Photo courtesy of Dina Potter. *Sunny Tree.* 48" × 60".

Intralesional therapy is a possible treatment option for patients with metastatic melanoma due to its good local response and tolerable adverse-event profile.

Developments in Intralesional Therapy for Metastatic Melanoma

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Background: *Locoregional advanced melanoma poses a complex clinical challenge that requires a multidisciplinary, patient-centered approach. Numerous agents have been studied for their suitability as intralesional therapy in the past decades, but few have successfully completed phase 3 clinical trial testing.*
Methods: *The relevant medical literature was searched for articles regarding use of intralesional therapies in metastatic melanoma. Therapies with data from phase 2 or higher studies were selected for review. This review also summarizes the mechanisms of action, adverse-event profiles, and clinical data for these agents.*
Results: *Intralesional therapies demonstrate promising effects in select patients with advanced melanoma. The optimal approach should be individually tailored and consist of a combination of intralesional therapies, regional perfusions, systemic immunotherapies, targeted therapies, and surgery, if necessary.*
Conclusions: *Due to its relatively good local response rates and tolerable adverse-event profile, intralesional therapy may be a treatment option for select patients with unresectable, locally advanced or metastatic melanoma.*

Introduction

Melanoma is accountable for most deaths related to skin cancer.[1] In 2016, an estimated 76,380 new cases of melanoma will be diagnosed and approximately 10,130 people will die from the disease in the United States alone.[1] Although cure rates are high if the disease is discovered when confined to its primary location, metastasis frequently occurs.[1] A unique clinical challenge posed by locoregional metastasis, also known as intralymphatic metastasis, occurs when metastasis develops between the primary melanoma and the draining lymph-node basin. This type of metastasis, which occurs in 5% to 10% of patients with melanoma, has traditionally been classified into 2 categories: satellite metastases (located < 2 cm from the primary tumor) and in-transit metastasis (located ≥ 2 cm from the primary tumor).[2,3]

Surgical resection is the standard of care for patients whose disease is limited enough to be rendered with no evidence of disease. If disease is confined to the limb, then unresectable disease can be amenable to locoregional treatment. For example, regional perfusion therapies, such as isolated limb infusion or hyperthermic-isolated limb perfusion, have demonstrated objective response rates (ORRs) of 50% to 90%.[4,5] These

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Submitted March 30, 2015; accepted July 14, 2015.

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These authors discuss the unlabeled/unapproved uses of 10% rose bengal for the treatment of metastatic melanoma.

Dr Sarnaik has received research funding from Provectus. Dr Sloot received a study grant from the Melanoma and Sarcoma Foundation (Groningen). Dr Zager has received honoraria and research funding from Provectus and Amgen. No significant relationships exist between the other authors and the companies/organizations whose products or services may be referenced in this article.

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treatments can be repeated multiple times, depending on response and rate of toxicity. The disadvantages of limb infusion and perfusion include associated regional toxicity, morbidity from a surgical procedure, and applicability to disease confined to the extremities alone (eg, not applicable to in-transit metastasis on the trunk). Although radiotherapy is frequently used to treat microscopic disease in an adjuvant setting, macroscopic melanoma is difficult to treat with radiotherapy and has been used to treat individual lesions or localized clusters with anecdotal success; however, wide-field irradiation is associated with morbidity and is not a preferred first-line modality.[6,7]

Patients with limited locoregional disease often have few symptoms. Consequently, physicians are less likely to recommend systemic or regional perfusion-based therapy that could expose asymptomatic patients to considerable toxicity. These patients may benefit from intralesional therapy, where the active agent is immediately injected into the tumor, exerting mainly local effects, with fewer adverse events than systemic or regional therapy.[3] Intralesional therapies have been extensively studied, but effective agents have not been available until recently.[6] However, similar to the rapid development of multiple new systemic treatments for stage 3/4 metastatic melanoma (nivolumab, ipilimumab, trametinib, dabrafenib, vemurafenib, pembrolizumab, cobimetinib, pegylated interferon), intralesional injections and topical therapies have seen major advances.[8,9] Due to their rate of efficacy and relatively low toxicity profile, these treatment modalities may be promising in select patients with locoregional disease.[3]

