Published in final edited form as:

Surg Clin North Am. 2020 February ; 100(1): 141–159. doi:10.1016/j.suc.2019.09.012.

Surgical Considerations and Systemic Therapy of Melanoma

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Keywords

Adjuvant therapy; neoadjuvant therapy; immunotherapy; targeted therapy; advanced melanoma

Introduction

The incidence of metastatic melanoma has rapidly increased over the last three decades with an associated increase in mortality worldwide when compared to other cancers^{1–3}. Data from the US Surveillance, Epidemiology, and End Results (SEER) program demonstrate that the incidence of melanoma quadrupled over the past four decades, increasing by 1.5% annually over the last ten years⁴. For patients with regional or distant melanoma, the treatment armamentarium remained unchanged for the first decade of the 21st century. Based on advancements in the understanding of the role of the immune system, new systemic strategies have transformed the therapeutic landscape and have led to survival improvements in patients with advanced melanoma. These successes have broadened the indications for surgery and there is now an enhanced justification for resecting oligometastatic disease either as first-line treatment or salvage therapy.

The eighth edition of the American Joint Committee on Cancer (AJCC) stratifies stage III melanoma into four categories based on histopathologic factors while stage IV disease is distinctly classified into four categories based on metastatic location including distant cutaneous, subcutaneous, or nodal disease (M1a), lung (M1b), noncentral nervous system visceral (M1c), and central nervous system metastasis with or without metastasis at other sites (M1d). These anatomic sites can be further sub-stratified based on serum lactate

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Disclosures: none

dehydrogenase (LDH) levels. In this chapter, we outline available evidence supporting resection of metastatic disease for both stage III and IV melanoma in the context of currently available systemic therapeutic options. We additionally review the evidence supporting the use of adjuvant systemic therapies and other treatment modalities including radiotherapy, chemotherapy, and vaccines in advanced melanoma. Lastly, we highlight the effort of translating the success of these therapies to the neoadjuvant setting and summarize active clinical trials.

Surgical Management of Metastatic Disease

Introduction

Approximately 9% of patients diagnosed with cutaneous melanoma in the United States present with regional disease. There is marked heterogeneity in prognosis ranging from a 10-year disease-specific survival (DSS) of 88% in stage IIIA to 24% in stage IIID. An additional 4% of patients present with synchronous distant metastatic disease, and these patients have a 5-year DSS of 10%⁵. For decades, systemic therapies with limited efficacy compelled clinicians to consider surgery in patients with good performance status and disease amenable to resection. The advent of effective systemic therapy has transformed this paradigm and while systemic therapies are now the mainstay of treatment for stage IV melanoma, surgical resection is an appropriate adjuvant treatment for selected patients and necessary for palliation, diagnosis and certain therapeutic regimens. Importantly, these recent advances in systemic therapy may support a rationale for a more aggressive surgical approach. The decision to resect metastatic melanoma should be based on a complete evaluation of the extent of metastasis, a thorough assessment of the patient's physiologic reserve and an optimal estimation of the biologic behavior of the disease. Confirmation of metastatic disease in patients with clinical or radiographically identified lymphadenopathy should be obtained with fine-needle aspiration biopsy (FNA) prior to surgical intervention. Furthermore, staging evaluation with cross-sectional imaging is warranted to ensure candidacy for surgical control of disease.

Surgery for Locoregional Disease

In the AJCC 8th edition, regional lymph node disease is further divided into clinically occult or clinically evident disease⁵. Importantly, these designations refer to the mode of detection of the nodal metastases with clinically occult disease detected by sentinel lymph node (SLN) biopsy and clinically evident disease detected by physical examination or radiographic imaging⁶. Based on the results of the Multicenter Selective Lymphadenectomy Trial-II (MSLT-II), either completion lymph node dissection (CLND) or observation may be offered to patients with a positive SLN, though most patients will not benefit from CLND⁷. However, current consensus guidelines suggest that those with high-risk features including extracapsular spread/extension, concomitant microsatellitosis of the primary tumors, more than three involved nodes, or more than two involved nodal basins be strongly considered for CLND⁸. For patients with clinically evident disease, once metastases have been histopathologically confirmed, and in the absence of extra-regional disease, therapeutic lymph node dissection is recommended given its established association with long-term survival outcomes and the absence of evidence to the contrary. In a large retrospective series,

38% of patients with resected clinically evident nodal melanoma remained disease-free after 5 years⁹. For axillary lymph node dissection, levels 1–3 should be excised. For inguinal lymph node dissection, controversy remains as to the extent of lymphadenectomy, though a 2011 retrospective study demonstrated that disease-free survival did not differ between patients who underwent superficial groin dissection and those who underwent superficial and deep groin dissection. Despite this finding, inguinopelvic lymphadenectomy (superficial and deep groin dissection) can be considered for patients with multiple positive lymph nodes on superficial groin dissection or abnormal pelvic nodes on cross-sectional imaging¹⁰. In the presence of cervical nodal disease, a modified radical neck dissection should be performed with excision of levels 2–5 and with consideration of levels 1 or 6, or a parotidectomy where appropriate. Following complete resection of nodal recurrence, adjuvant treatment with immunotherapy or targeted therapy is recommended as outlined in the section below.

