ORIGINAL ARTICLE

Limb Preservation With Isolated Limb Infusion for Locally Advanced Nonmelanoma Cutaneous and Soft-Tissue Malignant Neoplasms

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Objective: To demonstrate the efficacy of isolated limb infusion (ILI) in limb preservation for patients with locally advanced soft-tissue sarcomas and nonmelanoma cutaneous malignant neoplasms.

Background: Locally advanced nonmelanoma cutaneous and soft-tissue malignant neoplasms, including soft-tissue sarcomas of the extremities, can pose significant treatment challenges. We report our experience, including responses and limb preservation rates, using ILI in cutaneous and soft-tissue malignant neoplasms.

Methods: We identified 22 patients with cutaneous and soft-tissue malignant neoplasms who underwent 26 ILIs with melphalan and dactinomycin from January 1, 2004, through December 31, 2009, from 5 institutions. Outcome measures included limb preservation and in-field response rates. Regional toxic effects were measured using the Wieberdink scale and serum creatinine phosphokinase levels.

Results: The median age was 70 years (range, 19-92 years), and 12 patients (55%) were women. Fourteen patients (64%) had sarcomas, 7 (32%) had Merkel cell carcinoma, and 1 (5%) had squamous cell carcinoma. The median length of stay was 5.5 days (interquartile range, 4-8 days). Twenty-five of the 26 ILIs (96%) resulted in Wieberdink grade III or less toxicity, and 1 patient (4%) developed grade IV toxicity. The median serum creatinine phosphokinase level was 127 U/L for upper extremity ILIs and 93 U/L for lower extremity ILIs. Nineteen of 22 patients (86%) underwent successful limb preservation. The 3-month in-field response rate was 79% (21% complete and 58% partial), and the median follow-up was 8.6 months (range, 1-63 months). Five patients underwent resection of disease after an ILI, of whom 80% are disease free at a median of 8.6 months.

Conclusions: Isolated limb infusion provides an attractive alternative therapy for regional disease control and limb preservation in patients with limb-threatening cutaneous and soft-tissue malignant neoplasms. Short-term response rates appear encouraging, yet durability of response is unknown.

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Locally advanced soft-tissue sarcomas (STSs) and nonmelanoma cutaneous malignant neoplasms (ie, Merkel cell carcinoma [MCC] , eccrine carcinoma, apocrine carcinoma, and squamous cell carcinoma [SCC]) were treated with amputations until studies showed a high risk for progressive and metastatic disease[1] and a lack of survival benefit with amputations.[2-5] Currently, radical surgical resections with complex reconstruction and, in some cases, the addition of adjuvant radiation have become the standard of care to achieve limb preservation. These techniques are often accompanied by significant disfigurement, loss of function, and decreased quality of life.[6-8] Hyperthermic isolated limb perfusion (HILP) was introduced as regional therapy for control of locally advanced STS, and several institutional reports have demonstrated limb preservation rates of 58% to 89%.[9] Regional chemotherapy has demonstrated effective palliation in patients with locally advanced disease and, in some cases, has resulted in durable complete responses (CRs).[10]

Isolated limb infusion (ILI) for melanoma was introduced by John Thompson at the Sydney Melanoma Unit (SMU) in the late 1990s as a minimally invasive counterpart for HILP.[11] The role of ILI in the treatment of STS and nonmelanoma cutaneous malignant neoplasms is novel and has been described only in sporadic single-institution case series.[12,13] Response rates for locally advanced STS after ILIs have been reported as high as 90%. In addition, ILI has been used as neoadjuvant therapy, and studies have shown 65% CR rates in patients treated with neoadjuvant

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intent, with all patients undergoing intended resections.[13] Alternatively, the role of ILI has also been investigated as an adjunct to adjuvant radiation in sarcomas and has been shown to have response rates of 85%.[12,14] We retrospectively reviewed our multi-institutional pooled experience and report on the response and limb preservation rates after ILI for locally advanced STS and nonmelanoma cutaneous malignant neoplasms.

