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Regional Therapies for In-transit Disease

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INTRODUCTION

In-transit melanoma occurs in up to 10% of patients with melanoma, and is a pattern of recurrence that presents unique management challenges and opportunities for treatment. In-transit disease is defined as tumor deposits that usually occur somewhere between the primary lesion and its draining regional lymph node basin.^{1,2} Although often associated with distant metastases, the presence of in-transit disease is an independent adverse prognostic factor. Unique treatment modalities, in the form of regional chemotherapy, are often necessary because this pattern of recurrent disease is often not amenable to surgical resection.

BACKGROUND

Incidence

In-transit disease is uncommon, occurring in less than 10% of patients diagnosed with melanoma and accounting for 12% to 22% of melanoma recurrences. The presence of positive nodal disease significantly increases the risk of developing in-transit disease, with estimates suggesting risks as high as 31% when at least 3 positive nodes are present.³ Although initial disease stage seems to be the most important factor in predicting in-transit recurrences, lesion location may also play a role, with higher rates in the lower extremities versus upper extremities. Early observations also suggested an association between surgical lymphadenectomy and the development of in-transit disease, presumably caused by lymphatic trapping in which outflow obstruction of the draining lymphatic system led to stasis and trapping of tumor deposits. However, in recent larger studies, neither lymphadenectomy nor sentinel lymph node biopsy were associated with an increased risk of developing in-transit metastases.^{4–7}

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Biology

Although the true underlying biology of in-transit melanoma is unknown, it is thought to be related to small tumor emboli disseminating along the path of lymphatic drainage from the primary tumor to its draining nodal basin. These migrating tumor cells are thought to become ensnared in the draining dermal and subdermal lymphatics, eventually progressing to clinically detectable lesions. Although tumor deposits becoming trapped along the lymphatic drainage remains the most likely biological explanation, other mechanisms have been suggested, including hematogenous spread, similar to that of distant metastases.^{8,9} Supporters of this alternative theory argue that, if the lymphatic concept is true, wider margins during primary excision would be expected to include a higher proportion of trapped occult cells and lead to superior clinical outcomes, which is not consistent with current observations. However, the hematogenous theory is not supported by the significant differences in long-term survival observed for patients with stage III versus stage IV disease.

Nomenclature

Several different terms have been used in the literature to describe what is likely to be the same underlying oncologic process. In the past, terms such as satellitosis, locoregional recurrence, and in-transit disease have each been used to describe various clinical findings. Satellitosis was usually defined as a locoregional recurrence that was located within either 2 cm of the excision scar or 5 cm of the initial lesion, whereas the term in-transit disease was reserved for a recurrence occurring at greater distances from the initial lesion or scar. Because such lesions all likely reflect tumor deposits proliferating along paths of lymphatic drainage, it has more recently become apparent that distance from the primary lesion to the site of locoregional recurrence does not carry meaningful prognostic value.^{10–13} Consequently, the most recent American Joint Committee on Cancer (AJCC) staging system for melanoma does not distinguish between traditional satellitosis and in-transit lesions, with both being designated as N2 or N3 disease, depending on regional node status.¹⁴ To address the ongoing ambiguity arising from nomenclature issues, many authorities no longer use the term satellitosis, instead referring to all regional nonnodal metastatic disease as in-transit melanoma.

PATIENT EVALUATION OVERVIEW

Presentation

By definition, in-transit melanoma represents locoregionally advanced disease, and is typically discovered months to years after the initial surgical excision of the primary lesion, with a disease-free interval to recurrence ranging from 12 to 16 months.^{15,16} The clinical presentation usually involves from 1 to more than 100 small subcutaneous or cutaneous nodules, although it can be variable (Fig. 1). Individual lesions can range from submillimeter to multiple centimeters in diameter, and may take the form of superficial cutaneous (also called epidermotropic) or deeper subcutaneous nodules. For disease located in an extremity, the lesions are often clustered in proximity to the primary lesion, but can also involve the entire extremity extending from the primary tumor to its regional lymphatic basin. For truncal disease, the pattern of distribution can be even more inconsistent, with potentially extensive tumor burden depending on the location of the primary melanoma.