Intralesional therapy was first reported in 1893 by Coley,[10] which was prior to the report published by Handley[11] on wide local excision as the mainstay of melanoma treatment. Local therapy increases rates of efficacy and lowers rates of toxicity when compared with systemic administration by delivering an increased concentration of the drug locally.[3,12] A so-called "bystander effect" has been reported in select agents, including velimogene aliplasmid, 10% rose bengal, and talimogene laherparepvec, where noninjected (both visceral and nonvisceral) distant lesions respond to the locally injected drug.[9,13] Although the exact mechanism of action is under investigation, tumor antigens in the injected lesions may serve as an autologous vaccine, stimulating systemic immunity.[12,14] The occurrence of the bystander effect makes intralesional therapies appealing because local injections have been associated with a systemic reduction in tumor burden.[15]

Generally, lesions are treated using a 25- to 30-gauge needle using a "fanning" technique, where the needle is moved in multiple directions within the same lesion. Preferably, the same needle entry and needle stick are used to keep the number of needle tracks and cavities in the tumor limited to prevent intralesional injectate from leaking out and to maximize the delivered dose. Visible or palpable lesions can be injected in the ambulatory clinic, whereas deeper lesions can be injected using ultrasonographic guidance. Tumor response may be measured using caliper measurements, ultrasonography, or cross-sectional imaging (magnetic resonance imaging/computed tomography), depending on tumor size and location.[9] Evidence suggests that subcutaneous lesions are less responsive than cutaneous lesions, and tumors with smaller bulk are more likely to regress under treatment.[16-18] Investigators have attempted to limit intralesional volumes to 1 mL or less to minimize the local adverse events that result from injecting higher volumes.[16]

This review will summarize the mechanisms of action, adverse-event profiles, and clinical data for all agents currently in use and of historic importance (Tables 1 and 2).[9,12,13,16,18-41]

Velimogene Aliplasmid

Velimogene aliplasmid is an intralesional agent that advanced to phase 3 clinical trial testing based on results seen in phase 1/2 trials; however, both phase 3 trials conducted with velimogene aliplasmid failed to reach their primary end point (NCT00395070).[24,25] Velimogene aliplasmid is classified as a gene therapy because it contains plasmid DNA encoding for HLA-B7.[25] It recruits macrophages and T cells, which attack injected and noninjected lesions alike, bringing about immune responses against the alloantigen. Most of the initial studies were limited to study participants negative for HLA-B7; however, after no correlation between HLA status and response rate was found, other studies did not incorporate HLA status as an inclusion criterion.[16] Reported adverse events include paresthesias, asthenia, myalgias, fatigue, injection-site pain, rigors, and flulike symptoms.[16]

Velimogene aliplasmid was first investigated in 4 small phase 1 trials with up to 17 study participants and reported response rates reaching 50%.[20-23] The study of this drug advanced to 4 phase 2 trials that reported ORRs ranging from 10% to 28%.[16,25,27] The most frequently reported schemes used 2 mg velimogene aliplasmid per lesion with 1- to 2-week intervals.[16,27] The largest study was a dose-escalation/efficacy trial conducted by Bedikian et al,[16] who enrolled 133 patients and assigned them to groups that received 0.5 to 2 mg velimogene aliplasmid for 6 weeks with 1-week intervals. A total of 127 participants were treated with the highest dose; efficacy data were also available for all enrollees.[16] Complete response (CR) was reached in 3% and partial response (PR) in 9%.[16]

In the first phase 3 study, Richards et al[24] randomized 202 patients to either systemic dacarbazine/velimogene aliplasmid on days 3 and 10 out of 28 to the chemotherapeutic cycle (n = 98) or dacarbazine alone

Table 1. — Select Studies of Intralesional Therapies[a]

