Local and Regional Therapy for Primary and Locally Recurrent Melanoma

Justin G. Wilkes, MD,[1,2] Ayushi Patel, BS,[2] and Jonathan S. Zager, MD[1,2]

[1]Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, Florida
[2]University of South Florida Morsani College of Medicine, Tampa, Florida

Corresponding author:
Jonathan S. Zager, MD
Moffitt Cancer Center
10920 North McKinley Drive
Room 4.4123
Tampa, FL 33612
Tel: (813) 745-1085
Fax: (813) 745-5725
Email: Jonathan.Zager@moffitt.org

Abstract: In the vast majority of cases, cutaneous melanoma presents as localized disease and is treated with wide excision and sentinel lymph node biopsy, with shared decision making regarding completion lymph node dissection and adjuvant systemic therapy. The treatment of recurrent and in-transit disease is more complex, with further options for regional and systemic therapies and multiple variables to be factored into decisions. Rates of overall and complete response to regional therapies can be quite high in carefully chosen patients, which limits the need for systemic therapies and their inherent side effects. Ongoing trials aim to assess the efficacy of combination regional and systemic therapies and assist in deciding among these options. This review discusses the treatment of primary melanoma and regional nodal disease and offers an in-depth discussion of options for the treatment of recurrent melanoma and in-transit melanoma.

Keywords
Intralesional injections, in-transit melanoma, isolated limb infusion, melanoma, metastatic melanoma, regional perfusion chemotherapy, T-VEC

Introduction

Melanoma is the fifth most common cancer in the United States and the 17th-leading cause of cancer-related death, with recent declines in mortality following US Food and Drug Administration (FDA) approval of immunotherapy and targeted therapy agents.[1] Newly diagnosed melanoma most commonly presents as primary disease, accounting for 84% of patients. Regional nodal spread is present in 9% and distant disease in 4% of patients at diagnosis.[1] In the vast majority of cases, localized disease is treated with wide excision. The treatment of regional disease is complex and depends on its extent. The treatment of systemic disease has seen dramatic advances over the last decade and is not the focus of this review. Here, we discuss the treatment of primary melanoma and regional nodal disease, and we offer an in-depth discussion of options for the treatment of recurrent melanoma and in-transit melanoma.

Primary Melanoma

Wide Excision

The treatment of localized melanoma is wide excision to the level of the underlying fascia. The resection margin of healthy surrounding

tissue is 1 or 2 cm depending on the tumor Breslow depth of invasion (the penetration of tumor cells beyond the granular layer of the epidermis); the intent is to include microscopic extension and satellite lesions and to minimize local recurrence (LR).[2] For tumors with a Breslow thickness of less than 1 mm, the recommended margin is 1 cm, resulting in an LR rate of approximately 0% to 2%.[3-5] Wider margins have failed to decrease LR, nodal recurrence, or distant recurrence.[6,7] For tumors that are more than 2 mm thick, the recommended margin of excision is 2 cm, resulting in LR rates of approximately 2% to 4%; rates of LR, nodal recurrence, distant recurrence, or overall survival (OS) are not decreased with wider margins.[8,9] For tumors 1 to 2 mm thick, the recommended margin is 1 to 2 cm, depending on tumor characteristics (eg, ulceration, mitotic rate, and lymphovascular invasion). Some retrospective reviews have shown no difference in rates of LR (2%-3%) and 5-year disease-free survival (DFS; 85%-87%) in comparisons of 1- and 2-cm margins in this population, regardless of tumor characteristics. The only difference in outcome with wider excisions is an increased need for skin graft.[10]

Sentinel Lymph Node Biopsy and Regional Nodal Control

Melanoma spreads primarily via lymphatic networks, and the likelihood of spread is strongly correlated with Breslow depth. Sentinel lymph node (SLN) status is the single most important prognostic marker and invaluable to staging. For clinically node-negative patients with tumors less than 0.75 mm thick, the likelihood of lymphatic spread is less than 5%, and for those with tumors between 0.75 and 1.0 mm thick, the likelihood is approximately 6% to 8%.[11,12] Among patients with thick primary tumors (>4 mm), the sentinel lymph node biopsy (SLNB) positivity rate is as high as 36%.[13] SLNB is recommended for patients presenting with clinically node-negative disease (no palpable, abnormal lymph nodes) in whom the likelihood of a positive SLNB result (tumor thickness >0.8-1.0 mm) is greater than 5%.