METHODS

SELECTION OF PATIENTS

Institutional review board approval was obtained at each institution before this retrospective analysis. Patients who underwent ILI with melphalan and dactinomycin for nonmelanoma cutaneous and soft-tissue malignant neoplasms from January 1, 2004, through December 31, 2009, were identified from ILI databases at 5 referral centers. Eligible patients were those with locally advanced STS and nonmelanoma cutaneous malignant neoplasms, such as MCC and SCC. Lymph node dissections for palpable nodal disease were performed in a staged or concurrent fashion.

DOSING OF CHEMOTHERAPEUTIC AGENTS

The dose of melphalan was 7.5 mg/L limb volume for lower extremity and 10 mg/L limb volume for upper extremity, with a maximum total dose of 100 mg for lower extremity and 50 mg for upper extremity. Dactinomycin was used at 100 μg/L limb volume infused for both lower and upper extremities. Chemotherapy was admixed with heparinized normal saline at 400 mL for lower extremities and 300 to 400 mL for upper extremities. Limb volume was calculated by taking circumferential limb measurements from the distal extremity at 1.5- to 2-cm intervals. The last proximal measurement was taken at the inferior aspect where a tourniquet would rest at the time of ILI. Final limb volume was calculated by entering these measurements into an Excel software program (Microsoft, Redmond, Washington) that was developed by Anthony Perez-Tamayo, MD, PhD, to calculate the cylindrical volume of the limb.[15] Some centers used a water displacement method to measure limb volume. A corrected melphalan dose based on ideal body weight was used in most patients (84%). The calculation was performed in the following manner:

[Melphalan Dose per Liter of Limb Volume to be Infused (mg/L) × Calculated Volume of Extremity (L) × Ideal Body Weight (kg)]/Actual Body Weight (kg) = Corrected Melphalan Dose Based on Ideal Body Weight.

TECHNIQUE OF ILI

The ILI procedures were performed as described elsewhere.[11,16,17] Briefly, high-flow 5F to 6F arterial and venous catheters were inserted under fluoroscopic guidance into an uninvolved extremity and positioned with their tips in the involved extremity at a previously marked site distal to the tourniquet site. Heparin in a range of 5000 to 10 000 U was given at the time of catheter placement. The extremity was prewarmed with liquid warming blankets before the patient entered the operating room. Full systemic heparinization was used to achieve a target activated clotting time of 400 seconds or more. A pneumatic or Esmarch tourniquet was placed on the proximal aspect of the limb to isolate the limb and to avoid leakage of the chemotherapeutic agents. Two subcutaneous temperature probes were placed in the proximal and distal aspects of the involved extremity. Once subcutaneous temperatures of 37°C or greater were achieved, the tourniquet was inflated to 250 mm Hg (upper extremity) or 350 mm Hg (lower extremity), and 60 mg of papaverine hydrochloride was injected into the arterial catheter.

The catheters were then connected to form a closed circuit, and blood was circulated with either 1-way valves for unidirectional flow or 3-way stopcocks. The chemotherapy was rapidly infused for 5 to 10 minutes through the arterial side of the circuit and then manually circulated for 30 minutes using a 20-mL syringe. Perfusate blood gases were drawn at 25 and 30 minutes after the start of the infusion to document the degree of hypoxia and acidosis in the circuit. After 30 minutes of infusion, the limb was manually flushed with 750 to 1000 mL of isotonic crystalloid solution at room temperature using a pressurized circuit until the effluent was clear. The flush/effluent was manually extracted from the venous catheter and discarded. After the washout period, the tourniquet was deflated. The heparinization was reversed with protamine, and the catheters were removed when the activated clotting time was at or near baseline.