Reference	Treatment	Documented Bystander Effect	No. of Participants	Dosing	Dosing Interval	Treatment Duration	CR, %	PR, %	SD, %	PD, %
Bedikian[16]	Velimogene aliplasmid	Yes	127	0.5–2 mg	Once weekly	6 wk	3	9	25	63
Stopeck[19]	Velimogene aliplasmid	No	51	10 µg	Wk 1–4, 8, 9	≤ 6 cycles	2	16	24	59
Gonzalez[27]	Velimogene aliplasmid	No	77	10 µg	Once weekly/6 wk	≤ 3 cycles	3	7	23	68
Karakousis[28]	BCG	No	8	0.1 mL of 4 × 10" to 9 × 10" viable organisms/mL	NA	Once	75	0	0	25
Kidner[41]	BCG/imiquimod	No	19	3 × 106 cfu/5%	5–7 d/wk for every 2 wk	2 injections titrated to local inflammation	56	11	33	0
Marty[33]	ECT/Bleo	No	41[b]	≤ 1000 IU/cm^3, depending on tumor size	NA	Once	73	11	11	5
	ECT/Cis			≤ 2 mg/cm^3, depending on tumor size						
Byrne[20]	ECT/Bleo vs Bleo vs ECT	No	19	1 U/mL tumor volume	4, 8, or 12 wk	4, 8, or 12 wk	72	5	18	5
Heller[32]	ECT/Bleo vs Bleo vs electroporation	No	34	0.025 U, 1250 V/cm	Once	Once	89	10	1	0
Mir[31]	ECT/Bleo	No	20	18 or 27 U/m^2, 1300 V/cm	Once	Once	53	39	8	0
Ridolfi[34]	GMCSF, IL-2	No	16	150 ng, 3 million IU	Every 21 d	6 cycles	0	13	69	19
Boyd[46]	IL-2	No	39	10.4 MIU	Biweekly	4 cycles	51	31	18 (SD/PD)[c]	
Weide[18]	IL-2	No	48	0.3–6.0 MIU	3 × wk	1–32 wk	69	NR	NR	NR
Thompson[23]	10% rose bengal	Yes	80	NA	Wk 1, 8, 12, 16	≤ 4 cycles	26	25	18	31
		Yes	20	NA	Once	1 cycle	20	20	35	25
Senzer[38]	Talimogene laherparepvec	Yes	50	10^6 PFU first dose, then 10^8 PFU thereafter	First interval 3 wk, then every 2 wk	≤ 24	16	10	24	50
Andtbacka[39]	Talimogene laherparepvec	No	295	10^6 PFU first dose, then 10^8 PFU thereafter	First interval 3 wk, then every 2 wk	NR	11	16	73 (SD/PD)[c]	
	GMCSF	No	141	125 µg/m^2	Daily × 14 d every 4 wk	NR	1	5	94 (SD/PD)[c]	

[a]Only studies with sufficient data regarding responses are included.
[b]Multiple tumor types are included, but responses are not split for study patients with melanoma and without melanoma. Bleo/Cis is equally effective.
[c]Responses were not split out.
Bleo = bleomycin, Cis = cisplatin, CR = complete response, ECT = electrochemotherapy, GMCSF = granulocyte macrophage colony-stimulating factor, IL-2 = interleukin 2, NA = not applicable, NR = not reported, PD = progression of disease, PFU = plaque-forming unit, PR = partial response, SD = stable disease.

(n = 104). Response rates were 13.2% and 11.6%, respectively.[24] Adding velimogene aliplasmid did not cause any significant difference in median time to progression (1.9 vs 1.6 months) or survival (10.8 vs 9.2 months).[24] The second phase 3 trial was stopped early when no difference was shown in ORR at more than 24 weeks and in overall survival rate for the 390 study participants, who were randomized 2:1 to either velimogene aliplasmid or physician's choice of chemotherapy (dacarbazine or temozolomide; NCT00395070). No new trials are planned for velimogene aliplasmid.

Bacille-Calmette-Guerin

Bacille-Calmette-Guerin (BCG) has been historically used in intralesional therapy, but it has a severe adverse-event profile. The aim of using BCG for intralesional therapy against metastatic melanoma is to stimulate an immune reaction to eliminate the tumor using the patient's own immune system.[28] BCG is a live, attenuated strain of *Mycobacterium bovis*, which is an antigen that can trigger an immune reaction. In animal models, BCG produces a nonspecific immune response.[28] In humans, it has been used for intralesional therapy in patients who have already demonstrated an immune reaction to BCG to stimulate an immune response against the injected lesion.[28] Adverse events include fevers, chills, diaphoresis, arthralgias, malaise, and angioedema in patients positive for tuberculin and those with lymphadenopathy, pneumonitis, BCG granulomas, and granulomatous hepatitis.[21,28-30] Toxicity is caused by the patient having an immune response to BCG; thus, patients who have no immunity against BCG cannot demonstrate adverse events.