The value of SLNB has changed dramatically since several large, prospective trials have been reported. In the Multicenter Selective Lymphadenectomy Trial I (MSLT-I), initiated in 1994, patients who had node-negative melanoma with a thickness of at least 1.0 mm were randomly assigned to SLNB or to observation of the nodal basin.[14] Completion lymph node dissection (CLND) was performed in patients with a positive SLNB result, and therapeutic lymph node dissection (TLND) was performed in patients in the observation arm if nodal disease developed. Although performing SLNB failed to improve melanoma-specific survival (MSS) significantly in the overall study population, a subset analysis found that in the cohort with melanoma of intermediate thickness (Breslow depth of 1.2-3.5 mm) and the cohort with thick melanoma (depth of >3.50 mm), SLNB was associated with improved DFS (71% vs 65%; *P*=.01 and 51% vs 41%; *P*=0.03, respectively) and MSS (85% vs 62%; *P*<.001 and 65% vs 48%; *P*=.03, respectively). In further subset analysis, patients with a positive SLNB who underwent CLND had improved MSS at 10 years vs those in the surveillance cohort whose disease recurred in the nodal basin and who ultimately required TLND (62% vs 42%; *P*=.006). Desiring clarity as to whether SLNB and immediate CLND provided survival advantage over observation alone in patients with SLN-positive disease, the Multicenter Selective Lymphadenectomy Trial II (MSLT-II) compared CLND after a positive SLN vs active surveillance with regional nodal basin ultrasound in patients who had SLN-positive disease. Although locoregional control was more likely in the patients undergoing CLND than in those in the active surveillance group (92% vs 77%; *P*<.001), MSS (86%) did not differ between the groups.[15]

The German randomized clinical trial DeCOG-SLT, which was conducted virtually simultaneously, confirmed these results.[16] Taken together, the results indicate that SLNB alone confers durable regional DFS in the majority of patients, with a limited added value of immediate CLND. For several reasons (the absence of MSS benefit, the limited added staging value of CLND, the ability to conduct accurate surveillance with advancements in ultrasound technique and quality, the advent of efficacious systemic therapy, and the morbidity of CLND [lymphedema rate: ~6% for axillary dissection, 15%-35% for inguinal dissection]), recommendations have shifted to active surveillance of the SLN basin for SLN-positive patients, along with a discussion of the risks of, benefits of, and alternatives to adjuvant systemic therapy.[17,18]

Patients presenting with synchronous clinically positive nodes without systemic disease may benefit from TLND for control of regional nodal disease. Neoadjuvant treatment with immunotherapy or targeted therapy has resulted in a trend toward improved outcomes in these patients and is an active area of investigation.[19-23] Radiation to the involved lymph node basin is considered on the basis of burden of disease, size of the nodes, number of nodes involved, and the presence of extranodal extension. Although a detailed discussion of nodal basin radiation is beyond the scope of this review, because of its value in the era of efficacious systemic therapies, it is garnering new consideration.[24]

In-transit/Recurrent Disease

Workup/Staging

The treatment history of patients presenting with suspected recurrent melanoma should be scrutinized to

determine the location of the recurrence relative to that of the primary melanoma, adequacy of the initial resection, and length of the disease-free interval. Patients who underwent an adequate initial excision and have an LR within 2 cm of the initial tumor should be considered to have dermal lymphatic disease outside the boundaries of the initial excision. Decision making should be used to manage these patients, similar to that for patients who present with in-transit melanoma (ITM), defined as intralymphatic tumor in the skin or subcutaneous tissue more than 2 cm from the primary tumor, but not beyond the nearest nodal basin. Patients with a biopsy-confirmed LR or ITM should undergo whole-body staging with positron emission tomography/computed tomography to assess for distant metastases, in addition to magnetic resonance imaging or computed tomography of the brain.[25]

Excision

Patients who have LR or ITM without regional or distant metastases and with a small burden of disease, may benefit from surgical resection, which can produce long-term relapse-free survival.[26-28] In a retrospective review of 648 patients in whom LR (within 5 cm of the primary excision) was treated with surgical resection, no relapse occurred in 19%, another LR developed in 30%, ITM or lymph node metastases developed in 27%, and systemic metastases developed in 23%. The patients without relapse were disease-free at a median follow-up of 8 years.[29] In a retrospective review of 130 patients at a single institution with first in-transit events undergoing resection, local failure alone was uncommon (6%), but in-transit failure occurred in 30%, distant failure in 23%, and regional recurrence in 9%.[27] Although the high failure rates after the treatment of ITM with excision alone are discouraging, 19% to 29% of patients were cured with excision alone, and these studies were collected before the arrival of immunotherapy and BRAF-targeted therapy.