Non-nodal locoregional metastasis includes satellite disease and in-transit metastasis (ITM), which are all associated with a prognosis similar to that of patients with clinically detected nodes⁵. By convention, satellite lesions are differentiated from in-transit metastases by their distance from the primary site. Lesions within 2 cm of the primary melanoma are characterized as satellites, whereas in-transit metastases are located >2 cm from the primary tumor but proximal to the loco-regional lymph nodes¹¹. Due to the heterogeneity of this disease process, there have been few clinical trials comparing the efficacy of therapeutic options. As such, there is no classic definition of what amount of disease should be considered resectable as long as limb function can be maintained. Despite this ambiguity, definitive surgical resection with narrow negative margins remains the preferred treatment for limited satellite or in-transit metastatic deposits. Although its impact remains unknown, in the absence of clinically identifiable nodal metastases, lymphatic mapping with SLN biopsy may also be considered¹². Patients who present with both ITM and clinical regional nodal disease should be strongly considered for systemic therapy as a first-line approach given the high likelihood of subsequent distant disease. For patients in whom surgery is not feasible due to extensive lesions, evidence of distant metastatic disease, or patient-related factors, regional therapies such as isolated limb perfusion and intralesional therapies or systemic therapies may be used to achieve disease control. These modalities are detailed later in this issue.

Surgery for Distant Metastatic Disease

Improved long-term outcomes in patients undergoing metastasectomy for melanoma have been reported in several retrospective studies which demonstrate that 15–28% of patients may achieve a 5-year survival when distant metastases can be completely resected^{13–19}. Despite considerable selection bias in these studies, there is evidence demonstrating that resection of distant metastases may be associated with improved survival in carefully selected patients, particularly those with long disease-free intervals and favorable performance status. These findings have been further confirmed in two large-scale, multicenter trials. The Southwestern Oncology Group's prospective multicenter trial of patients with surgically resectable stage IV melanoma found that despite a short relapse-free survival of 5 months, complete resection conferred a median overall survival (OS) of 21 months versus historical rates of 6–10 months with systemic therapy²⁰. In the Multicenter

Selective Lymphadenectomy Trial-I (MSLT-1), retrospective analysis of patients who were longitudinally followed and developed distant metastases found that metastasectomy conferred a survival advantage, even in patients who developed high-risk visceral metastases. If surgery was performed, the median survival was 15.8 months compared to 6.9 months in those treated with systemic therapy alone, with an improved 4-year survival compared to systemic medical therapy alone (20.8% vs 7.0%, HR=0.41, $p<0.0001$)²¹. Unfortunately, these data may have limited applicability in the current paradigm of systemic therapy.

The results of the 2006 Canvaxin™ trial were likely some of the most transformative data at their time in support of aggressive surgery. This phase III trial compared adjuvant treatment with Bacillus Calmette–Guerin (BCG) and an allogenic melanoma vaccine to BCG with placebo after complete resection of stage IV disease. While the study did not show any benefit in the vaccine-treated arm, 5-year OS rates following complete surgical resection were approximately 40% in both groups, substantially higher than would have been expected if the patients had been treated with the systemic therapies that were available at the time²². While these data provide a foundation for the application of surgery in metastatic disease, they remain limited by the facts that this was a highly selected subset of patients and that modern effective systemic therapy was not available as a comparator or adjunct.

Although only present in about 2–4% of patients with melanoma, gastrointestinal metastases in stage IV disease are common, accounting for up to 40% of all metastases. With appropriate patient selection, resection of gastrointestinal metastases has also been associated with improved survival²³. A retrospective review of 1623 patients with localized intra-abdominal metastases confined to the gastrointestinal tract, liver, adrenal glands, pancreas, and the spleen demonstrated an improvement in median OS of 18 months after metastasectomy compared to 7 months in those who only underwent treatment with systemic drug therapy²⁴. Several other studies have recapitulated these findings with 5-year OS rates of 20.5% after resection of liver and adrenal metastases^{25,26}.

The lungs are another common site of visceral metastases, comprising 15–35% of patients with metastatic melanoma¹⁸. Several studies have shown improved survival after pulmonary metastasectomy, with median survival from 10–28 months and 5-year survival rates up to 35%^{27,28}. Selection for pulmonary metastasectomy should be based on ability to achieve complete resection, disease-free interval greater than one year, fewer than three pulmonary nodules, absence of extra-thoracic and lymph node metastasis, and response to chemotherapy or immunotherapy.

