenously every 3 weeks for 1 year, until disease recurrence or therapy was discontinued because of AEs. At median follow-up of 15 months, the pembrolizumab group had significantly improved RFS compared with the placebo group (75% vs 61%, $P<.001$). Grade 3 or higher AEs were reported in 15% of patients treated with pembrolizumab.[29]

SWOG S1404 is an active phase 3 randomized controlled trial comparing the efficacy of pembrolizumab with either ipilimumab or high-dose INF-α. Patients with stage IIIA (N2), IIIB, IIIC, or IV (M1a, b, and c) disease are eligible for enrollment. Primary outcomes are OS and RFS.[30] This trial will provide a head-to-head comparison of pembrolizumab against 2 other immunotherapy options that have been shown to be active in advanced melanoma.[22–24]

Safety of Checkpoint Immunotherapy

Randomized trials examining the efficacy of checkpoint inhibition with adjuvant nivolumab or pembrolizumab have demonstrated less toxicity compared with ipilimumab.[22,24,26,29] The most common AEs are fatigue, skin reactions (rash, pruritis), diarrhea, nausea, arthralgias, and endocrinopathies. The incidence of grade 3 or 4 treatment-related AEs occurred in approximately 46% of the patients treated with high-dose ipilimumab, compared with 14.4% for nivolumab, and 14.7% for pembrolizumab.[23,26,29] The incidence of grade 5 toxicity was also lower in pembrolizumab and nivolumab compared with ipilimumab (0.2%, 0%, and 0.4%–1.1%, respectively).

The most common grade 3 or higher immune-related AEs were gastrointestinal (colitis), endocrine (diabetes mellitus, hypophysitis), and pulmonary/thoracic (pneumonitis, interstitial lung disease).[23,26,29]

ADJUVANT-TARGETED THERAPY IN ADVANCED MELANOMA

BRAF Pathway and Cutaneous Melanoma Implications

Melanoma is a heterogenous malignancy that can be broadly divided into 4 categories based on the mutational profile: BRAF mutant, NRAS mutant, NF1 mutant, and wild type.[31] BRAF is a serine-threonine protein kinase that is responsible for signal transduction within the cell and for normal cell growth, proliferation, differentiation, and survival.[32] Activation of BRAF is via the upstream RAS GTPase protein, which then subsequently activates the downstream ERK pathway.[32–34] Approximately half of patients with metastatic cutaneous melanoma have an activating mutation in the BRAF gene, leading to a constitutively active mitogen-activated protein kinase intracellular pathway.[33,35,36] Most activating mutations are located on the V600 residue, most commonly V600E (90%), but sometimes V600K or others.[36,37] Melanomas that harbor the V600E mutation are active independent of upstream signaling molecules, ultimately leading to cell survival, proliferation, tumor angiogenesis, and metastasis.[33,34] Because of this common mutation, BRAF inhibition (BRAFi) has become a target for intervention.

BRAF-Targeted Therapy

Multiple trials have investigated the efficacy of adjuvant BRAFi in patients with melanoma. In particular, 2 prospective, double-blind, randomized controlled trials have looked at the benefit of adjuvant BRAFi in patients with resected melanoma.[38,39] The BRIM8 trial included patients with AJCC, Seventh Edition stage IIC–III (IIIA with at least 1 lymph node metastasis >1 mm in diameter or stage IIIB/C without intransit disease) resected melanoma with a BRAF V600 mutation. The use of single-agent vemurafenib versus placebo improved 2-year disease-free survival (62% vs 53%; HR 0.65 [0.50–0.96], $P = .0013$) and 2-year distant metastasis-free survival (72% vs 65%; HR 0.70 [0.52–0.96], $P = .027$), but the effect on 2-year OS was not statistically significant (90% vs 86%; HR 0.76 [0.49–1.18], $P = .2165$).[38] The COMBI-AD trial included patients with resected AJCC, Seventh Edition stage III (IIIA with at least 1 lymph node metastasis >1 mm in diameter or stage IIIB/C) disease with BRAF V600E/K mutation. Patients were randomized to BRAF/MEK inhibitor combination dabrafenib/trametinib versus placebo and demonstrated improved 3-year RFS (58% vs 39%; HR 0.47 [0.40–0.65], $P<.001$), and reduced risk of distant metastasis (25% vs 35%; HR 0.51 [0.40–0.65], $P<.001$). The 3-year OS was higher in the dabrafenib/trametinib group (85% vs 77%; HR 0.57 [0.42–0.79], $P = .0006$) but did not meet the prespecified interim boundary. A subgroup analysis showed significantly better RFS in patients treated with dabrafenib/trametinib versus placebo in those with BRAF V600E.[39] Based on the COMBI-AD trial, the FDA-approved dabrafenib/trametinib combination therapy for all patients with resected stage III or recurrent disease who have the BRAF V600 activating mutation. Adjuvant combination BRAF/MEK inhibitor therapy should be considered for all patients with stage III melanoma with a BRAF activating mutation.