SLNB for recurrent melanoma or ITM is controversial. The biopsy success rate is reported to be as high as 96% to 100%, and the positivity rate is reported to be as high as 40% to 47%. The successful node biopsy rate is lower in patients who have had a prior SLNB.[30]

Intralesional Therapy

Intralesional therapy is the direct injection of a therapeutic agent into tumor. The goal of intralesional injection therapy is local tumor destruction and immune stimulation promoting the destruction of remote disease (bystander or abscopal effect). William Coley first described intralesional injections in 1893, with erysipelas injections for inoperable sarcoma and carcinoma.[31] Multiple new injection therapies have since been developed. Intralesional therapies for ITM, including their mechanisms of action, efficacy, and safety, are discussed in this section.

Bacillus Calmette-Guérin. One of the first intralesional therapies used for ITM was bacillus Calmette-Guérin (BCG), a live, attenuated strain of *Mycobacterium bovis*. In 1976, Karakousis and colleagues described intralesional BCG in 8 patients with melanoma and found partial tumor necrosis and lymphocytic infiltration after just one injection.[32] A more recent pooled analysis of 15 noncontrolled trials demonstrated a pathologic response in 45% of patients, including a complete response (CR) in 19%.[33]

The use of BCG became limited owing to the associated toxicity and lack of OS benefit.[26,34] Adverse events include anaphylactic and complement-dependent (Arthus) reactions, severe hypotension, and disseminated intravascular coagulation.[35,36] BCG injection of regional lymph nodes also has been studied as adjuvant therapy in patients with high-risk disease, but no DFS or OS benefit has been demonstrated.[37]

Interleukin 2. Interleukin 2 (IL-2) is a pleiotropic cytokine produced by T lymphocytes that plays a role in the proliferation and activation of cytotoxic CD8+ T cells and natural killer cells. It also promotes the differentiation of CD4+ T cells into T helper 1 and T helper 2 cells, and blocks T helper 17 cell and T follicular helper cell differentiation.[38] IL-2 was first administered as a high-dose intravenous bolus to treat stages III and IV melanoma. The FDA approved IL-2 for the treatment of metastatic melanoma in 1998. Later studies demonstrated an overall response rate (ORR) of 10% to 15%, but the dose was often reduced or treatment halted owing to systemic toxicity.[39,40]

IL-2 has also been used as an intralesional agent. A systematic review of 6 observational trials, comprising 2182 lesions among 140 patients, demonstrated a CR in 78% of lesions and 50% of patients. Although the treatment was well tolerated, many patients had localized swelling, pain, and mild flu-like symptoms.[41] The use of IL-2 as an intralesional therapy is limited owing to the high cost of treatment, the need for frequent injections, and the lack of a documented bystander effect in noninjected lesions.[42]

Granulocyte-Macrophage Colony–Stimulating Factor. Granulocyte-macrophage colony–stimulating factor (GM-CSF), a growth factor with immunomodulatory effects, plays a role in the proliferation and activation of T cells and the maturation of dendritic cells.[43,44] GM-CSF is used primarily in combination with other agents as a promoter of immune response. Studies of intratumoral GM-CSF monotherapy are limited. In a phase 1 study, 13 patients underwent GM-CSF injection

into 2 subcutaneous metastases with different dosing schemes. A partial response (PR) in injected or noninjected metastases occurred in 3 patients, and among the patients with responding lesions, increased numbers of T-cell infiltrates, particularly CD4+ T cells, were noted.[45] In another study, 16 patients were injected in 1 lesion and in normal skin for 10 consecutive days at 4 different dose levels. An increase in dendritic cells and T cells was observed at all dose levels, but no antitumor activity.[46] Clinical studies of GM-CSF encoded in an oncolytic virus have shown more promising results, as described below.[47]

PV-10 (Rose Bengal). PV-10, also known as rose bengal, is a water-soluble xanthene dye that was first used as a diagnostic agent for testing liver function; currently, it is used as a diagnostic tool in ophthalmology.[48] The agent is taken up by lysosomes, and although cell death occurs primarily via necrosis, some cell death also occurs through caspase-mediated apoptosis.[49] PV-10 treatment also results in the lysis of melanoma cells via cytotoxic T cells and induces tumor-specific T cell–mediated immunity, resulting in the regression of tumor metastases distant from the injected lesion.[50] Possible potentiation of the immune response by combining PV-10 with blockade of the programmed death 1/programmed death ligand 1 (PD-1/PD-L1) pathway has been demonstrated in murine models.[51]