The impact of metastasectomy is multifactorial. Surgical resection can render an individual disease-free in a short amount of time with minimal morbidity in carefully selected patients. Furthermore, excision can yield consistent results with iterative metastasectomy. Surgery also decreases the amount of tumor-secreted immunosuppressant potentially allowing the host's immune system to generate an improved response to remaining cancer cells²⁹. This concept was supported by a recent study which demonstrated that pathologic specimens from progressive foci of disease demonstrate a high percentage of T-regulatory cells and low

T-effector cells suggesting a mechanism of immune escape. Resection of these progressive foci in the setting of other stable lesions, resulted in median survival of 9.5 months³⁰.

Patient selection for metastasectomy is paramount and should take into consideration several factors that may give insight into tumor biology. Disease-free interval, longer tumor doubling time, number of metastatic lesions, and stabilization on systemic therapy have all been shown to be favorable indicators for benefit from surgery³¹. One of the most ambiguous considerations in the current era is how to optimally interface surgery and systemic therapy. Given improvements in our armamentarium, surgery may play a larger role as “consolidative” therapy (i.e. to achieve complete response when patients have largely responded but only have limited disease remaining) or more aggressive resections may be considered in otherwise healthy patients with the knowledge that adjuvant therapy has a significant impact on disease response. Although the survival benefits of tumor debulking remain unclear, there is certainly a benefit to palliative resection in symptomatic patients in whom surgery offers the potential for alleviating symptoms.

Adjuvant Therapy

Introduction

For decades, the management of metastatic melanoma was limited to a small number of largely ineffective drugs including dacarbazine and high dose interleukin-2 (IL-2). With the introduction of immune checkpoint inhibitors and targeted agents, the treatment of melanoma was revolutionized. Additionally, the recent Food and Drug Administration (FDA) approval of talimogene laherparepvec (TVEC), a genetically engineered virus which secretes granulocyte-macrophage colony-stimulating factor (GM-CSF) selectively inside the tumor cells thus initiating a tumor directed immune response, has incited additional enthusiasm. In this section, we outline landmark studies in the development of adjuvant therapy, the currently accepted indications for initiation of adjuvant therapy in both surgically resected, high-risk melanoma as well as advanced, unresectable melanoma and discuss other emerging options.

Indications for Adjuvant Therapy

The goal of adjuvant therapy is to improve survival by treating occult metastatic disease after known sites of malignancy are resected or otherwise treated. Early and late adjuvant therapy have been characterized as treatment after resection of a primary lesion and its associated synchronous metastatic disease (early) or after recurrence and resection of disease, including metastasectomy (late). The differentiation of these two treatment groups is important as patients who undergo early adjuvant therapy are considered lower-risk when evaluating long-term survival outcomes and the risk of adverse events is higher given their longer survival³². At present, adjuvant therapy is approved for patients with stage IIIA disease or higher with trials currently underway investigating the role of systemic therapy in patients with resected high-risk Stage IIB and C disease.

Adjuvant Immunotherapy

Immunotherapy entails the administration of monoclonal antibodies, T-cells or immuno-stimulatory cytokines aimed at priming the immune system and activating immune responses against residual tumor cells. The first immunomodulatory agent to be approved for the treatment of advanced melanoma was IL-2 in 1998. Subsequently, for two decades prior to FDA approval of adjuvant ipilimumab in 2015, interferon- α (IFN- α) was the only approved agent for the adjuvant treatment of high-risk cutaneous melanoma. This agent had such a high rate of side effects that only 50% of patients were able to successfully complete the entire year of intended therapy³³. Additionally, on long-term follow-up, this drug had no impact on distant metastasis-free survival or OS³⁴.

More recently, newer and more effective therapeutic agents have emerged. Agents targeting cytotoxic T-lymphocyte associated protein-4 (CTLA-4) and the programmed death-1 (PD-1) regulatory pathway have shown considerable success in the adjuvant and metastatic setting. Together, these therapies are known as checkpoint inhibitors, as they are antibody therapies directed against negative immunologic regulators.

Ipilimumab, a monoclonal antibody against CTLA-4, was granted FDA approval in 2011 after a phase III clinical study by Hodi, et al. found a significant improvement in median OS in patients with unresectable stage III or IV melanoma treated with ipilimumab as compared to control (10 vs. 6.4 months respectively; HR 0.66, $p=0.0026$)³⁵. Its approval was subsequently expanded for use in the adjuvant setting in 2015 after the phase III international EORTC 18071 trial compared adjuvant high-dose ipilimumab to placebo in patients with completely resected stage III melanoma. The trial demonstrated a median recurrence-free survival (RFS) of 26.1 months with ipilimumab versus 17.1 months with placebo (HR 0.75, 95% CI 0.64–0.9, $p=0.0013$)³⁶. A subsequent analysis demonstrated that ipilimumab resulted in significantly higher rates of 5-year RFS (40.8% versus 30.3%, $p < 0.001$), 5-year distant metastasis-free survival (48.3 versus 38.9, $p = 0.002$), and 5-year OS (65.4% versus 54.4%, $p = 0.001$) when compared to placebo³⁷. Despite these improvements in RFS and OS, ipilimumab is associated with a high incidence of adverse events. Grade 3 or 4 immune related adverse events (irAEs) which include diarrhea, hepatitis, thyroiditis, and adrenal insufficiency appear to be dose-related at 10 mg/kg, and the rate of grade 3 or 4 adverse events has been reported in 43% of patients³⁶. Based on these data, ipilimumab was approved for adjuvant therapy. When administered, NCCN guidelines recommend ipilimumab monotherapy at 3 mg/kg until disease progression in patients with resected stage IIIA with metastases >1 mm, resected stage IIIB-C, or resected nodal recurrence³⁸. However, given its associated toxicity and the arrival of newer agents, adjuvant ipilimumab is no longer routinely administered.