Table 1. Wieberdink Acute Limb Toxicity Scale

Grade	Clinical Characteristics
I	No subjective or objective evidence of reaction
II	Slight erythema or edema
III	Considerable erythema or edema with some blistering; slightly disturbed motility permissible
IV	Extensive epidermolysis or obvious damage to the deep tissues causing definite functional disturbances; threatened or manifest compartmental syndromes
V	Reaction that may necessitate amputation

POSTOPERATIVE CARE AND TOXICITY

Postoperatively, patients were monitored in the step-down or intensive care unit for 24 hours for serial neurovascular checks and were then subsequently transferred to the surgical ward. The serum creatinine phosphokinase (CPK) level was measured daily while patients were in the hospital. Once CPK levels started to decrease after peak levels were identified (usually around postoperative day 4), the patient was discharged. Patients who developed grade IV serologic toxicity (CPK levels >1000 IU/L) were treated with intravenous hydration with normal saline to maintain a urine output greater than 0.5 mL per kilogram per hour and corticosteroids (4 mg of dexamethasone every 6 hours) until their CPK levels decreased to less than 1000 IU/L.

Limb toxicity was determined and recorded by close physical examination throughout the hospitalization and at 2, 6, and 12 weeks postoperatively using the scale proposed by Wieberdink et al[18] (**Table 1**). Severe acute limb toxicity was defined as Wieberdink grade III or higher.

OUTCOME MEASURES

Response rates were measured by the clinical response to the ILI at 3 months postoperatively and every 3 months thereafter. When cross-sectional imaging was used for follow-up (eg, in STS), response was measured using the modified Response Evaluation Criteria in Solid Tumors criteria[19] as well as possible in a retrospective fashion for soft-tissue tumors imaged by cross-sectional imaging or using caliper measurements and physical examination for cutaneous lesions (MCC and SCC). Patients who underwent a second

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Table 2. Outcomes of Infusions on Patients With Locally Advanced Nonmelanoma Cutaneous Malignancies After an ILI (Stratified by Extremity Type)

Characteristic	Overall (N=26)	Upper Limb (n=10)	Lower Limb (n=16)	*P* Value
Limb volume, median (IQR)	5.6 (2.8 to 7.0)	2.3 (1.7 to 2.9)	6.6 (5.6 to 7.2)	.001
Melphalan dose, median (IQR), mg	31.0 (20.0 to 42.0)	19.0 (15.0 to 26.0)	41.1 (34.0 to 46.0)	.001
Dactinomycin dose, median (IQR), μg	370 (200 to 470)	200 (160 to 280)	450 (385 to 680)	.002
Dose adjusted for corrected ideal body weight, %	77	70	81	.51
Papaverine use intraoperatively, %	73	70	75	.78
Ischemia time, median (IQR), min	56 (49 to 77)	56 (50 to 71)	57 (49 to 83)	.53
Perfusate blood gas, 30 min				
Base excess, median (IQR), mEq	−10.1 (−14.7 to −6.9)	−14.4 (−14.9 to −10.1)	−8.2 (−12.1 to −3.8)	.07
Pa_{O_2}, median (IQR), mm Hg	12.0 (5.6 to 18.0)	15.0 (11.0 to 18.0)	9.0 (5.0 to 17.0)	.13
pH, median (IQR)	7.12 (7.08 to 7.21)	7.08 (7.06 to 7.10)	7.18 (7.10 to 7.22)	.01
Peak CPK, median (IQR), U/mL	93 (69 to 2292)	127 (69 to 2479)	93 (65 to 2292)	.78
Day of peak of CPK, median (IQR)	3.0 (2.0 to 6.0)	2.0 (1.5 to 3.0)	4.0 (2.5 to 6.0)	.03
Length of stay, median (IQR), d	5.5 (4.0 to 8.0)	4.5 (4.0 to 8.0)	6.5 (5.0 to 8.5)	.14
Wieberdink toxicity, No. (%)				.69
Grade I	17 (65)	7 (70)	10 (62)	
Grade III	9 (35)	3 (30)	6 (38)	
Overall response rate (CR + PR), %	79 (21 + 58)	78 (33 + 45)	80 (13 + 67)	.89

Abbreviations: CPK, creatinine phosphokinase; CR, complete response; ILI, isolated limb infusion; IQR, interquartile range; PR, partial response.

ILI were coded as having progressive disease at the last follow-up before the repeat procedure.