In a phase 2 trial that included 11 patients, 26 target lesions were injected with PV-10, and 28 nontarget lesions were observed for a bystander effect. Of the target lesions, 36% showed a CR and 12% showed a PR. Among the nontarget lesions, the CR and PR rates were 15% and 12%, respectively. In the lesions receiving high-dose PV-10, the ORR was 69%. When a response occurred in target lesions, a response in nontarget lesions was more likely to occur.[52] In a phase 2 study, 80 patients with refractory disease received intralesional PV-10 up to 4 times a week over 16 weeks. The ORR was 51%, and the CR rate was 26%. Among the 42 patients with bystander lesions, 26% showed a CR, with a strong correlation between bystander lesion response and target lesion response. All patients experienced one or more adverse events (AEs), most grade 1 or 2, and 15% of patients experienced at least one grade 3 AE.[53] More recent studies have demonstrated ORRs as high as 87% and CR rates as high as 42%.[54] PV-10 in combination with pembrolizumab (Keytruda, Merck) has shown promising results in phase 1b studies, with a CR rate of 10% (75% in target lesions), a PR rate of 57%, and a PFS of 11.7 months.[55] A phase 1b/2 study of patients with disease resistant to checkpoint blockade treated with the combination of PV-10 and pembrolizumab also is showing promising early results, with an ORR of 36%.[56]

Talimogene Laherparepvec. Talimogene laherparepvec, also known as T-VEC (Imlygic, Amgen), is a genetically modified herpes simplex virus type 1 that is an FDA-approved oncolytic viral therapy for treating locoregionally advanced melanoma. Oncolytic viruses cause the selective lysis of tumor cells while inducing a systemic immune response against tumor remote from the injection site.[57,58] In the construction of T-VEC, the gene for GM-CSF is substituted for neurovirulence factor ICP34.5. These alterations allow enhanced MHC class I presentation and a tumor-specific immune response.[59]

The phase 3 OPTiM trial compared intralesional T-VEC with subcutaneous injection of GM-CSF alone. The primary endpoint was the durable response rate (DRR), defined as the rate of continuous responses lasting for at least 6 months and beginning within the first 12 months of treatment. The DRR was significantly higher with T-VEC than with GM-CSF (16% vs 2%; $P<.0001$). The ORR also was higher in the T-VEC arm (26% vs 6%), with a median OS of 23 months with T-VEC vs 19 months with GM-CSF. Of note, the durable responses were most profound in patients with stage IIIB/C and stage IVM1a disease (rates of 33% and 16%, respectively), whereas patients with stage IVM1b and IVM1c disease had minimal responses (rates of 3% and 7%, respectively).[47,60] T-VEC is safe and well tolerated, with local inflammation, erythema, fever, fatigue, and chills the most common side effects.[61] Grade 1 or 2 AEs are noted in approximately 85% of patients.[61,62] None of the grade 3 or higher AEs, at a rate of 36% in the T-VEC arm and 21% in the GM-CSF arm, were attributed to the injections. The 10 fatal events in the T-VEC arm were determined to be unrelated to treatment; rather, they occurred because of progression of disease.[47] In a follow-up study assessing the bystander effect, T-VEC caused a decrease in size of more than 50% in 64% of the injected lesions, in 34% of the noninjected nonvisceral lesions, and in 15% of the noninjected visceral lesions. These data validated T-VEC as an inducer of systemic immunotherapeutic effects.[60]

A retrospective analysis of the standard-of-care experience from Moffitt Cancer Center reviewed 27 patients treated with T-VEC. Of the 23 patients who met the criteria for response analysis, 44% experienced a CR, 13% experienced a PR, and 22% had stable disease.[63] In a larger, multi-institutional study looking at standard-of-care T-VEC use after approval, Louie and colleagues evaluated 80 patients. After a median follow-up of 9 months, the researchers noted a CR in 39% of patients and a PR in 18% of patients.[64] A multi-institutional review of patients treated with T-VEC after failure of immunotherapy has shown an ORR of 43% and an in-field CR rate of 23%.[65] Overall, these data indicate that following FDA approval, the standard-of-care experience with T-VEC may demonstrate a

Table 1. Completed Trials of Intralesional Therapy in Combination With Immunotherapy for Melanoma

Author	Study Design	Study Agents	No. Pts	CR, %	PR, %	OS rate at 18 mo, %
Zager et al[56]	Phase 1b/2	PV-10 + pembrolizumab	11	9	27	NR
Agarwala et al[55]	Phase 1b/2	PV-10 + pembrolizumab	21	10	57	NR
Puzanov et al[66]	Phase 1b	T-VEC + ipilimumab	19	22	28	67
Chesney et al[67]	Phase 2	T-VEC + ipilimumab	98	13	26	NR
		Ipilimumab	100	7	11	
Long et al[70]	Phase 1b	T-VEC + pembrolizumab	21	33	29	NR

CR, complete response; mo, months; No., number; NR, not reported; OS, overall survival; PR, partial response; pts, patients; T-VEC, talimogene laherparepvec.

higher CR rate (likely owing to the selection of patients with fewer and/or less bulky lesions) than initially demonstrated by trial data, and shows good effect in patients whose disease has failed to respond to immunotherapy.