Pembrolizumab and nivolumab are both antibodies that target PD-1 and received FDA approval in the metastatic setting in 2014 and 2017, respectively, initially for use in patients with disease progression after receiving first-line therapy. Two phase III studies demonstrated the efficacy of nivolumab in stage III or IV melanoma and further established its superiority to chemotherapy in advanced melanoma. CheckMate 037 randomized patients with unresectable or metastatic melanoma to receive either nivolumab or chemotherapy with a primary end-point of objective response. Results demonstrated an overall response rate

(ORR) of 32% in patients from the nivolumab group as compared to 11% in chemotherapy group³⁹. CheckMate 066 was designed to analyze OS in nivolumab-treated patients and randomized patients with metastatic melanoma to treatment with nivolumab or dacarbazine. OS at one year was reported 73% in the nivolumab group versus 42% in the dacarbazine group ($p<0.001$)⁴⁰. The success of this agent was further established in the CheckMate 238 trial which led to the 2017 FDA approval of nivolumab as adjuvant therapy. This trial randomized patients with high-risk, completely resected stage IIIB, IIIC or IV melanoma to receive either nivolumab or ipilimumab. RFS, the primary endpoint, was 71% at 12 months for patients assigned to adjuvant nivolumab, compared with 61% for adjuvant ipilimumab (HR 0.65, 95% CI 0.51–0.83, $p<0.001$). Nivolumab also had a better safety profile, with a 14.4% incidence of grade 3 or 4 treatment-related adverse events, compared with 45.9% for ipilimumab⁴¹. As such, adjuvant nivolumab is preferred over high-dose ipilimumab based on improved efficacy and less toxicity, even in the absence of superior survival data.

The efficacy and safety of pembrolizumab were confirmed in KEYNOTE-002, a phase II study which randomized patients to either 2 mg/kg pembrolizumab, 10 mg/kg pembrolizumab or chemotherapy. Findings demonstrated a significant improvement in progression-free survival (PFS) in patients treated with either 2 mg/kg (HR 0.57, $p<0.0001$) and 10 mg/kg (HR 0.5, $p<0.0001$) compared to chemotherapy⁴². The 2019 FDA approval of pembrolizumab in the adjuvant setting was based on the results of the randomized, phase III EORTC 1325/KEYNOTE-054 trial, in which pembrolizumab was compared to placebo as adjuvant therapy for patients with resected, high-risk stage III melanoma. At a median follow-up of 15 months, pembrolizumab was resulted in a 1-year RFS of 75.4% compared to 61.0% in the placebo group (HR 0.57, 95% CI 0.43–0.74, $p<0.001$)⁴³. The efficacy of PD-1 inhibition and CTLA-4 blockade were further compared in KEYNOTE-006, a phase III clinical trial for patients with advanced melanoma. Results demonstrated that response rates were significantly better in patients who received pembrolizumab every 2 weeks (34%) and every 3 weeks (33%) compared to patients who received ipilimumab (12%). Additionally, pembrolizumab prolonged PFS and OS with comparatively less high-grade toxicity in patients with advanced melanoma⁴⁴. Overall, this study led to the conclusion that anti-PD1 should be considered as first-line therapy in all patients with advanced melanoma, regardless of mutation status. Similar to ipilimumab, immune related adverse events of anti-PD1 inhibitors include fatigue, diarrhea, nausea, anemia, and decreased appetite with a grade 3–4 incidence of approximately 14%⁴⁵. However, these do not appear to be significantly affected by the dose level.

Given their different mechanisms of action, several studies assessed the synergistic effect of combining CTLA-4 and PD-1 inhibitors demonstrating significant improvements in PFS and OS in advanced melanoma^{46–48}. In CheckMate 067, the combination of nivolumab and ipilimumab was compared to monotherapy in patients with unresectable stage III or stage IV disease. The combination therapy showed a significantly higher PFS of 11.2 months compared to 5.3 months with nivolumab monotherapy. Treatment-related adverse events of any grade that led to discontinuation of the study therapy occurred in 7.7% of the patients in the nivolumab group, 14.8% of patients in the ipilimumab group, and 36.4% of the patients in the combination group⁴⁷. This trial led to FDA approval of the combination therapy of nivolumab and ipilimumab in 2015 for use in metastatic or unresectable melanoma.