Presently, adjuvant BRAF inhibitor treatment is not recommended for patients with stage I/II disease. For patients with high-risk stage II disease, clinical trials can be considered and are currently under investigation regarding the role of checkpoint immunotherapy in this setting.[6,7] Enrollment in clinical trials for those with high risk of recurrence after lymphadenectomy or borderline resectable lymphadenopathy

should be considered. There are insufficient data regarding BRAF-targeted therapy in the neoadjuvant setting for early-stage melanoma. Neoadjuvant BRAF-targeted therapy for patients with resectable stage III/IV disease has shown promising results and is currently under investigation.[40–45]

Safety of BRAF/MEK Inhibitors

Both BRAFi monotherapy and BRAF/MEK combination therapy demonstrate similar risk profiles with grade 3 to 5 toxicities. In particular, both BRAF monotherapy and BRAF/MEK inhibitor combination therapy are associated with high rates of flulike symptoms, including pyrexia, chills, fatigue, headaches, arthralgias, myalgias, and gastrointestinal symptoms (eg, diarrhea, nausea, vomiting). BRAF/MEK inhibitor combination is associated with higher rates of pyrexia and diarrhea, whereas BRAF monotherapy is associated with increased rates of musculoskeletal complaints. Alopecia, rash, and other skin toxicities are common in both BRAF and BRAF/MEK therapies with occurrence ranging from 6% to 73%.[39,46–49] Notably, BRAFi monotherapy is associated with increased risk of hyperproliferative skin toxicities, including hyperkeratosis, palmoplantar disorders, keratoacanthoma, and cutaneous squamous cell carcinomas compared with BRAF/MEK combination therapy. Specifically, in the BRIM-8 trial, adjuvant vemurafenib was associated with an increase in hyperproliferative cutaneous AE compared with placebo (16% vs 2%).[38] This increase in hyperproliferative cutaneous AEs was not seen in the dabrafenib/trametinib combination therapy as it was with vemurafenib monotherapy.[9] Therefore, the FDA has not approved vemurafenib monotherapy because of the improved efficacy and safety of BRAF/MEK inhibitor combination.

Grade V toxicities are rare in both BRAFi monotherapy and BRAF/MEK combination and include cardiovascular, cerebrovascular, infection, and multiorgan failure events. There are certain rare patients who experience toxicity attributed to MEK inhibition, including deep venous thrombosis, retinal problems, and immunosuppression. In these situations, combination therapy should be discontinued. Other reported AEs include QT prolongation, decreased ejection fraction, and the development of new primary malignancies.[46–50]

Most AEs related to BRAF-targeted therapy manifest within the first few months of therapy, although they can continue throughout the course of treatment. Although time to onset of AEs varies, there is some evidence that development of grade 3 or 4 toxicity was longer in the BRAF/MEK combination therapy group. Most AEs related to treatment toxicity resolved within 3 months of discontinuing therapy.[51–54]