In an effort to improve the efficacy of T-VEC, it has been combined with immunotherapy in multiple trials. A phase 2 trial that studied a combination of T-VEC and the anti–cytotoxic T-lymphocyte–associated antigen 4 monoclonal antibody ipilimumab (Yervoy, Bristol Myers Squibb) found a higher ORR for combination therapy than for ipilimumab monotherapy (39% vs 18%, respectively). Visceral lesions decreased in size in 52% of the patients given combination therapy, compared with 23% in the ipilimumab-alone group. Although these results are promising, the response rate is somewhat lower than in trials of T-VEC alone. Regardless, combination treatment is relatively safe, with a 26% to 45% rate of grade 3/4 AEs.[66,67] T-VEC combination therapy with the anti–PD-1 agent pembrolizumab has shown very promising phase 1 results, with an ORR of 62% and an acceptable safety profile.[68] Observational studies have shown extensive overlap in the use of immunotherapy with T-VEC in clinical practice (see Table 1).[69,70] Multiple studies are ongoing of combinations of T-VEC with immunotherapy (NCT04068181, NCT02965716), targeted therapy (NCT03088176), and intra-arterial therapy (NCT03555032). Other studies are exploring whether the antigens of a resectable melanoma should be used to advantage before they are excised by administering neoadjuvant intralesional T-VEC (NCT02211131, NCT03842943, NCT04427306). Certainly, intralesional therapy has yielded exciting early results and is a very active area of ongoing research (see Table 2).

Intra-arterial Therapy

Another consideration for the management of unresectable ITM is intra-arterial therapy. This can be divided into isolated limb perfusion (ILP; HILP if the perfusate is hyperthermic) and isolated limb infusion (ILI). Both methods allow high concentrations of cytotoxic agents to circulate in an extremity while avoiding systemic toxicity. Although these procedures are well tolerated overall, a potential exists for systemic leak in addition to limb toxicities.[71] In 1982, Wieberdink and colleagues first described a toxicity grading system that is commonly used to report acute tissue reactions and regional toxicities associated with these procedures. Grade 1 indicates no reaction, grade 2 slight erythema and/or edema, grade 3 considerable erythema and/or edema with blistering, grade 4 extensive deep tissue damage causing functional impairment or compartment syndrome, and grade 5 reactions that may necessitate amputation.[72] In the balance between safety and efficacy, grade 3 toxicity is deemed acceptable and likely strikes a more appropriately aggressive balance than does no toxicity or grade 1/2 toxicity. The mechanisms, safety, and efficacy of ILI and ILP are discussed below.

Isolated Limb Perfusion. The systemic use of nitrogen mustards is highly toxic, and the antitumor effects of tolerable doses are limited. In response to this problem, Creech and colleagues in 1958, 15 years after the systemic use of nitrogen mustards began, described a method in which an affected extremity was isolated so that high-concentration chemotherapy could be delivered to it with limited systemic effect.[73] ILP is performed in the operating room with the patient under general anesthesia. The major arterial inflow and venous outflow of an affected extremity are isolated and cannulated to create a closed circuit. A proximal tourniquet isolates the extremity from the systemic circulation, and a cardiopulmonary bypass circuit is used to allow chemotherapeutic agents (typically heated to 39°-40°C) to circulate through the affected limb for 60 to 90 minutes. The most commonly used chemotherapeutic is melphalan hydroxide, although in Europe it is frequently combined with tumor necrosis factor alpha (TNF-α).[26,74] Longer perfusion times and higher temperatures have produced more robust responses, but at the cost of greater toxicity. No consensus exists on the ideal balance between time and temperature.[75]

Table 2. Ongoing Trials of Interventional Intralesional and Intra-arterial Melanoma Therapy Registered With ClinicalTrials.gov