STATISTICAL ANALYSIS

All statistical analysis was performed using Stata, version 9 (StataCorp, College Station, Texas). Associations were tested with the Fisher exact test, the χ^2 test, and the Wilcoxon rank sum test, as appropriate. Multivariate models were not used, given the small sample size in our study. A 2-tailed *P* value less than .05 was considered statistically significant.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

We included 22 patients who underwent 26 ILIs during the study period of January 1, 2004, through December 31, 2009, including 1 from Emory University, 1 from University of Florida, 5 from Roswell Park Cancer Institute, 7 from Duke University, and 8 from Moffitt Cancer Center. Ten patients (45%) were men, and the median age was 70 years (range, 19-92 years). Fourteen patients (64%) had STS, 7 (32%) had MCC, and 1 (4%) had SCC. Of the 14 patients with STS, 5 (36%) had pleomorphic undifferentiated sarcoma, 3 (21%) had epithelioid sarcomas, 2 (14%) had fibrous histiocytomas, 1 (7%) had Kaposi sarcoma, 1 (7%) had myxoinflammatory fibroblastic sarcoma, and 1 (7%) had angiosarcoma. In addition, 1 patient (7%) had a high-grade sarcoma not otherwise classified. Ten (38%) of the 26 infusions were in the upper extremity.

Of the 8 patients with cutaneous malignant neoplasms (7 with MCC and 1 with SCC) undergoing 10 ILIs, the median age was 78.5 years (interquartile range [IQR], 72-84 years), and 4 of the 8 (50%) were women. Eight of the 14 patients with STS undergoing ILI were significantly younger (median age, 68.5 years [IQR, 51-77 years]; *P* = .03) but had a similar sex distribution (57% were women; *P* = .57).

ILI PROCEDURE AND INTRAOPERATIVE PARAMETERS

The intraoperative parameters are shown in **Table 2**. As would be expected, limb volume and, therefore, dosage of melphalan and dactinomycin, were much higher in the lower limb infusions. A greater degree of acidosis was achieved in the upper limbs (median pH at 30 minutes, 7.08 vs 7.18; *P* = .01), although hypoxia levels and base excess reached were not statistically significantly different (median base excess, −14.4 vs −8; *P* = .07; and median Pa_{O_2} at 30 minutes, 15 mm Hg vs 9 mm Hg; *P* = .13) (Table 2). Intraoperative parameters were similar in patients undergoing ILI for cutaneous malignant neoplasms vs for STS (median pH at 30 minutes, 7.14 vs 7.10; *P* = .60; base excess at 30 minutes, −11.4 vs −10.1; *P* = .97; Pa_{O_2} at 30 minutes, 14.3 vs 10 mm Hg; *P* = .92, and median ischemia time, 64 vs 55.5 minutes; *P* = .89).

LENGTH OF STAY AND TOXICITY

The median length of stay for patients undergoing lower limb infusions was longer than that for patients undergoing upper limb infusions (6.5 vs 4.5 days; *P* = .14); however, this was not statistically significant. The median Wieberdink toxicity was grade II, and it did not differ between the upper and lower limb (grade II for both). Median CPK levels were similar in both extremities but peaked later for lower extremities (4 vs 2 days; *P* = .03). Toxicities were not significantly different between patients with cutaneous malignant neoplasms and those with sarcomas (median toxicity, grade II for both; *P* = .75; and median peak CPK, 76.5 for cutaneous malignant neoplasms and 177 for sarcomas; *P* = .18) (Table 2).

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Table 3. Response Rates by Histologic Subtype for Patients With Locally Advanced Nonmelanoma Cutaneous Malignant Neoplasms After an ILI

Patients With Evaluable Response at 3 mo	Per Infusion, %	Per Patient, %	Last Known Status
With soft-tissue sarcomas (12 patients, 14 infusions)			7 NED, alive; 2 SD, alive; 2 SD, died of metastatic disease; 1 progressive disease
Overall response rate	**78**	**75**	
Complete response rate	14	17	
Partial response rate	64	58	
With Merkel and squamous cell carcinoma (8 patients, 10 infusions)			2 NED, alive; 1 NED, died of other causes; 1 SD, alive; 1 SD, died of metastatic disease; 2 progressive disease, alive; 1 progressive disease, died of metastatic disease
Overall response rate	**80**	**75**	
Complete response rate	30	25	
Partial response rate	50	50	

Abbreviations: ILI, isolated limb infusion; NED, no evidence of disease; SD, stable disease.