Table 2. — Select Treatment-Related Adverse Events of Intralesional Therapy

Type of Therapy	Adverse Events
Bacille-Calmette-Guerin[21,28-30]	Angioedema (with positive tuberculin test) Arthralgia Bacille-Calmette-Guerin granulomas Chills Diaphoresis Disseminated intravascular coagulation Granulomatous hepatitis Lymphadenopathy Malaise Pneumonitis
Electrochemotherapy + bleomycin/cisplatin[22,35]	Pain at injection site Ulcerations
Granulocyte macrophage colony-stimulating factor[34]	Flulike symptoms
Interleukin 2[18,36]	Flulike symptoms Injection site pain/erythema
Rose bengal 10%[12,13,23,37]	Blistering Edema Headache Local pain Inflammation Pruritus Skin discoloration Vesicles
Talimogene laherparepvec[9,39,40]	Cellulitis Chills/rigors Fatigue Pyrexia
Velimogene aliplasmid[16,19,24-27]	Asthenia Fatigue Flulike symptoms Injection-site pain Myalgia Paresthesia Rigor

Seigler et al[29] recruited 160 patients with locally recurrent melanoma who were treated with intralesional BCG using a 4-stage approach. In the first stage, participants who were immune sensitive to BCG were selected; in the second stage, a delayed hypersensitivity reaction to BCG was stimulated in participants with booster therapy; in the third stage, adoptive immunity was achieved by harvesting participant lymphocytes, which were exposed to tumor cell samples and reinjected into the participants; and, in the fourth stage, to further increase antitumor responsiveness, the participants were injected with a vaccine of tumor cells and BCG.[29] Of the 70 study patients evaluated in stage 1, 44% (31) were sensitive to BCG, and, as those study patients progressed through the 4 stages, they demonstrated increased rates of antitumor immune responsiveness.[29] Of the 62 participants examined for cell-mediated, tumor-specific immunity, 69% (n = 43) had a prolonged response, with 60% mean tumor lysis.[29] Of the 19 study patients who never developed immunity against melanoma, all of them progressed and died of complications from diffuse, distant metastatic disease.[29] Although results from early clinical trials correlated well with the rationale for BCG intralesional therapy, the adverse-event profile of BCG is a limitation to its broad implementation.[21,28-30] And, although BCG uses *M bovis* to stimulate an immune, antitumor response, it also produces complications associated with that same immune response, leading to adverse events and disseminated intravascular coagulation at a rate of 12%.[45] Because of these inflammatory reactions and the concomitant high risk of morbidity, BCG treatment requires that patients be closely observed. Prophylactic treatment should be provided, such as antihistamines and isoniazid, because of the morbidity of these adverse events.[30] In addition, to minimize the morbidity of these reactions when they do occur, signs or symptoms of these complications should be treated with hydration, antituberculosis therapy, steroids, antihistamines, and supportive care.[30]

Electrochemotherapy

Electrochemotherapy (ECT) is used as an intralesional therapy that delivers agents into the treated lesion. ECT applies high-intensity, pulsed electrical current to the treated lesion that renders the tumor cells permissive for the uptake of drugs, viruses, or genetic material.[31,46] By contrast, electroporation delivers the current to the lesion without the need of additional agents. Therefore, ECT can be used to deliver therapeutic agents.