Identifier	Study Agents	Phase	Enrollment	Completion Date	Location
Intralesional					
NCT03445533 (ILLUMINATE-301)	Ipilimumab +/- IMO-2125	3	454	2021	International, multicenter
NCT02366195 (TVEC-325)	Immune response to T-VEC	2	112	2021	International, multicenter
NCT03618641	CMP-001 + nivolumab	2	34	2021	UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania
NCT03190824	Oncolytic virus OBP-301	2	4	2021	Research site, Morristown, New Jersey
NCT01740297	Ipilimumab +/- T-VEC	1/2	217	2021	International, multicenter
NCT04200040	OrienX010 + dacarbazine	2	165	2022	Beijing Cancer Hospital, Beijing, China
NCT03544723[a]	*TP53* gene therapy + immune checkpoint inhibitors	2	40	2022	US, multicenter
NCT04526730	Tavokinogene telseplasmid (tavo) + electroporation + intravenous nivolumab	2	33	2022	Moffitt Cancer Center, Tampa, Florida
NCT03435640/ REVEAL[a]	NKTR-262 + bempegaldesleukin (NKTR-214) +/- nivolumab	1/2	393	2022	US, Multicenter
NCT02857569/ NIVIPIT	Intratumoral ipilimumab + intravenous nivolumab	1/2	90	2022	Gustave Roussy, Villejuif, France
NCT02706353	APX005M + pembrolizumab	1/2	41	2022	University of Texas MD Anderson Cancer Center, Houston, Texas
NCT04291105[a]	Voyager V1 + cemiplimab	2	152	2023	US, multicenter
NCT03132675/ KEYNOTE695	Tavo + pembrolizumab	2	125	2023	International, multicenter
NCT04570332/ SPOTLIGHT203	BO-112 + pembrolizumab	2	40	2023	Spain, multicenter
NCT04093323	Polarized dendritic cell (aDC1) vaccine, interferon alpha-2, rintatolimod, and celecoxib	2	24	2023	Roswell Park Cancer Institute, Buffalo, New York
NCT03684785[a]	Cavrotolimod + pembrolizumab or cemiplimab	1/2	130	2023	US, multicenter
NCT04387071[a]	CMP-001 and INCAGN01949	1/2	42	2023	US, multicenter
NCT03993678[a]	IP-001 following thermal ablation	1/2	39	2023	Switzerland
NCT03567889/Neo-DREAM	Neoadjuvant daromun	3	186	2024	US, multicenter
NCT03767348/ IGNYTE[a]	RP1 +/- nivolumab	2	300	2024	International, multicenter
NCT04152863	Pembrolizumab +/- V937	2	135	2024	International, multicenter
NCT04427306	Neoadjuvant T-VEC	2	62	2024	UC Davis Comprehensive Cancer Center, Sacramento, California
NCT04139902	Neoadjuvant dostarlimab (TSR-042) +/- TSR-022	2	56	2024	UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania
NCT03958383	IT-hu14.18-IL2 with radiation, nivolumab, and ipilimumab	1/2	61	2025	University of Wisconsin Carbone Cancer Center, Madison, Wisconsin

Table continues on next page.

Table 2. (*continued*) Ongoing Trials of Interventional Intralesional and Intra-arterial Melanoma Therapy Registered With ClinicalTrials.gov

Identifier	Study Agents	Phase	Enrollment	Completion Date	Location
Intra-arterial					
NCT01920516/ILI	ILP with melphalan	NA	40	2020	Italy
NCT04460053 (ILP-NfL)	Neurofilament light protein as a biomarker for neurotoxicity after ILP	NA	10	2020	Sweden
NCT03376126	Minimally invasive isolated limb perfusion	NA	10	2022	Sahlgrenska University Hospital, Gothenburg, Sweden
NCT04332874	Pembrolizumab + ILI	2	30	2023	Memorial Sloan Kettering Cancer Center, New York, New York
NCT03685890 (NivoILP)	Nivolumab + ILP	1/2	74	2023	International, multicenter
NCT03555032 (TITAN)[a]	T-VEC and ILP	1/2	15	2024	United Kingdom

[a]Trial includes nonmelanoma cancers.
ILI, isolated limb infusion; ILP, isolated limb perfusion; NA, not applicable; tavo, tavokinogene telsaplasmid; T-VEC, talimogene laherparepvec.