CheckMate 915 is currently evaluating the use of combination ipilimumab and nivolumab as adjuvant treatment for patients with fully resected stage IIIB, IIIC, IIID, or IV cutaneous melanoma and the results of this trial are eagerly awaited.

Adjuvant Targeted Therapy

The treatment of melanoma was also revolutionized with the identification of the BRAF mutation in 2002⁴⁹. BRAF and its product, BRAF kinase, regulate the mitogen-activated protein kinase (MAPK) RAS-RAF-MEK-ERK pathway which further regulates transcription and translation of proteins that promote cell division and survival. The mutated BRAF gene transcribes a constitutively activated BRAF kinase which promotes cell proliferation and prevents apoptosis^{50,51}. BRAF V600E mutations were found to be very common in melanoma, and it is estimated that nearly 40–50% of tumor samples of patients with metastatic melanoma contain BRAF V600E mutations^{49,52}.

Vemurafenib was the first BRAF inhibitor approved by the FDA in 2011 after a phase II trial which included patients with previously-treated metastatic melanoma demonstrated a response rate of 50% with a median duration of 6.7 months and median OS of 15.9 months⁵³. Since that initial approval, the combination of BRAF and MEK inhibitors has proved superior to single agent BRAF inhibitors. In the metastatic setting there are now three combinations that are approved: vemurafenib and cobimetinib, dabrafenib and trametinib, and encorafenib and binimetinib. In the COMBI-AD trial, patients with BRAF V600E or V600K-mutated stage III cutaneous melanoma who had undergone complete resection were randomized to receive either combination therapy with dabrafenib plus trametinib or placebo. After a median follow-up of 2.8 years, the 3-year RFS was 58% for the combination arm versus 30% for the placebo arm with a higher rate of overall and distant metastasis-free survival. The main toxicities of treatment include pyrexia, fatigue, and nausea. Serious adverse events were noted in 36% of patients in the combination arm⁵⁴.

BRAF inhibitors may induce acquired resistance with continuous dosing, and half of the patients treated with BRAF-targeted therapies will relapse within six months⁵⁵. The challenge now is to develop therapies which may prevent this resistance, and this approach may hinge on harnessing the potential of BRAF inhibitors to alter the tumor microenvironment. Indeed, investigations studying combination therapy of BRAF inhibitors with immunotherapy or T-cell therapy are currently under way⁵⁶.

Adjuvant Radiation Therapy

In the current era of effective systemic therapies, the role of radiation therapy (RT) remains controversial. However, there are distinct scenarios where adjuvant radiation should be considered. The ANZMTG trial was a prospective multicenter phase III study in which 250 patients with high-risk disease were randomized to either observation or regional nodal basin RT. Results demonstrated that after a median follow-up for 40 months, RT significantly reduced the risk of loco-regional recurrence. However, there was no difference in OS⁵⁷. The North Central Cancer Center Treatment Group conducted a single-arm phase II trial to assess the role of adjuvant RT for patients with desmoplastic melanoma. Results demonstrated a 2-year locoregional recurrence rate of 10% and 5-year OS of 77%⁵⁸. There

is also a current randomized trial comparing adjuvant RT (48 Gy in 20 fractions) to observation for patients with primary melanoma of the head and neck region with neurotropism (). As we await results from these trials, RT holds promise and should be considered after regional lymph node dissection of macroscopic lymph node disease in patients with extracapsular extension, lymph node diameter >3 cm (neck or axilla), or 4 cm (groin), or at least one involved lymph node in the parotid lymph node region, two in the neck and axillary region, or three in the groin region⁵⁹. Radiation may also be considered after failure of previous regional lymph node dissection, and after resection of desmoplastic or other melanoma subtypes with neurotropism. Furthermore, stereotactic radiation surgery is gaining wider acceptance in the management of brain metastases, as several retrospective studies have demonstrated one-year local tumor control rates of 72–100% for patients with limited disease^{60,61}. However, prospective randomized trials are needed to determine the benefit of radiation therapy for melanoma brain tumors.

Other Adjuvant Therapeutic Options: Vaccine Strategies, Intralesional Therapies and Isolated Limb Perfusion

Various melanoma vaccine strategies are currently under investigation. Cancer vaccines can be categorized based on the type of tumor-associated antigen (TAA) involved including whole tumor cells, cancer cell lysates, peptides, DNA/RNA strands, and stimulated dendritic cells used for antigen presentation. The antigens may be shared across many melanomas, or they may be neoantigens that are uniquely expressed through malignant transformation.

