Neoadjuvant Therapy for Melanoma

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KEYWORDS

• Melanoma • Immunotherapy • Targeted therapy • Neoadjuvant

KEY POINTS

- Early data from small neoadjuvant clinical trials in melanoma confirm the need to preform larger randomized clinical trials to confirm these results.
- Patients with macroscopically detected resectable stage III disease should receive neoadjuvant therapy on a clinical trial.
- Patients treated with neoadjuvant immunotherapy that experience complete pathologic responses are less likely to relapse in small studies with term short term follow up.

ROLE OF NEOADJUVANT THERAPY IN MELANOMA

Stage III melanoma represents a wide variety of patients, including those with microscopic disease found on sentinel lymph node evaluation as well as those with in-transit or clinically detected lymph nodes at the time of diagnosis. Although both populations are at risk for recurrence, patients with in-transit and clinically detected disease have poorer prognosis. Historically, patients with clinically detected lymph nodes without in-transit metastases have a 5-year recurrence rate of 68% to 89%.[1,2] Patients with stage IIID melanoma (high-risk primary lesion and multiple nodes involved) have prognosis similar to patients with stage IV disease.[3]

For patients with regional disease, conventional management includes excision of the primary and any resectable in-transit disease, if present; therapeutic lymphadenectomy; and adjuvant therapy. Historically adjuvant therapy consisted only of high-dose interferon or ipilimumab.[4,5] These therapies had limited efficacy and high toxicities that limited their widespread use. Recent trials have shown significant improvements in overall survival (OS) and/or recurrence-free survival for Programmed cell death protein-1 (PD-1) inhibitors and BRAF/MEK targeted therapies in the adjuvant setting.[6–8] These improvements, however, over either placebo or ipilimumab

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leave a clear unmet need to further improve outcomes. Data in other solid tumors, including breast, bladder, and esophageal, among others, suggest neoadjuvant therapy could have considerable impact on disease response, operability, and survival rates.[9–11] Early studies in melanoma suggest similar results.

This review outlines the current data for both immunotherapy and targeted therapy in the neoadjuvant setting and determines how neoadjuvant therapy should fit into the current paradigm of treatment of patients with resectable clinically detected regional disease.

WHY NEOADJUVANT THERAPY?

Given the advances in both the metastatic and adjuvant settings, neoadjuvant strategies have been the logical next frontier in the treatment of melanoma. Neoadjuvant treatments ideally would improve both recurrence-free survival (RFS) and overall survival (OS) for melanoma patients. Other endpoints, however, potentially will benefit patients even if RFS and OS are not changed. Decreasing surgical morbidity, understanding disease biology/responsiveness to therapy, prognostic data of pathologic response, and perhaps identifying biomarkers to determine future adjuvant therapy are just some of the potential benefits to a neoadjuvant paradigm.

Preclinical evidence has shown that mice treated with neoadjuvant anti–PD-1 antibody prior to resection had a better survival then mice treated after surgery.[12] In addition, tumor resistance can occur via changes to the tumor microenvironment through the course of therapy, thus making earlier treatment a promising paradigm to prevent resistance.

Beyond direct patient benefit, the neoadjuvant paradigm has the potential to promote scientific advancement in the field. If endpoints, such as pathologic complete response (pCR), are established as a predictor of survival, drugs may be tested in the neoadjuvant setting in order to predict outcomes for metastatic patients. This method would be more cost-effective and faster compared with randomized phase III trials. Although a pooled analysis of early neoadjuvant trials in melanoma shows pCR to be a predictor of improved outcomes, data correlating pCR to OS benefit have yet to be established.[13]

NEOADJUVANT IMMUNOTHERAPY

Long-term survival in stage IV melanoma has been seen with anti–PD-1 antibodies as single agents and in combination with cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibodies. CheckMate 067 reported a 52% OS of stage IV melanoma patients treated with ipilimumab and nivolumab and 44% OS for patients on nivolumab monotherapy.[14] Similar results have been seen with pembrolizumab monotherapy, with KEYNOTE-001 demonstrating a 5-year OS of 34%.[15] In light of these significant survival improvements in the stage IV setting, use of anti–PD-1 with and without anti–CTLA-4 antibodies have been explored in the neoadjuvant setting (**Table 1**).

Remarkably, even a single dose of pembrolizumab has been shown to elicit a pathologic response in patients with metastatic resectable melanoma. A single-institution trial enrolled 29 patients with resectable stage IIIB, IIIC, and stage IV melanoma, and patients were treated with 1 dose of pembrolizumab and then went to surgical resection. Of 27 patients who were evaluable for pathologic response, 5 had pCR and 3 had a pathologic major response (less than 10% viable tumor). The patients with pCR and pathologic major response remained disease-free at the time of publication.[16] This small study demonstrates the potential prognostic significance of pathologic response.