Numerous studies have demonstrated both safety and efficacy for ILP in patients with unresectable melanoma. The largest US experience, a randomized controlled trial that included 124 patients (ACOSOG Z0020), compared ILP with melphalan alone vs ILP with melphalan and TNF-α. The responses to treatment were similar in the 2 arms at 3 months but were better sustained at 6 months in the TNF-α cohort than in the melphalan-alone cohort, with CR rates of 42% vs 20% (P=.101), respectively, and ORRs of 56% vs 48%, respectively (P=.460). The potentially improved response rate did come at a cost, however, with a higher rate of grade 3 and higher AEs (48% vs 38%) and 2 amputations.[76] Most other studies on ILP, although not randomized controlled trials, demonstrate higher CR rates and ORRs than the aforementioned US trial, with less toxicity. A systematic review by Moreno-Ramirez and colleagues of 22 studies, including 2018 HILPs, demonstrated a CR rate of 58%, an ORR of 90%, and a 5-year OS rate of 37%. Grade 3 or higher AEs occurred in 20% of patients, with amputation required in 0.7%. Of the 22 studies, 18 were performed in Europe (10 in the Netherlands), likely explaining the more-frequent adoption of ILP for ITM in Europe than in the United States, where the experience has been less promising.[77]

Isolated Limb Infusion. ILI, first described by Thompson and colleagues in the early 1990s, is a less invasive approach to intra-arterial therapy. Percutaneous catheters are inserted into the vascular inflow and outflow of an affected extremity under fluoroscopic guidance. A tourniquet isolates the vasculature of the extremity, and chemotherapeutic agents (melphalan with or without actinomycin D) that have been heated to 40°C are infused manually.[78] ILI has been shown to be well tolerated by older patients with medical comorbidities, who may not be able to tolerate ILP, and has the advantage of being more readily repeated in cases of persistent disease.[79-85]

In an international multicenter study, Miura and colleagues found an ORR of 64% (29% CR rate and 35% PR rate) among 687 patients undergoing ILI for the first time. The median OS was 38 months, with a median follow-up of 47 months. In-field and distant progression-free survival (PFS) was significantly longer in the patients who had a CR or PR, with a median OS of 46.5 months among responders.[80] An international comparison of ILI outcomes in the United States vs those in Australia reported similar CR rates, of 30% in Australia and 29% in the United States, despite procedural differences among the 687 ILIs analyzed.[82,83] An additional review looking at ILIs in octogenarians and nonagenarians with stage IIIB/IIIC melanoma across 9 international centers demonstrated response rates and toxicity similar to those in the general population, showing the safety of ILI in the elderly. In this study, OS (29 vs 40 months) and melanoma-specific survival (46 vs 78 months) were shorter among octogenarians and nonagenarians than in younger patients (<80 years).[85,86]

Grade 3 toxicity is seen in approximately 28% to 32% of ILIs.[84,87] Grade 4 toxicity is rarely seen. Perioperative factors associated with grade 3/4 limb toxicity are female gender, younger age, lower-limb procedures,

higher melphalan doses, longer drug circulation and ischemia times, increased tissue hypoxia, papaverine use, and high peak levels of creatinine kinase.

Although ORRs are somewhat lower with ILI than with ILP in most studies, patients treated with ILI have shown equivalent survival in many retrospective comparisons. In a retrospective review of 203 first-time ILI or HILP procedures by Dossett and colleagues, the ORR was 53% for ILI and 80% for ILP. However, survival was not significantly different (46 months for ILI vs 40 months for ILP).[81] In a Duke University study, the ORR was 81% for ILP and 43% for ILI among 188 patients undergoing first-time ILP or ILI. Again, no difference in OS was demonstrated, and the spectrum of toxicity was similar for the 2 modalities, although the likelihood of limb loss was much greater with ILP.[88]

More recent studies have explored the combination of ILI with systemic immunotherapy. In a phase 2 trial by Ariyan and colleagues, patients were treated with ILI followed by ipilimumab. At 3 months, the ORR was 89% (65% CR rate and 24% PR rate).[89] The PFS rate at 1 year was 58%, and clinical response was associated with an increase in T-cell infiltration.[90] These results indicate that the rates of response to ILI may be improved with combination therapy, which will be explored further (see Table 2).

Systemic Therapy

The advent of immunotherapy and targeted therapy for unresectable metastatic melanoma has revolutionized the care of the patient with metastatic melanoma. Immunotherapy has achieved an ORR of 58% and has improved median OS to longer than 5 years.[91] Targeted therapies with BRAF/MEK inhibitors have shown similar ORRs of 64% to 70% and significantly prolong OS as well.[92-94] Although an in-depth discussion of these therapies is beyond the scope of this review, systemic therapy is certainly relevant to a discussion of recurrence and ITM. However, it is important to note that patients with ITM were not analyzed separately in these large, randomized trials, nor did they represent a significant proportion of the study populations. Patients are often referred for the treatment of ITM after they have already begun systemic therapy or their disease has failed to respond to such treatment. The high ORRs seen with intralesional or intra-arterial therapy, without systemic toxicity, suggest that referral for regional therapy can be considered earlier, at the time of diagnosis of ITM, because systemic therapy will be available as an option should regional therapies fail. The opposite is not always true if up-front systemic therapy results in progression of disease in distant sites.[82]