Of all the agents used in combination with ECT, bleomycin is the most commonly reported (0.025 units delivered with ECT at 1250 V/cm).[32] ORRs up to 98% have been reported and CR in more than 50%; however, case series have been small and limited by short follow-up periods.[33] No significant adverse events have been noted.[22,35] Marty et al[33] conducted the European Standard Operating Procedures of Electrochemotherapy study, based on the experience of leading European cancer centers, that has been a landmark trial in the field.[33] Prior to the report by Marty et al,[33] which was published in 2006, different study groups used a variety of protocols with different pulse parameters, pulse generators, electrode types, and dosages of chemotherapy. Marty et al[33] generated standard operating procedures in a prospective study with 2 years of follow-up using bleomycin or cisplatin. For bleomycin, they used either intravenous 15,000 IU/m^2 in a bolus lasting 30 to 45 seconds or various intratumoral doses, depending on the tumor size. Cisplatin was administered based on tumor size.[33] Depending on the number of nodules treated, study participants either received local anesthesia or general anesthesia.[33] Procedures were performed on an outpatient basis or during a 1-day admission.[33] Using 5000 Hz electric pulses was more effective than using 1 Hz.[33] Melanoma nodules showed a lesional response of 80% and a CR rate of 66.3%.[33]

Subsequently, a meta-analysis of 44 studies analyzed intralesional treatment with ECT on 1,894 lesions.[46] Results were reported for both bleomycin and cisplatin.[46] When the clinical responses in all histological diagnoses were evaluated, the CR rate was 59.4% and the ORR was 84.1%.[46] When the melanoma results were evaluated, the rate of CR and ORR of treated melanoma tumors were 56.8% and 80.6%, respectively.[46] No adverse events were reported.[29] Although these results are encouraging, the data are limited due to their small size and lack of long-term follow-up. Therefore, further studies are required to determine which patients may benefit from ECT.

Granulocyte Macrophage Colony-Stimulating Factor

Use of granulocyte macrophage colony-stimulating factor (GMCSF) for intralesional therapy against metastatic melanoma is based on 2 mechanisms.[47] GMCSF stimulates dendritic cells that then induce antitumor immune responsiveness.[47] The result is twofold: direct destruction of the injected lesion and enhanced antigen presentation, leading to an immune response against metastatic melanoma. T cells treated with GMCSF have demonstrated increased antitumor responsiveness.[47] Reported adverse events have generally been tolerable and typically constitute flulike symptoms.[9,34,47]

In addition to increasing the antitumor responsiveness of T cells, GMCSF also appears to reduce the immune-inhibitory effects of metastatic melanoma by having an effect on the cells implicated as mediators of decreasing the immune response against cancer.[9,47] GMCSF has been shown to decrease T-regulator, suppressor, and myeloid-derived suppressor cells, which are all mediators of decreased T-cell antitumor activity.[9,47] Patients with a higher T-cell composition of the tumor infiltrate with higher interleukin 2 (IL-2) receptor expression are more likely to demonstrate a clinical response to therapy.[9,47] Phase 1 data showed increased CD4, CD8, lymphocyte, histiocyte, and eosinophil tumor infiltrate in the injected lesions and a higher likelihood of clinical response in patients with a higher T-cell composition of the tumor infiltrate with a higher IL-2 receptor expression.[48] Phase 1/2 studies showed ORRs up to 26%.[34,35,48] Efforts are underway to further evaluate mechanisms to enhance the immune response against melanoma.

Interleukin 2

IL-2 is a naturally occurring glycoprotein secreted by T cells to augment the immune response and was first used in clinical cancer studies in the early 1980s.[49] This glycoprotein promotes T-lymphocyte proliferation and stimulates cytotoxic T cells and natural killer cells.[50] IL-2 has been used as immunotherapy for nearly 40 years, although it has mostly been employed as an intravenous agent.[50] Its use for intralesional therapy is limited due to logistical problems because patients require multiple injections per lesion and IL-2 is costly.[50]

The immune-stimulating mechanism of IL-2 has already been applied to melanoma and other solid tumors as a systemic therapy.[50-52] It produces a relatively high rate of morbidity when considering its relatively low response rates, which range from 10% to 15%.[52] Because IL-2 has the potential to induce durable responses, high-dose systemic IL-2 was the mainstay for the treatment of tumors like melanoma and renal cell carcinoma up until the 2000s.[51,52] Although its usage has recently tapered off as more effective drugs are now available, IL-2 is still considered a treatment option for unresectable melanoma.[51,52] Treatment of tumors has been reported using intralesional and perilesional injections of IL-2, whereby an IL-2 injection into the tumor has been shown to be effective.[53] Intralesional IL-2 has been studied in many forms, including use as viral vectors, xenogeneic monkey fibroblasts, and IL-2 cultured lymphocytes harvested from patients with melanoma, as well as adjunctive therapy with other systemic therapy and topical agents.[17,49,54-57] Response rates were low and erratic until human recombinant IL-2 was developed, which has provided consistent and promising results.