Nivolumab has also been studied in the neoadjuvant setting as single agent and in combination with ipilimumab. A phase II trial by Amaria and colleagues[17] evaluated neoadjuvant immunotherapy in resectable stage III and stage IV melanoma patients, who were randomized to 2 treatment arms: nivolumab, 3 mg/kg, intravenous, every 2 weeks × 4 cycles prior to resection (n = 11), or ipilimumab, 3 mg/kg, and nivolumab, 1 mg/kg, every 3 weeks for 3 cycles prior to surgery (n = 12). With nivolumab monotherapy, the response evaluation criteria in solid tumors (RECIST) response rate was 25% and pCR was 25%. With combination nivolumab/ipilimumab therapy, the RECIST response was 73% with pCR rate of 45%. The rate of grade 3 or higher adverse events in the nivolumab/ipilimumab combination arm, however, was 73% compared with 8% in the nivolumab only arm.[17]

A phase Ib study by Blank and colleagues[18] evaluated both neoadjuvant and adjuvant immunotherapy in clinical stage III patients only. Patients received either adjuvant ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) every 3 weeks for 4 cycles after surgery (n = 10) or neoadjuvant ipilimumab plus nivolumab for 2 cycles prior to surgery and another 2 cycles postoperatively (n = 10). On the neoadjuvant arm there were 3 pCRs, 3 patients with major response (less than 10% viable tumor), and 1 patient with partial pathologic response (10%–50% viable tumor). Of the pCR and near–complete response (CR) patients, none had recurred at the time of publication, again suggesting prognostic significance of pCR. On the adjuvant arm, 4 of the 10 patients treated had relapsed at that the time of publication.[18] With small numbers of subjects, it is difficult to make any firm conclusions comparing neoadjuvant to adjuvant therapy from this trial.

Combination therapy clearly has a higher response rate, but with that comes higher rates of toxicity.[14,19] Therefore the OpACIN-neo trial attempted to optimize dosing in order to minimize adverse events. Three neoadjuvant dosing schedules were evaluated: arm A—ipilimumab, 3 mg/kg, plus nivolumab, 1 mg/kg, for 2 cycles; arm B—ipilimumab, 1 mg/kg, plus nivolumab, 3 mg/kg, for 2 cycles; and arm C—ipilimumab, 3 mg/kg, every 2 weeks for 2 cycles followed by nivolumab, 3 mg/kg, every 2 weeks for 2 cycles. Adjuvant therapy was not given on any arm of the study. Thirty patients were enrolled on first 2 arms and 26 patients were enrolled on the third. Serious adverse events (grades 3 and 4) occurred in 40%, 20%, and 50% in the 3 arms, respectively. pCR rates were 47%, 57%, and 65%, respectively. Due to the lower toxicity and comparable pCR rate of arm B (ipilimumab, 1 mg/kg, with nivolumab, 3 mg/kg), this was concluded by the investigators to be the best dosing and schedule.[20]

These 4 trials provide considerable evidence to support the hypothesis that neoadjuvant therapy with proved combinations of immunotherapy will result in high rates of pathologic response. Given the lack of long-term follow-up from any of these studies, correlations between pathologic response and melanoma-specific survival cannot be drawn. Optimizing combinations of immunotherapy and timing/duration of adjuvant therapy will provide further guidance in creating the optimal neoadjuvant therapy schema.

NEOADJUVANT TARGETED THERAPY

Several trials in stage IV melanoma have established that inhibition of the MAP kinase pathway in BRAF-mutated melanoma leads to survival benefit. Although initial studies showed single-agent BRAF inhibition had OS benefit for stage IV patients, a multitude of studies have now established that combination BRAF with MEK inhibitors is superior to single-agent therapy in both progression-free survival and OS. Three different