Alternative Therapies for In-Transit/ Recurrent Disease

Carbon dioxide (CO_2) laser ablation provides adequate control of local metastases with relatively low morbidity rates, but it has largely been replaced by other modalities. One of the major disadvantages of CO_2 laser ablation is that it provides little bystander effect; in addition, multiple sessions and general anesthesia are often required to target all disease effectively. CO_2 laser ablation is occasionally used in the palliative setting and as an up-front therapy with the intention of limb infusion/perfusion in case of failed control.[95]

Imiquimod is a topical immune response modifier that has been used extensively in the treatment of lentigo maligna and melanoma in situ that is not amenable to resection. Rates of clearance of lentigo maligna are reported to be as high as 76%.[96] The role of imiquimod with regional metastases is unclear, and its study as a sole therapy is limited. Imiquimod has shown promising results when cutaneous lesions are treated twice daily over months, but these results have not been obtained with dermal or subcutaneous lesions.[97] It has been studied more thoroughly in combination with other immune modulators, topical agents, and injection therapies, with very high response rates; however, its role in the therapy of deeper lesions is yet to be defined.[98]

Diphencyprone (DPCP), another topical immunotherapy, has been used with success in cutaneous metastases in small series and as a combination therapy.[99]

Radiation for regional disease is used mostly for patients with microscopically positive margins that are not amenable to re-resection, or for palliation. In the setting of limited disease, radiation has produced CR rates as high as 64% and ORRs near 100%. Lack of a bystander effect and difficulty with wound healing limit the use of radiation as a primary treatment of ITM.[100]

Lastly, amputation is a rarely used option for ITM. In the uncommon scenario of disease isolated to a limb that does not respond to systemic, regional, or local therapies, amputation is a consideration.

Appropriate Choice of Therapy for In-Transit or Recurrent Disease

The treatment of locally recurrent melanoma/ITM limited to an extremity is complex, and it is reasonable to consider referral to a center that frequently tackles these decisions. Excision of ITM is best suited to patients with a limited number (1-3) of lesions. With an increasing burden of disease comes a greater suspicion of unrecognized microscopic disease. The disease-free interval is also important to consider; the likelihood of unrecognized disease is higher when

the time to recurrence after primary resection is relatively short (<2 years).

Although the choice between intralesional therapy and intra-arterial therapy is decided on a case-by-case basis, some generalizations can be made. Intralesional therapy is most easily performed on visible or easily palpable lesions and can be done with the aid of ultrasound. It does require weekly to biweekly treatments for many months and a patient who is amenable to frequent visits.[63] Intra-arterial therapy is limited to patients with appropriate comorbidities. Its use is limited primarily on the basis of level of disease because a tourniquet must be placed above the highest level of disease. However, it is possible to achieve locoregional control by means of intra-arterial therapy in combination with local resection, or even TLND proximal to tourniquet placement.[101] Patients with a large burden of disease are less likely to respond to either mode of therapy.[84,102]

As stated above, the use of systemic therapy for ITM is controversial. The effect of systemic therapy on the subsequent ability to use regional therapies is poorly understood to date. However, it is important to note that failed regional therapies frequently do not preclude the use of systemic therapies. On the other hand, for a patient who has a severe AE that limits further treatment, who experiences an increase in regional bulky disease, or in whom distant progression occurs during systemic therapy, the regional options are limited.[82] Further study of the interplay of systemic therapies and regional therapies is ongoing (see Table 2).

Conclusion

Wide excision of the primary tumor, SLNB, and decision making based on SLN status form the backbone of treatment in primary melanoma. The treatment of patients with recurrent melanoma or ITM is complex, with many options beyond systemic therapy in the form of intra-arterial and intralesional therapies. Depending on the burden of disease, one can see ORRs of up to 80% to 90% with ILP and ILI, with CR rates of up to 50%. Therefore, side effects of systemic therapies can be limited by reserving systemic therapy use if regional therapies fail in treating regionally metastatic melanoma. Ongoing trials aim to assess the efficacy of combining regional and systemic therapy, and to provide data that will assist clinicians and patients in deciding among these options.

Disclosures

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ORCID Identifiers

Dr Zager: 0000-0002-6886-4468
Dr Wilkes: 0000-0002-8080-8450

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