Unlike systemic IL-2, which has a morbid adverse-event profile, intralesional IL-2 typically produc-

es flulike symptoms alone.[36] Local adverse events such as injection-site pain and erythema have also been reported.[12,13,18,23,36,37] The number of study patients in published reports has been small: 7 participants treated in 1 documented case series and 23, 39, and 48 study patients in 3 phase 2 studies.[18,39,58,59] Response rates consistently exceed 80%.[36,58,59]

Boyd et al[36] reported improved overall 5-year-survival rates in study patients with CR (51% of 39 patients) and study patients with PR (21% of 39 patients). The reported 5-year survival rates were 80% and 33%, respectively.[36] Complete responders had a significant overall survival benefit when compared with partial responders ($P = .012$).[36] Despite demonstrating a high response rate with minimal rates of morbidity, IL-2 has not demonstrated a significant bystander effect, despite its immune-mediated mechanism.[36] Studies so far conducted have used an onerous administration scheme requiring multiple injections each week; furthermore, because IL-2 is a costly drug to purchase, it is not broadly pursued in research.[36]

Rose Bengal

Rose bengal (10%) is an investigational agent for use as an intralesional therapy. The 10% rose bengal solution is a water-soluble stain used to diagnose liver and eye cancers and ocular damage, as well as in food coloring in Japan and as an insecticide, with medical reports being published as early as the 1920s.[37,60] Because of the wide variety of its application, experience with the drug is extensive, and its safety profile has been well established.[12,13,23,37] As an xanthine dye, the hypothesized mechanism of action of 10% rose bengal is that it creates reactive oxygen by reacting with visible and ultraviolet light, thereby mediating phototoxic reactions. It is selectively absorbed by lysosomes of cancer cells, inducing autolysis,[61,62] and 10% rose bengal is currently under investigation for melanoma and liver tumors (NCT00986661, NCT02557321, NCT02288897).[12,13,23,37] Responses have been reported in study patients refractory to previous systemic ipilimumab, anti–programmed death ligand 1, and vemurafenib, and therapeutic responses have been seen in study patients progressing after a median of 6 treatments.[12,23]

A bystander effect has been observed in 10% rose bengal.[23,62] Use of 10% rose bengal leads to increased tumor-specific, interferon-γ secretion in a mouse model, induces an increase in circulating, cytotoxic $CD3^+/CD8^+$ T cells, and recruits dendritic cells to drain lymph nodes.[12,62] Injection into the non–tumor-bearing flanks of mice had no effect on distant lesions.[62] Rather, the agent must be injected into a tumor lesion to induce a bystander effect. The rate of morbidity is generally considered to be low, although most patients report some local adverse events, most commonly pain (≤ 80%).[60] Local blistering (40%) has been correlated with a better outcome.[60] Other reported adverse events include vesicles, edema, skin discoloration, inflammation, headache, and pruritus around the treatment site.[60]

The first phase 1 trial of 10% rose bengal included 11 study patients.[37] Treatment with 0.5 mL/cc per lesion induced an ORR in more than one-half of participants (both CR and PR, 27%).[37] The effect was dose-dependent, as target lesions receiving less than 0.2 mL 10% rose bengal had a significantly lower response rate than lesions receiving a higher dose (25% vs 69%).[37] A bystander effect was seen in 27% of the study patients and correlated with the response of the injected lesion.[37] In another phase 1 trial, Thompson et al[23] enrolled 20 patients, injecting a single dose of 10% rose bengal in up to 20 lesions per participant. Response rates were comparable with those seen the first phase 1 study.[23,37] ORR was achieved in 40% of study patients, including a 20% complete response rate, and a bystander effect was reported in 15% of study patients.[23]