Evaluation

The work-up of patients with in-transit melanoma starts with a thorough skin examination, and in patients with an unclear diagnosis and suspicious lesions it is our practice to use a 3-mm to 5-mm punch biopsy for small superficial lesions and fine-needle aspiration biopsy for larger lesions to obtain pathologic confirmation of melanoma. All major nodal basins should be examined for the presence of clinically involved nodes, and preoperative cross-sectional imaging should be performed to evaluate for distant metastatic spread. In patients who have disease isolated to an extremity and are candidates for general anesthesia, regional chemotherapy should be considered as a first-line therapy.

Dosing

Drug doses for regional therapy are typically based on limb volume, either measured directly or imputed. For hyperthermic isolated limb perfusions (HILPs), melphalan doses of 10 mg/L for the lower limb and 13 mg/L for the upper limb are typically used.¹⁷ For isolated limb infusion (ILI), slightly lower doses are used; typically 7.5 mg/L for the lower limb and 10 mg/L for the upper limb, both usually with the addition of 50 to 100 µg/L of actinomycin-D.^{18,19}

Multiple techniques to determine the optimal dose for regional therapy have been developed, with the simplest methods relying on patient body weight and/or ideal body weight, offering simple and fast calculations.²⁰ In recent years such techniques have largely been abandoned, because they have been shown to produce substantial variability compared with more accurate limb volume measurements.^{21,22} The original methods described by Wieberdink and colleagues²³ for estimating limb volume relied on a method of measuring water displacement from the submerged limb. Although accurate and still used, this method is hampered by logistical issues related to the nature of the water reservoir apparatus.

An alternative method that has more recently gained popularity is calculation based on limb circumference. In this approach, circumference measurements are taken at standardized intervals (usually 1.5 cm) along the length of the extremity. By calculating the volume of each theoretic slice based on the limb circumference at that level, and summing across the limb, highly accurate estimates of limb volume can be obtained.^{22,24} This method offers distinct advantages compared with water displacement techniques, in that it is inexpensive, does not require specialized equipment or facilities, and can be performed at the bedside and on immobile or otherwise functionally impaired individuals.

Although numerous techniques for limb volume calculation have been described, further adjustment is often required, particularly in the setting of obesity in order to avoid excessively large doses of chemotherapy being delivered to limbs that have a disproportionately large amount of fat. Although there remains some debate regarding the role of weight-based dose adjustment for ILI,²⁵ in our experience, multiplying the calculated limb volume by the quotient of ideal body weight (IBW) and actual body weight to obtain an IBW-adjusted limb volume has helped minimize unnecessary toxicity without compromising clinical response.²⁴ Furthermore, recent work by Podleska and colleagues²² has confirmed

that this method gives lean limb volume estimates that correlate extremely well with no-fat computed tomography scans, which digitally subtract subcutaneous fat tissue.

REGIONAL CHEMOTHERAPY

History, Concept, and Overview

The origins of limb infusion can be traced back to 1950, when Klopp and colleagues²⁶ discovered that intra-arterial infusion of nitrogen mustards proved substantially more effective than intravenous administration. However, it was not until 1958 that Creech and colleagues²⁷ first described what is now considered limb perfusion, adopting advances in cardiopulmonary bypass to isolate and oxygenate the relevant area and administer high-dose intra-arterial chemotherapy. A decade later, Stehlin²⁸ added hyperthermia to the treatment, with improved results.

The fundamental concept of regional chemotherapy for in-transit melanoma entails vascular isolation of the affected limb, followed by high-dose chemotherapy delivery at doses up to 20 times larger than can be tolerated systemically. Because regional therapy requires isolation of the affected limb compartments, the major inflow and outflow vessels to the area of interest must be accessed and cannulated, and the treatment region must then be completely isolated from the systemic circulation, usually by means of a pneumatic or Esmarch tourniquet. The 2 general approaches to accomplishing this are HILP and ILI. Although both procedures involve regional delivery of high-dose chemotherapy, they differ in several important technical and conceptual aspects.