A recent publication in *Nature* described the results of a melanoma vaccine targeting up to 20 personal tumor neoantigen administered in six patients with resected stage III-IV melanoma. Four stage III patients had no recurrence at 25 months after vaccination, while the two patients with metastatic disease who did recur later experienced complete response when treated with anti-PD-1⁶². Similarly, Sahin, et al. developed a personalized RNA-based vaccine to treat thirteen patients with stage III-IV melanoma. Among the eight patients with no detectable disease at the time of vaccination, most experienced prolonged DFS. Importantly, among five patients with evident metastatic disease at the time of vaccination, two experienced vaccine-related objective responses⁶³. These data provide a strong rationale for further development of this approach, both alone and in combination with checkpoint blockade or other systemic therapies.

Intralesional therapies are yet another option for patients with stage III ITM. In 2015, the FDA approved the oncolytic virus (herpes simplex virus 1)-derived therapy talimogene laherparepvec (T-VEC) for the treatment of cutaneous melanoma. T-VEC replicates selectively in tumor cells and encodes GM-CSF, lysing cells in injected tumors which are then taken up by antigen-presenting cells. The OPTiM randomized phase III study compared intralesional T-VEC to subcutaneous GM-CSF and demonstrated a median OS of 41 months in the T-VEC arm compared to 21.5 months in the GM-CSF arm. Additionally, T-VEC had a higher durable response rate (16.3% vs 2.1%, $p<0.001$) and ORR (26.4% vs 5.7%, $p<0.001$). Subset analyses also demonstrated a bystander effect in 15% of non-injected visceral metastases decreasing in size by more than 50%. Common toxicities for T-VEC included fatigue, chills, flu-like symptoms, and injection-site pain⁶⁴. It has been proposed that

intralesional therapies will be combined with systemic therapies to offer a synergistic effect in the mechanism of action of these two modalities. A double-blind, placebo-controlled phase III study has been designed to include 660 patients with unresectable stage III-IV melanoma who will be randomized to receive T-VEC plus pembrolizumab or placebo injections plus pembrolizumab (). We currently await the results of this promising trial.

For patients with extensive regional disease not amenable to local therapy or resection, isolated limb perfusion (ILP) remains a viable option. This technique was introduced in 1958 by Creech, et al. and is currently a well-established treatment of ITM that develop in 6–10% of patients^{65,66}. ILP entails obtaining vascular access to either axillary or femoral vessels and administering hyperthermic chemotherapy with melphalan. Moreno-Ramirez and colleagues published a systematic review on ILP analyzing 22 studies which included over 2000 patients with primary endpoints of ORR and survival. The median complete response rate to ILP was of 58%, with a median ORR of 90%. The recurrence rate was reported as 40%, with a median survival of 10.5 months until local recurrence⁶⁷. While ILP remains an option, isolated limb infusion (ILI), which was later developed in the 1990's, is generally a preferred option for managing unresectable locally advanced disease. Unlike ILP, access is obtained percutaneously and melphalan is infused at a lower rate in combination with actinomycin D⁶⁸. Given its less invasive nature, this remains the preferred option for patients being considered for regional therapy, especially those with a compromised performance status. In the largest study to date reporting the long-term outcomes for ILI, the complete response rate was 28.9% and ORR was 64.1%. Importantly, significant limb toxicity only developed in 3.9%⁶⁹. In a recent study comparing 3-month response rates and regional toxicity between the two techniques, ILP was associated with a higher ORR of 81% compared to 57% in ILI ($p<0.001$), and overall both therapies were well tolerated with a less than 3% risk of major toxicity. Despite the difference in response rates, there was no significant difference in median OS (40 months vs 46 months, $p=0.31$) which has led to the continued predilection towards use of the less invasive technique⁷⁰. While effective, ILP and ILI are labor intensive and limited to centers with the expertise to perform these procedures and manage the associated potential complications.

Neoadjuvant Therapy

Introduction

The concept of neoadjuvant therapy is well-established in many solid tumors including breast, rectal, and gastric cancer. However, the role for neoadjuvant therapy in melanoma is not as well-defined, and the current standard of care for patients with clinical stage III melanoma is surgery followed by adjuvant therapy. However, following the recent successes with adjuvant therapy in the treatment of advanced melanoma, there is evidence that a trial of preoperative therapy may be the best course of action.

Compared to adjuvant therapy, neoadjuvant therapy in stage III melanoma can provide several advantages including determining therapy efficacy for tailoring of subsequent adjuvant treatment, reducing tumor burden prior to planned surgery, and eventually correlating pathological response data to long-term outcomes including relapse-free and OS.