Thompson et al[23] injected up to 20 lesions per study patient at day 0 and repeated the injection if needed after 8, 12, and 16 weeks. A total of 80 study patients were included, the majority of whom responded after fewer than 2 injections, resulting in an ORR of 51%, of which the CR rate was 26%.[23] A bystander effect was seen in 40% of 35 evaluable study patients and was correlated with the response of injected lesions (CR rate, 31%; PR rate, 9%).[23] Both visceral and cutaneous lesions were susceptible to this effect.[23] Overall responses were correlated with initial treatment of all discernible disease, with a CR rate seen in 50% of study patients for whom all baseline disease was treated; CR was not seen in study patients with stage 4 melanoma.[23]

Based on these results, expanded access of this trial became available (NCT02288897). As of publication, more than 100 patients with melanoma have been enrolled in this trial. In the phase 3 trial, patients with stage 2C/3B disease will be randomized 2:1 to either 10% rose bengal or systemic chemotherapy, allowing crossover, with progression-free survival as the study's primary end point.

Talimogene Laherparepvec

Talimogene laherparepvec was approved by the US Food and Drug Administration in 2015.[63] It shows a trend toward improved survival rates and a robust bystander effect.[39] Talimogene laherparepvec is an oncolytic, immune-enhanced herpes simplex virus type 1, and its various genetic modifications include deletions of ICP34.5, ICP47, and insertion of GMCSF. Oncolytic viruses like talimogene laherparepvec are designed to selectively multiply in tumor cells.[64] At

least 9 virus groups are being investigated in clinical trials.[65] Oncolytic viruses have direct effects on the metabolic processes of cancer cells. They selectively replicate in tumors, thereby destroying and infecting cancer cells due to their direct effects on the metabolic processes in the cell as well as their ability to induce immune responses that target the cancer cell. This action is thought to be aided by the activation of nuclear factor κB and the release of chemokines and cytokines from the cancer cell.[65] Oncolytic viruses demonstrate limited systemic applicability due to the immune responses of the host, but they are suitable for intralesional injection. Specifically with talimogene laherparepvec, ICP47 deletion helps to prevent blocking antigen presentation and enhances virus growth and replication in tumor cells.[38,66] Replacing the coding sequence for neurovirulence factor ICP34.5 with the human cytokine GMCSF enables talimogene laherparepvec to initiate a systemic antitumor response by enhancing immune response to tumor antigens.[66] The most common adverse events seen with this agent are fatigue, chills, and pyrexia.[49]

Senzer et al[38] investigated the effectiveness of talimogene laherparepvec in study patients with stages 3 (n = 10) and 4 (n = 40) melanoma in a single-arm, phase 2 trial. Study patients received intralesional injections of either talimogene laherparepvec or GMCSF.[38] The initial injection had a volume of up to 4 mL of 10^6 pfu/mL followed 3 weeks later by 4 mL of 10^8 pfu/mL, every 2 weeks, for up to 24 treatments.[38] The protocol allowed injection with or without ultrasonographic guidance and included cutaneous, subcutaneous, and nodal lesions. An ORR based on Response Evaluation Criteria In Solid Tumors was 26% (CR rate, 8%; PR rate, 5%).[38] After 1 and 2 years, the overall survival rates were 58% and 52%, respectively.[38]

Based on these data, a phase 3 study was conducted.[14,39] This study randomized 436 patients 2:1 to intralesional talimogene laherparepvec (n = 295) or subcutaneous GMCSF (n = 141) and used the same talimogene laherparepvec regimen as the phase 2 trial.[39] The ORRs were 26.4% for those assigned to talimogene laherparepvec and 5.7% for those assigned to GMCSF.[39] The results showed a significant difference in durable response rates (ie, PR or CR rate for > 6 months), with 16.3% in the talimogene laherparepvec group and 2.1% in the GMCSF group ($P < .001$); durable response rates were higher in study patients with stage 3B/C melanoma (33% for the talimogene laherparepvec group vs 0% for those in the GMCSF group).[39] Six previously unresectable study patients were converted to resectable. Fewer than 3% of study patients experienced grade 3/4 adverse events.[39] For the entire patient population, the overall survival rates trended toward statistical significance (23.3 months for the talimogene laherparepvec group vs 18.9 months for the GMCSF group; $P = .051$).[39] A subgroup analysis showed survival benefit in patients with stage 3B/C and 4 M1a disease, and the effect was stronger when talimogene laherparepvec was given as first-line therapy as opposed to second-line therapy or higher.