Isolated Limb Perfusion

HILP as originally described by Creech and colleagues²⁷ is performed under general anesthesia, and requires exposure and direct cannulation of the vasculature supplying the affected limb. An oncologic regional lymphadenectomy is typically performed concurrently, which has the added benefit of aiding vascular exposure, particularly when accessing the iliac vessels. A proximal tourniquet is then placed, and perfusion is initiated via the cannulated vessels, using a standard extracorporeal bypass circuit with membrane oxygenation to maintain physiologic limb oxygen tension and acid-base status (Fig. 2). To achieve hyperthermia with a goal of 40°C, the circuit is heated and external warming blankets are placed on the involved limb. Chemotherapy is typically perfused through the limb circuit for 60 minutes, followed by a washout period of 20 to 30 minutes with crystalloids to facilitate removal of the cytotoxic agents. During the perfusion portion of the procedure, leakage of perfusate into the systemic circulation can pose substantial risks of toxicity, particularly when high-dose tumor necrosis factor alpha (TNF- α) is used in conjunction with cytotoxic therapy. In the past, such leakage was monitored by injecting intravenous fluorescein into the perfusion circuit, and watching for evidence of staining proximal to the tourniquet. More recently, administration of a radiolabeled tracer into the HILP circuit with continuous monitoring of systemic radiation exposure using a precordial gamma probe has provided a more precise method of leak detection. At the conclusion of the procedure, the cannulas are removed, the blood vessels repaired, the tourniquet is removed, and a careful vascular and musculoskeletal examination is performed.

Isolated Limb Infusion

ILI was first described by Thompson and colleagues²⁹ in the mid-1990s as a less-invasive alternative to HILP. During ILI, the target limb vessels are cannulated using percutaneously placed catheters inserted with the aid of fluoroscopy. Similar to HILP, the limb is isolated using an external tourniquet, and is then wrapped in heating blankets. In contrast with HILP, ILI is performed without extracorporeal perfusion and oxygenation, and the perfusate is manually circulated using a syringe and 3-way stopcock (Fig. 3). As a result, the limb becomes markedly acidotic and hypoxic during the procedure, which some clinicians have suggested augments the effectiveness of the melphalan chemotherapy.³⁰ Although warming blankets and a heat exchanger are typically used, limb temperatures observed during ILI are typically lower than those seen during HILP, and often do not exceed 38.5°C to 39.0°C.^{19, 31}

One of the primary benefits of ILI compared with HILP is the simplicity and substantially less-invasive nature of the procedure. The infusion of chemotherapy is typically maintained for 30 minutes, followed by washout with crystalloid in a similar manner to HILP. Melphalan doses are often lower than those used in HILP, and treatment-associated morbidity is substantially less, particularly severe morbidity. As a result, ILI can be offered to patients with higher comorbidity burdens and who might not tolerate the more invasive groin exposure required for HILP. Similarly, because of its less-invasive nature, ILI can be offered as salvage therapy and repeated in situations of treatment failure or recurrent disease. As a result, repeat ILI can be an integral component in the management of recurrent or progressive in-transit disease following failure of initial regional therapy. Although some clinicians have proposed intentionally leveraging this advantage and using ILI as a means of delivering fractionated chemotherapy over the course of multiple treatments, this has not been shown to improve survival compared with single full-dose ILI.³²

Drugs and Dosing

For any therapeutic agent to be considered for regional therapy, it must not require metabolic transformation to take on a biologically active form. Melphalan has long been established as the primary chemotherapy choice for HILP and ILI. Melphalan is an alkylating agent derived from phenylalanine, which plays a key role in melanin synthesis and is preferentially taken up by melanocytes. Because of this, melphalan has the theoretic advantage of producing selective toxicity in melanin-containing melanoma cells. Systemically, the effective dose of melphalan has been found to exceed the maximally tolerated dose, limiting use as a systemic agent. In contrast, the effective dose is easily achieved with regional therapy, without associated systemic toxicity.

Several other agents have been used, either instead of or in combination with melphalan, for regional therapy treatment of in-transit melanoma. Cisplatin showed significant potential in preclinical studies, and early clinical reports revealed promising response rates, but further developments were limited by concerns over limb-threatening toxicity.^{33–37} Similarly, TNF- α held early promise, particularly when combined with interferon-gamma, but widespread use of TNF- α has been limited because of significant concerns over toxicity.³⁸ When combined with melphalan, TNF- α was effective in preclinical models, but the 2006 ACOSOG (American College of Surgeons Oncology Group) Z0020 trial was terminated

early after interim analysis confirmed significantly increased toxicity with the combination therapy without any improvement in clinical response compared with melphalan alone.³⁹ Temozolomide is a newer alkylating agent that is closely related to melphalan and does not require hepatic conversion to take on an active form. Early results in preclinical animal models of regional therapy showed superior results compared with melphalan.⁴⁰ A recently completed multicenter (Duke, Moffitt, and MD Anderson) phase I clinical trial was able to define the maximally tolerated dose of intra-arterial temozolomide in patients with regionally advanced melanoma of the extremity and showed that some patients who did not respond to ILI with melphalan could achieve a complete response to ILI with temozolomide (Fig. 4) (Beasley and colleagues,⁴¹ in press).