Neoadjuvant Immunotherapy

A recent trial by Amaria, et al. sought to assess the benefit of neoadjuvant nivolumab versus combined ipilimumab with nivolumab in 23 patients with clinical stage III or oligometastatic stage IV melanoma. Unfortunately, the trial was stopped early due to observed disease progression preventing resection in the nivolumab treatment arm and substantial toxicity in the combination arm, but results did demonstrate a 58% pathologic complete response in the combination arm with an associated longer distant metastasis-free survival⁷¹. A recently published trial demonstrated a rapid response to neoadjuvant anti-PD-1 treatment in patients with stage IIIB, IIIC or stage IV melanoma. All 29 patients received a single dose of pembrolizumab, followed by complete resection three weeks later and continued adjuvant therapy for one year. Approximately 30% of patients had a complete or major pathologic complete response all of which remain disease free at 24 months⁷². Although the results of these studies suggest that neoadjuvant immunotherapy offers promise in the treatment of patients with stage III–IV oligometastatic melanoma, evidence remains premature and the optimal neoadjuvant treatment regimen is unclear for now. Notably, a recent study also demonstrated the safety of ipilimumab use in the perioperative setting with a grade 1 wound complication of 17% and no associated grade 3–5 complications³⁰. Trials involving immunotherapy in the neoadjuvant setting are gaining attention, both with individual agents and in combination (Table 3).

Neoadjuvant Targeted Therapy

The high and rapid response rate and good safety profile of BRAF-targeted agents provide an unprecedented opportunity for a neoadjuvant approach in melanoma. A recent phase II trial by Amaria, et al. randomized 21 patients with stage IIIB, IIIC or oligometastatic stage IV BRAF-mutated melanoma to upfront surgery and adjuvant therapy or neoadjuvant plus adjuvant dabrafenib and trametinib. After a median follow-up of 18.6 months, PFS was 71% versus 0% in the standard of care arm. Importantly, therapy was well-tolerated with no grade 4 adverse events⁷³. Additionally, a recent study demonstrated that patients presenting with stage III, BRAF V600E-positive, non-resectable melanoma can be treated with BRAF inhibitors and achieve a successful R0 resection⁷⁴. Questions that remain in the use of neoadjuvant targeted therapy include the optimal timing of therapy, the extent of surgery after therapy, and the use of pathologic response information to help guide post-operative therapy.

Summary

The management of advanced stage melanoma has changed dramatically with the development of molecularly targeted therapies and immunotherapies, both of which have demonstrated a survival benefit for patients with advanced stage III and IV melanoma. Currently, dabrafenib and trametinib are approved for use in the adjuvant setting along with nivolumab and pembrolizumab. Novel ways to further modulate the immune system are under investigation, and developing additional salvage strategies for advanced melanoma will hinge on using combination therapies and other strategies such as T-cell therapy. Given this expanding realm of systemic therapy, indications for metastasectomy continue to expand as this can render patients disease-free or can serve as a complementary treatment in patients

receiving systemic therapy who demonstrate progressive lesions in the setting of otherwise stable disease. Additionally, palliative surgery remains an option for patients presenting with symptomatic resectable metastases.

With this recent breakthrough in the adjuvant treatment of melanoma and the availability of multiple effective agents, efforts are now focused on translating these therapies to the neoadjuvant setting. In addition to potentially improving survival outcomes, tumor resectability, and local control, neoadjuvant therapy has the major advantage of allowing us to assess the clinical and pathologic response of treatment. Several studies of neoadjuvant combination immunotherapy are currently under way to address the choice of agent and the timing of treatment for a neoadjuvant protocol. The information presented in this article aims to integrate the latest advancements in the treatment of advanced melanoma while acknowledging that the clinical decisions should take into consideration the physician's expertise and judgment and, more importantly, be individualized to each patient's needs and wishes.

Financial support:

Supported in part by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number TL1TR002382 and the Katz Foundation

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Synopsis

Recent advances in effective medical therapies have markedly improved the prognosis for patients with advanced melanoma. This chapter aims to highlight the current era of integrated multi-disciplinary care of patients with advanced melanoma by outlining current approved therapies including immunotherapy, targeted therapy, radiation therapy and other strategies used in both the adjuvant and neoadjuvant setting, as well as the evolving role of surgical intervention in the changing landscape of advanced melanoma.

Key Points

- The management of unresectable stage III and stage IV melanoma involves a multimodal treatment including surgery, systemic immunotherapies and targeted therapies.
- Resection of progressive foci of disease may modulate the immunosuppressive effects of melanoma.
- Checkpoint inhibitors have dramatically improved survival for patients with metastatic melanoma. Nivolumab, pembrolizumab, and ipilimumab are currently approved for the adjuvant and metastatic setting.
- Small studies have already demonstrated the benefit of both systemic immunotherapy and targeted therapy in the neoadjuvant setting. Clinical trials are ongoing.

Table 1.