A lesion-level analysis of the phase 3 trial of 3,219 lesions in 286 patients showed a 50% reduction in 64% of the injected lesions, 32% of the uninjected nonvisceral lesions, and 16% of the uninjected visceral lesions.[14] These findings indicate a bystander effect and, thus, a systemic immune response from the local injection of talimogene laherparepvec.[14]

A phase 1b study of talimogene laherparepvec added to ipilimumab in 19 participants suggested a higher CR rate for the combination than for either agent alone.[40] Grade 3/4 adverse events occurred in 32%.[40] Two study patients had possible immune-related grade 3/4 adverse events, and, of the 17 study patients with investigator-assessed response, the ORR was 41% (CR rate, 24%; PR rate, 18%) and stable disease was seen in 35%.[40] Median time to response was 2.9 months (NCT01740297).

Topical Therapies

Topical therapies have shown some success in superficial lesions and are generally associated with low rates of morbidity.[41,67-70] Typically, they are more suited for thinner lesions. Topical diphencyprone cream is a synthetic contact sensitizer that has been used to treat alopecia and warts.[71,72] The largest trial to date was conducted by Damian et al,[67] who studied 58 patients, 50 of whom were treated for more than 1 month. A total of 46% achieved CR and 46% achieved PR; however, the results of this study should be interpreted with caution, as the majority of results came from the same research group.[67-70]

Imiquimod is a toll-like receptor agonist approved by the US Food and Drug Administration for the treatment of genital warts, keratosis, and superficial basal cell carcinomas.[73] A treatment regimen for melanoma has not been established, as the application of imiquimod ranges from once weekly to twice daily and from 2 to 88 weeks.[74] Since 2000, it has been used for advanced melanoma in various case reports and small case series.[6,75-77] The largest case series is of 5 patients treated with combination topical imiquimod/fluorouracil; a response was elicited in 44 of 45 lesions.[77] Combined treatments with IL-2 and BCG have also been reported.[41,57] More evidence is available for patients with lentigo maligna, including a large case reporting that more than 90% of study patients with lentigo maligna experience regression with daily or twice-daily application of an imiquimod cream.[74,78]

Conclusions

The standard of care for patients with locoregional

advanced or metastasized melanoma is to render a patient free of disease as long as the disease is sufficiently limited. When this is no longer feasible, intralesional therapy is a possible option due to its good local response and tolerable adverse-event profile, as well as the option to provide outpatient treatment. A bystander effect observed in various agents adds to its appeal. During the last few decades, other agents have been tested for intralesional therapy with varying success. Many intralesional compounds now available produce a broad range of local response rates. The ideal agent should have a low toxicity profile, be easy to administer, lead to fast responses, and trigger a systemic immune response, thereby creating a bystander effect. These criteria were predominantly met in the results of trials using 10% rose bengal and talimogene laherparepvec in up to 40% of study patients.

Most agents (Bacille-Calmette-Guerin, interferon, granulocyte macrophage colony-stimulating factor) demonstrated inconsistent rates of efficacy, but the treatment field changed when velimogene aliplasmid, 10% rose bengal, and talimogene laherparepvec were introduced. Velimogene aliplasmid did not meet its primary end point in a phase 3 trial, but talimogene laherparepvec did meet its phase 3 trial objectives, demonstrating a survival benefit in select study patients. The results of phase 2 results of 10% rose bengal trials are also promising and a phase 3 is still recruiting (NCT02288897). Other options include combinations of intralesional therapies and systemic therapies, including ipilimumab/talimogene laherparepvec and pembrolizumab/rose bengal (NCT02557321).

Our treatment approach should be individualized per patient, based on the extent of disease, tumor characteristics, and disease-free interval, as well as patient characteristics such as age, performance status, and comorbidities, and work to maintain quality of life for as long as possible. An appropriate approach is often not a single therapy but rather a combination of injectable treatments, regional perfusion therapies, and systemic therapies.

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