TREATMENT COMPLICATIONS

Some degree of tissue toxicity is typically seen following regional therapy, presumably because of the high concentration of cytotoxic agents administered. Numerous different grading systems have been proposed to standardize toxicity reporting following treatment. Of these, the most commonly used is that developed by Wieberdink and colleagues,²³ wherein toxicity scores range from grade I, or no evidence of any adverse reaction, to grade V, representing a severe and potentially limb-threatening reaction (Table 1). Although in larger series up to 85% of patients experienced grade I to II toxicity, less than 1% of patients experienced grade V toxicity.⁴² Although the overall range of toxicity is similar for ILI and HILP, the latter carries a higher risk of higher-grade toxicity, including risk of possible limb loss. Although limb loss is rare, with rates ranging from 0.3% for ILI to 2% for HILP, severe muscle toxicity and the development of compartment syndrome necessitating fasciotomy is uncommon but well described, occurring in about 5% of patients depending on how melphalan is dosed. Despite these risks, for both HILP and ILI, most adverse reactions are temporary, often resolving within the first month after surgery.

Strategies to Minimize Complications

Numerous strategies have been developed to reduce the risk of complications associated with regional therapy, in addition to IBW-adjusted dosing as discussed previously. For patients with disease located proximally on the limb, treatment of the hand or foot is often not required from an oncologic perspective. In such cases, a second tourniquet can be applied to the wrist or ankle, respectively, to exclude the distalmost portion of the extremity from exposure to chemotherapy. Exclusion of the hand or foot from the circuit can substantially reduce treatment-related morbidity to these areas, which are particularly prone to skin and neurologic toxicities.⁴³ After surgery, limb elevation may help reduce edema and allow more accurate clinical assessment of limb compartments. It is our practice to measure daily serum creatine kinase (CK) levels to monitor for early evidence of significant muscle toxicity, and to prophylactically administer systemic steroids if CK levels exceed 1000 µg/L. Although CK levels can be informative and raise suspicion, the diagnosis of compartment syndrome and need for urgent fasciotomy are based primarily on careful clinical examination. In some cases, muscle compartment pressures can be measured directly with a hand-held intra-compartmental pressure monitor, and prove useful in situations in which clinical examination is difficult or unclear.

EVALUATION OF OUTCOME

Reports of outcomes following HILP are widely variable, likely reflecting diverse patient populations and adjunctive treatment strategies, but responses to regional therapy are typically seen within 6 to 12 weeks (Figs. 5 and 6). Although single-center studies have described complete response rates of 39% to 82% and overall response rates of 81% to 100%,^{44–49} the multicenter ACOSOG Z0020 study reported complete response rates of only 25%.³⁹ Furthermore, responses are often not durable, with 50% to 60% recurrence rates in the first year and overall 5-year survival of 30% to 40%.⁵⁰ Compared with HILP, outcomes following ILI are generally inferior, with complete response rates of 23% to 44% and overall responses of 43% to 100%.^{19,31,47,51–54} In comparing patterns of recurrence, ILI has been associated with significantly shorter time to first recurrence (8 months vs 23 months) and an overall higher probability of recurrence (85% vs 65%) compared with HILP.⁵⁵ Despite these differences, to date no significant differences in overall survival have been identified between the two treatment approaches.

FUTURE DIRECTIONS AND LONG-TERM RECOMMENDATIONS

Although regional therapy has been established for management of extremity in-transit melanoma for several decades, recent advances in immune modulation may have implications for future treatment of loco-regionally advanced disease. Immune checkpoint blockade, via anti-CTLA-4 and anti-PD-1, has generated considerable interest in recent years as a potential therapy for advanced melanoma. Responses that are clinically meaningful may be linked to immune activation, and a growing body of evidence suggests that therapeutic responses may be linked to immune activation.^{56–60} Regional therapy itself has been shown to generate an immune response, which may work in concert with cytotoxic chemotherapy to generate a tumor response.