OUTCOME MEASURES

The median duration of follow-up was 11 months (IQR, 7-14 months; range, 1-63 months) among 21 evaluable patients, whereas the median follow-up after each of the 25 infusions was 8.6 months (IQR, 4.4-14.2 months; range, 1.5-63 months). This difference exists because patients who underwent repeat ILI had their follow-up separated for each infusion. The overall response rate at 3 months was 79% (21% CR and 58% partial response [PR]). The response rate for patients with STS was 75% (17% CR and 58% PR) per patient and 78% (14% CR and 64% PR) per infusion, whereas that for cutaneous malignant neoplasms was 75% (25% CR and 50% PR) per patient and 80% (30% CR and 50% PR) per infusion (**Table 3**). The response rate per ILI for the 7 patients with MCC was 78% (33% CR and 45% PR) in 9 infusions. There were no patients with progressive disease, and 2 of the 9 infusions (22%) resulted in stable disease, both of which were repeat ILIs. The patient with SCC who underwent an ILI had a PR at 3 months, with stable disease at 11 months.

Of the 4 patients who underwent repeat ILI, 2 had STS (1 patient with Kaposi sarcoma and 1 with pleomorphic high-grade sarcoma), and 2 had MCC. All 4 patients had a response after the initial infusion (100% response rate: 25% CR and 75% PR) but relapsed or progressed after 6 months (range, 3-8 months). Of the 3 patients with evaluable 3-month follow up after a repeat ILI, 2 had stable disease and 1 underwent resection of the recurrence to render her without evidence of disease. The fourth patient had a short-term follow-up at the time of the study, with no evidence of progression.

Nineteen of the 22 patients (86%) had successful limb preservation after ILI, and 1 (5%) underwent an amputation and 2 (9%) underwent a hip disarticulation. The limb preservation was 100% for the 7 patients with MCC and the 1 with SCC, whereas 11 (78%) of those with STS had limb preservation. Of the 22 patients, 17 (77%) were alive at last follow-up. Of the 5 deaths, 4 were from metastatic disease (80%), and 1 patient (20%) died of other causes. Four of the 5 patients (80%) who died had a 3-month in-field PR, and 1 patient had stable disease at 3 months after an ILI. All these patients developed in-field progressive disease subsequently (Table 3).

The median time to progression was 6.5 months (IQR, 4.5-12.5 months) for patients with MCC, whereas it was 8.9 months (IQR, 6.1-22.6 months) for those with STS (with censored follow-up). The 1 patient with SCC did not develop progression of disease. We were able to resect the residual disease in 5 of the 22 patients undergoing ILI, with 4 (80%) of the patients who underwent resection remaining free of disease at last follow-up (median, 8.6 months [IQR, 8.3-11.3 months]). Of the 5 patients who underwent resection, 2 had MCC, and 3 had STS (2 malignant fibrous histocytomas and 1 epithelioid sarcoma). One patient developed progressive disease after resection and underwent a repeat ILI, after which he achieved stable regional disease but developed distant metastatic disease. Of the 3 patients who underwent amputations, 100% remained disease free at last follow-up (median, 8.9 months [IQR, 6.1-50.7 months]).

COMMENT

In this era in which advanced cutaneous and soft-tissue malignant neoplasms of extremities are treated with the goal of preserving limb function, ILI is a viable alternate therapy to achieve disease response and local control for advanced soft-tissue tumors that would otherwise require disfiguring surgery with extensive reconstruction or amputation.