Table 1
Completed neoadjuvant studies in locally regionally advanced melanoma

Study	No. of Patients	Design	Regimen	Findings
Neoadjuvant immunotherapy				
Huang and colleagues,[16] 2019	30	Phase I, single arm	Pembro, 200 mg, 1 dose followed by surgery after 3 wk; then, q3wk pembro, for 1 y	• 30% complete or near-complete (<10% viable tumor) pathologic response • 1 y RFS of 55%
OpACIN: Blank and colleagues,[18] 2018	20	Phase Ib	Arm A: adjuvant IV ipi, 3 mg/kg q3wk,+ IV nivo, 1 mg/kg q3wk for 12 wk Arm B: IV ipi, 3 mg/kg q3wk, + IV nivo, 1 mg/kg q3wk for 6 wk, bracketing surgery	• Neoadjuvant ipi + nivo led to 3 pCR, 4 near-pCR (microscopic metastatic disease) and 1 PR • Grade 3–4 adverse events in 18/20 patients
OpACIN-neo, phase II; 2019[20]	90	Phase II, 3 arms	Arm A: ipi (3 mg/kg) + nivo (1 mg/kg) q3wk for 6 wk before surgery Arm B: ipi (1 mg/kg) + nivo (3 mg/kg) q3wk for 6 wk before surgery Arm C: ipi (3 mg/kg) q3wk for 6 wk followed immediately by nivo, 3 mg/kg q2wk for 4 wk	• Grade 3/4 adverse events: 40% in arm A, 20% in arm B, and 50% in arm C • Complete radiologic response rate: 7% in arm A, 10% in arm B, and 4% in arm C • pCR rate: 47% in arm A, 47% in arm B, and 23% in arm C
Amaria and colleagues,[19] 2018	23	Phase II	Arm A: neoadjuvant nivo, 3 mg/kg IV q2wk × 4 doses, followed by adjuvant nivo, 3 mg/kg IV q2wk × 13 doses Arm B: neoadjuvant nivo, 1 mg/kg + ipi 3 mg/kg q3wk × 3doses, followed by adjuvant nivo, 3 mg/kg IV q2wk × 13 doses	• Arm A: 25% pCR and 25% radiological response rate • Arm B: 45% pCR and 73% radiological response rate • Grade 3 adverse events—8% in arm A vs 73% in arm B

Neoadjuvant targeted therapy				
Long and colleagues,[24] 2019	35	Phase II, single arm	Dabrafenib + trametinib × 12 wk before surgery, followed by dabrafenib + trametinib for 40 wk	• 17/35 (49%) had pCR • 2-y RFS 63.3% in patients with pCR
Combi-Neo, Amaria and colleagues,[25] 2018	21	Phase II, double arm	Arm A: 7 patients—surgery + SOC adjuvant therapy Arm B: 14 pts—neoadjuvant dabrafenib + trametinib for 8 wk, adjuvant dabrafenib + trametinib for 44 wk	• Median event-free survival 19.7 mo (arm B) vs 2.9 mo (arm A) • pCR rate of 58% and pathologic partial response rate of 17%
Neoadjuvant oncolytic viral therapy				
Andtbacka & Gyorki,[27] 2018	150	Phase II, double arm	Arm A: 6 cycles of neoaduvant T-VEC followed by surgical resection Arm B: upfront surgical resection	• pCR rate of 21% and overall response rate (CR + PR) of 14.7% in arm A • 11 patients in arm A had progressive disease before surgery

Abbreviations: ipi, ipilimumab; IV, intravenous; nivo, nivolumab; pembro, pembrolizumab; PR, partial response; SOC, standard of care.

combination therapies (BRAF inhibitor plus MEK inhibitor) have been approved for the treatment of stage IV BRAF V600–mutated melanoma (vemurafenib plus cobimetinib, dabrafenib plus trametinib, and encorafenib plus binimetinib).[21–23] Dabrafenib and trametinib also have been approved for the treatment of resected stage III melanoma given the improved RFS compared with observation.[7]

Several small studies are available that show activity of these agents in the neoadjuvant setting. In a phase II trial by Long and colleagues,[24] dabrafenib and trametinib was administered to 35 patients with stage IIIB/C BRAF V600E/K–mutated melanoma. Patients were treated for 12 weeks and then underwent therapeutic lymph node dissection followed by 40 weeks of adjuvant targeted therapy. Of the 35 patients, 17 achieved a pCR rate of 49%. At median follow-up of 27 months, recurrence was noted in 20 patients; 2-year RFS was 63.3% in patients with pCR compared with 24.4% in patients who did not achieve pCR. Ten patients (29%) experienced grades 3 to 4 adverse events, most commonly pyrexia.[24]