In light of these advances, clinical trials exploring the role of immune activation with ipilimumab, a human IgG1-kappa monoclonal antibody to CTLA-4, in combination with cytotoxic regional chemotherapy have already started. Specifically, a trial investigating the role of adjuvant ipilimumab administered following melphalan ILI is currently enrolling patients at Memorial Sloan Kettering Cancer Center ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01323517): NCT01323517). Similarly, a multicenter trial based at Duke University exploring neoadjuvant ipilimumab before melphalan ILI is expected to begin enrolling patients by the end of 2014 ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02115243): NCT02115243).

SUMMARY

In-transit disease is an uncommon but clinically important manifestation of melanoma recurrence, and often allows unique treatment opportunities in the form of regional therapy. Over the past half-century, numerous advances in regional therapy have been made, including HILP and ILI. With recent innovations in immune manipulation and checkpoint blockade for the treatment of locally advanced and metastatic disease, future applications of regional therapy are likely to involve combination therapy with cytotoxic agents and novel immune modulators. Despite this changing landscape in melanoma treatment, regional

therapy provides unique opportunities for the treatment of unresectable disease, and offers a unique platform for investigation of novel therapeutics in early-stage clinical trials.

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KEY POINTS

- In-transit disease is a challenging pattern of recurrence to manage, occurring in up to 10% of patients with melanoma.
- Regional therapy, by isolated limb infusion or hyperthermic isolated limb perfusion, offers treatment options for patients with non-resectable disease.
- Regional therapies are generally well tolerated, and offer complete response rates of 25% to 50%, although long-term responses are often not durable.
- Future management of in-transit melanoma is likely to involve combination therapies, joining cytotoxic regional therapy and systemic immune-modulating drugs such as anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) and anti-programmed cell death 1 surface protein molecule agents.

FIGURE 1.
The spectrum of clinical presentation for patients with in-transit melanoma of the extremity. Disease can manifest as (A) low-volume disease or solitary nodules, (B) multifocal unpigmented lesions, (C) multifocal disease with diffuse dermal spread, or (D) traditional multifocal dark pigmented lesions.

FIGURE 2.
HILP. (From Coleman A, Augustine CK, Beasley G, et al. Optimizing regional infusion treatment strategies for melanoma of the extremities. *Expert Rev Anticancer Ther* 2009;9(11):1600; with permission.)

FIGURE 3.
ILI. (From Coleman A, Augustine CK, Beasley G, et al. Optimizing regional infusion treatment strategies for melanoma of the extremities. *Expert Rev Anticancer Ther* 2009;9(11):1602; with permission.)

FIGURE 4.

A complete durable response following temozolomide ILI in a patient who previously progressed after melphalan ILI. (A) Progressive disease within 3 months following initial treatment with melphalan ILI. (B) The same patient showing complete pathologic response following a subsequent temozolomide ILI, with evidence of residual nonmalignant pigmentation out to 12 months after infusion.

FIGURE 5.
Typical time course of a complete response following regional therapy, showing steady resolution of in-transit melanoma lesions over a 12-week postoperative period.

FIGURE 6.

Patterns of tumor regression in 2 patients who experienced complete responses following regional therapy. Nonpigmented lesions (*A*) typically resolve visually, whereas pigmented lesions (*B*) following complete response often leave a tattooed-appearing area consisting of pigment-laden macrophages with no viable tumor on biopsy.

TABLE 1

Wieberdink toxicity grading scale for severity of complications following regional therapy.

Grade I	No subjective or objective evidence of reaction
Grade II	Light erythema and/or edema of limb
Grade III	Considerable erythema and/or edema of limb with some blistering; slightly disturbed motility/mobility
Grade IV	Extensive epidermolysis and/or obvious deep tissue damage, causing definite functional disturbances; threatening or manifest compartment syndrome
Grade V	Reaction that may necessitate amputation/limb loss

Adapted from Wieberdink J, Benckhuysen C, Braat RP, et al. Dosimetry in isolation perfusion of the limbs by assessment of perfused tissue volume and grading of toxic tissue reactions. *Eur J Cancer Clin Oncol* 1982; 18:908; with permission.