Isolated limb infusion enables delivery of regional chemotherapy at almost 10-fold–greater concentrations than systemic chemotherapy and has the advantage of being able to be repeated for recurrent or persistent disease.[11,12] Even though reports of significant tumor shrinkage after ILI are not common for cutaneous and soft-tissue malignant neoplasms, 2 of our patients were able to undergo resection of the primary lesion after an ILI. Previous reports have suggested the use of regional chemoperfusion as neoadjuvant therapy to shrink tumor size and potentially to facilitate surgical resection.[11,13,20-23] Our study did not specifically evaluate the role of ILI as a neoadjuvant therapy, yet 4 patients were rendered disease free at a median follow-up of 8 months, which is a promising result.

The SMU published their report on the use of ILI in STS and had a 90% response rate (57% CR and 33% PR), which is higher than the 79% response rate in our study.[12] The SMU does have a longer experience with ILI, even

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for STS, and the agents that were used have varied over the years, including mitomycin C and melphalan, melphalan, doxorubicin and cisplatin, and, more recently, melphalan and dactinomycin. The overall follow-up duration is longer in the SMU series than in our series (28 months at SMU vs 11 months in the current study), and this may explain why our limb preservation rate is higher than theirs (76% at SMU vs 86% in the current study). In addition, we used ideal-body-weight-corrected dosing of chemotherapeutic agents and have found that this leads to lower toxicity in patients with melanoma, with equivalent CR rates but slightly lower PR rates.[15-17,24] None of our patients developed grade IV toxicity, whereas 14% of the patients at SMU developed grade IV toxicity. The effect of this correction on response rates in cutaneous and soft-tissue malignant neoplasms is unknown.

Regional chemoperfusion with HILP for STS has historically demonstrated limb preservation rates of 58% to 89%, and the rate is significantly higher with the use of regional tumor necrosis factor (TNF).[9,10,25] The efficacy of chemotherapy alone without TNF has been questioned in recent unpublished trials[26] and in older studies.[22,25] European groups have shown remarkable success with the addition of TNF after pioneering studies by Lejeune et al[21] and Olieman et al.[27] Trials with TNF have shown a 20% to 30% complete remission rate and a 50% PR rate.[9,28,29]

The pharmacokinetics of drug distribution in HILP and ILI are different, given the degree of acidosis, the hypoxia, and the lower flow rates in the latter. The comparable response rates seen with melphalan alone in ILI[12,13] suggest this may be an alternative to HILP with melphalan and TNF for locally advanced STS and cutaneous and soft-tissue malignant neoplasms. The regional and systemic morbidity of HILP is significantly greater, especially when melphalan is combined with TNF in patients with melanoma (36% grade III or IV toxicity vs 16%-17% toxicity of HILP alone), and is also greater than ILI alone (14%).[12,30] Serious early complications, including reoperation, occur in almost 20% of patients, and delayed complications (neuropathy and functional morbidity) develop in another 21% of patients, whereas functional morbidities from ILI remain minimal.[14]

A 79% short-term response rate at 3 months may be an overestimate of the true long-term response rate because more patients are likely to relapse with in-field recurrences over time. However, ILI offers patients good function preservation with minimal morbidity (median toxicity, Wieberdink grade II). Our study is limited in its evaluation of long-term survival and disease-free survival and does not provide information on the long-term limb preservation rate. In addition, the role of radiation therapy in the local control of advanced tumors was not adjusted for in our study. Although most physicians would agree that short-term limb preservation for limb-threatening malignant neoplasms provides significantly improved quality of life, it remains to be determined which modality, regional chemotherapy (ILI/HILP) or radiation therapy, provides the better response with the more acceptable toxicity.

We report a promising limb-preservation rate for advanced nonmelanoma cutaneous and soft-tissue malignant neoplasms of the extremities and believe that the role of ILI may be expanded to include neoadjuvant therapy, which may allow for surgical resection of tumors without sacrificing vital structures. Despite the heterogeneity of sites, our common experience reinforces the validity of this method as a limb preservation technique. The effect of ILI on the quality of life, its role in the management of specific tumors, and its effect on the overall outcome of patients with regionally advanced disease will need to be further evaluated because this initial study suggests there are some encouraging responses in a group of tumors that are generally difficult to treat.

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