Adjuvant Therapy FDA Approval and Indications

Drug Name	FDA Approval	Indication	Trial Leading to Approval	Dosing Regimen
High-dose IFN α	1996	High-risk resected melanoma	ECOG 1684	Initiation: 20 million IU/m ² for 4 weeks Maintenance: 10 million IU/m ² for 11 months
Ipilimumab	2015	Resected stage III melanoma	EORTC 18071	3 mg/kg Q2W for up to 2 years
Nivolumab	2017	Resected stage III or IV melanoma	Checkmate-238	3 mg/kg Q2W for 4 doses, then 3 mg/kg Q2W for up to 2 years
Dabrafenib + trametinib	2018	Resected stage III melanoma with BRAF V600 mutations	COMBI-AD	350 mg PO daily + 2 mg PO daily until disease progression
Pembrolizumab	2019	Resected stage III melanoma	EORTC 1325	2 mg/kg Q3W for up to 2 years
Vemurafenib	Unknown status	Stages IIC-IIIB resected melanoma	BRIM8	960 mg BID until disease progression or unacceptable toxicity

Table 2.

Active Adjuvant Trials in Stage III or IV Melanoma

Trial	Adjuvant Treatment	N	Treatment Duration	Primary Endpoint	Estimated Completion
	Dabrafenib + trametinib vs standard of care	21	Neoadjuvant 8 weeks Adjuvant 44 weeks	Relapse-free survival	2019
	High-dose (HD) ipilimumab or low-dose (LD) ipilimumab vs HDI	1673	Adjuvant: q3w × 4 then every 3 months × 4 vs 1 year	Recurrence-free survival Overall survival	2020
	Pembrolizumab	27	Neoadjuvant: 3 weeks Adjuvant: 1 year	Adverse events	2022
	Ipilimumab + nivolumab	25	Adjuvant: 6 months	Toxicity Recurrence-free survival Overall survival	2019
	PEG-IFN	1200	Adjuvant: 2 years	Relapse-free survival	2019
	Pembrolizumab	1378	Adjuvant: 1 year	Relapse-free survival Overall survival	2023
	Pembrolizumab	556	Neoadjuvant: 9 weeks Adjuvant: 11–14 weeks	Event-free survival	2022
	Dabrafenib + Trametinib	78	Neoadjuvant: 8 weeks Adjuvant: 44 weeks	Relapse-free survival	2019
	Autologous Dendritic Cell vaccine	120	Adjuvant: daily injection × 5 days	Relapse-free survival	2019
	Nivolumab + Placebo or Nivolumab + Ipilimumab or Double Placebo Control	312	Adjuvant: one year	Progression-free survival	2021
	Drug: Nivolumab Biological: PD-L1/IDO peptide vaccine	50	Drug: indefinitely Biological: 15 vaccines	Adverse events	2019
	Pembrolizumab + Imiquimod	10	2 years	Overall survival Progression-free survival	2021

Table 3.**Active Neoadjuvant Melanoma Clinical Trials**

Trial	Neoadjuvant Treatment	Treatment Duration	Primary Endpoint	Estimated Completion
Immunotherapy				
	Group A: Nivolumab Group B: Nivolumab + Ipilimumab	Neoadjuvant: 7 weeks Adjuvant: 6 months	Pathologic complete response	2020
	Nivolumab + HF 10	12 weeks	Pathologic complete response	2022
	Pembrolizumab Procedure: Surgery Radiation: IMRT	12 weeks	Disease free survival	2025
	Pembrolizumab and high dose interferon alfa-2b (HDI)	6–8 weeks	Adverse events	2019
	Group A: Dabrafenib + Trametinib THEN Pembrolizumab Group B: Dabrafenib + Trametinib + Pembrolizumab Group C: Pembrolizumab ONLY	Neoadjuvant: 6 weeks Adjuvant: 46 weeks	Pathologic complete response	2019
	Ipilimumab + Nivolumab	6 weeks	Response rate Recurrence free survival	2020
	Pembrolizumab	One dose	Number of adverse events	2022
	Pembrolizumab	9 weeks	Event-free survival	2022
	Group A: VX15/2503 + Nivolumab + surgery Group B: VX15/2503 + Ipilimumab + surgery Group C: VX15/2503 + Nivolumab + Ipilimumab Group D: VX15/2503 + surgery	Two doses	Extent of CD8 T-cell infiltration following treatment	2031
Targeted Therapy				
	Drug: Vemurafenib + Cobimetinib	8 weeks	Resectability rate	2022
	Drug: Dabrafenib + Trametinib	8 weeks	Relapse-free survival	2019
	Drug: Vemurafenib + Cobimetinib	4 weeks	Resectability rate	2019
	Group A: Atezolizumab + Vemurafenib + Cobimetinib Group B: Atezolizumab + Cobimetinib	12 weeks	Pathologic complete response	2023
	Group A: Dabrafenib + Trametinib THEN Pembrolizumab Group B: Dabrafenib + Trametinib + Pembrolizumab Group C: Pembrolizumab ONLY	Neoadjuvant: 6 weeks Adjuvant: 46 weeks	Pathological response rate Resectability rate	2019
Other Therapies				
	GM-CSF	14 days	Th1/Th2 ratio	2019
	Daromun	4 weeks	Recurrence free survival	2020