Resistance to BRAF Inhibitors

BRAFi resistance has been shown to be related to the reactivation of the MAP kinase signaling pathway via additional mutations.[55–58] Other mechanisms of resistance involve upregulation of the PI3K-ATK-mTOR signaling, increased expression of growth factor receptors on the cell membrane, amplification or activation of target kinases, and other unknown mechanisms.[58–60] Once BRAF-mutant melanomas become resistant to BRAF inhibitors, their ability to metastasize is increased, and they are more likely to be aggressive with higher rates of progression.[55] There are emerging data to suggest that BRAFi resistance may not be permanent. Phase 1/2 trials evaluating the response to dual BRAF/MEK inhibition after initial progression on BRAFi alone or combination BRAF/MEK inhibition show a relative risk of 13% to 32%, suggesting that BRAF-targeted resistance may be reversible.[61–63] The best patient selection for re-treatment is under investigation; additional questions remain

about timing, sequence, and optimal drug selection when treating patients who have progressed after first-line therapy.

Radiation Therapy

Adjuvant RT after wide local excision (WLE) of primary tumors is generally unnecessary because local recurrence after excision with adequate margin has low recurrence rates (1%–9% depending on site of primary).[64] Desmoplastic neurotropic melanomas (DNM) have been associated with higher rates of local recurrence after WLE, and data suggest adjuvant radiation in this setting can be helpful. A retrospective review looking at 128 patients with DNM (27 receiving RT) showed similar rates of local recurrence (6% vs 7% with RT) despite those patients having less favorable clinicopathologic features.[65] Strom and colleagues[66] reported on 277 patients with DNM, of which 113 (40.8%) received adjuvant RT. On multivariable analysis, RT was associated with better local control (HR 0.15, CI 0.06–0.39, $P<.01$) after a mean follow-up of 43 months. Subgroup analysis of 35 patients with positive margin showed a local recurrence rate of 14% in patients who received RT compared with 54% in patients not receiving RT ($P = .004$). For patients with negative resection margin, RT was no longer significant in reducing the local recurrence rate ($P = .09$). However, for those patients with negative margins and high-risk features, thickness greater than 4 mm, head and neck location, on univariate analysis RT was found to significantly reduce the rate of local recurrence ($P<.05$). These data are further supported by a retrospective review of 130 patients with DNM treated at MD Anderson Cancer Center. The authors found that the rate of local recurrence in patients receiving adjuvant RT was significantly lower than for patients with surgery alone (7% vs 24%). On multivariable analysis, RT remained a significant determinant of disease recurrence ($P = .009$).[67] Although these data are promising, they are limited by their single-institution experience and retrospective nature, and randomized trials are needed to definitely determine which patients with DNM benefit from adjuvant RT. Study NCT00975520 is currently accruing and should aid in further defining the role of adjuvant therapy in DNM.[68]

There has been 1 prospective phase 3 randomized controlled trial looking at the utility of adjuvant nodal RT after lymphadenectomy. The ANZMTG 01.02/TROG 02.01 trial randomized 123 patients to adjuvant RT and 127 to observation. After median follow-up of 73 months, nodal relapse occurred in 23 (21%) of the adjuvant RT group compared with 39 (36%) in the observation group (HR 0·52, CI [0.31–0.88], $P = .023$). There was no difference in OS or RFS between the 2 groups. Grade 3 to 4 toxic adverse events were experienced in 22% of the RT group.[69] This outcome is supported by similar results in a large retrospective analysis by Agrawal and colleagues.[70] They examined 615 patients who had undergone lymphadenectomy for metastatic melanoma with 509 (83%) receiving adjuvant RT. At median follow-up of 60 months, patients who received adjuvant RT were less likely to develop a regional nodal recurrence compared with patients who were observed after resection (10.2% vs 40.6%). On multivariable analysis, RT was significantly associated with lower risk of regional recurrence. At 5-year follow-up, the rate of lymphedema was 19%.[70]

Although these data suggest a potential benefit to adjuvant RT in well-selected patients, most data are from before the era of immunotherapy. Treatment with immunotherapy after lymphadenectomy in patients who otherwise would have been considered for adjuvant nodal radiation may potentially limit its benefit because the expected rate of nodal recurrence is much lower. Thus, it would seem reasonable to first treat with immunotherapy when appropriate and reserve RT for salvage rather than adjuvant therapy.

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