Amaria and colleagues[25] also evaluated the role of neoadjuvant dabrafenib and trametinib in 21 patients with resectable stage III or oligometastatic stage IV resectable BRAF-mutated melanoma. Patients were randomized in a 1:2 ratio to either upfront surgery followed by standard of care adjuvant dabrafenib/trametinib or neoadjuvant dabrafenib plus trametinib for 8 weeks, followed by surgery, followed by 44 weeks of adjuvant therapy. This trial was stopped early at a predetermined interim analysis because a significant improvement in RFS was noted in the neoadjuvant arm. Of the 12 patients in the neoadjuvant arm, 58% achieved pCR. In addition, as seen in other studies, patients with pCR had a significantly longer distant metastasis–free survival (hazard ratio 0.082; 95% CI 0.001–0.88; $P = .04$).[25]

ONCOLYTIC VIRAL THERAPY

Talimogene laherparepvec (T-VEC) is a genetically modified herpes simplex virus that specifically infects and replicates in human tumor cells. It is approved for the treatment of unresectable stage III and stage IV melanoma and had the highest efficacy in those with limited disease.[26] Given that most patients with resectable melanoma have limited volume of metastatic disease that is potentially injectable, T-VEC was rationally considered for patients with resectable and injectable stage III and stage IV melanoma. A phase II trial randomized 150 patients with resectable melanoma to either surgery or 6 doses of neoadjuvant T-VEC for up to 12 weeks. A pCR rate of 21% was found in patients undergoing neoadjuvant T-VEC and surgery, but 11 patients had progression of disease before planned surgical resection.[27] With a significant portion of patients becoming unresectable and the lower pCR rate compared with other agents in the neoadjuvant space, single-agent T-VEC has more limited utility as a neoadjuvant treatment.

SUMMARY OF EARLY TRIALS

On behalf of the International Neoadjuvant Melanoma Consortium, Menzies and colleagues,[13] completed a pooled analysis of the 6 trials evaluating neoadjuvant immunotherapy or BRAF-targeted therapy. Patients with RECIST measurable and surgically resectable stage III disease who underwent surgery were included in the analysis. A total of 184 patients were pooled; 133 were treated with immunotherapy and 51 were treated with targeted therapy. Overall, pCR was observed in 41% of patients. At median follow-up of 13 months, 44 (24%) experienced a recurrence. Of patients with pCR, 7% experienced a recurrence; all of these recurrences occurred in patient receiving targeted therapy. None of the patients receiving immunotherapy

experienced recurrence. One-year RFS was significantly longer in patients experiencing pCR compared with patients without pCR (95% vs 62%, respectively; $p<0.001$).[13]

Data from the individual trials and this pooled analysis suggest that neoadjuvant therapy provides a high rate of pathologic response and acceptable tolerability. Despite what appears to be an association between pathologic response and RFS, it is not possible to make correlations between pathologic response and long-term outcomes. Ongoing trials, some of which are larger and powered to address the impact of neoadjuvant therapy on survival, may answer broader questions about the more universal application of neoadjuvant therapy in melanoma.

SUMMARY

The neoadjuvant treatment approach to advanced resectable regional disease is the logical next step in the progress that has been made in the treatment of advanced melanoma. The agents available for use in the neoadjuvant setting are safe and effective, and early trial data have confirmed that the overwhelming majority of patients are able to complete surgical resection. A small minority of patients who are unable to complete surgery have developed systemic disease while on neoadjuvant therapy; most clinicians believe that in these unfortunate circumstances an operation would have provided limited, if any, benefit. Ongoing and future clinical trials must balance the toxicities of systemic therapies with the goal of performing a potentially curable operation for all resectable patients.

In addition to the long-term survival impact that is likely to result from neoadjuvant therapies, administering checkpoint blockade and BRAF-targeted therapies before surgical resection offers an incredible amount of histologic and immunologic data. The neoadjuvant approach will enable investigators to test novel drug combinations, including next-generation immune checkpoint blockade targets like TIGIT, Tim-3, Lag-3, and OX40, among others. The ultimate goal is to identify which patients are most likely to benefit from which of the following: neoadjuvant therapy, upfront surgery followed by adjuvant therapy, and definitive systemic therapy. Large studies comparing neoadjuvant with adjuvant therapy already are under way and will definitively determine if all patients with resectable regional melanoma should undergo systemic therapy prior to their definitive operation. Continued work is required to fully characterize the long-term patterns of response to and relapse from neoadjuvant treatment. As neoadjuvant therapy continues to develop, new targets will be identified to increase response rates with less toxicity. Great strides have been made in the treatment of advanced melanoma patients, and this work continues to expand in the neoadjuvant setting. The authors still feel strongly that all patients with resectable regional melanoma should receive neoadjuvant treatment on a clinical trial when feasible. This will build on the tremendous momentum gained to date and ultimately result in an improvement in the prognosis of this historically devastating disease.

DISCLOSURE

The authors have no disclosures.

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