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HILP may be an effective option to preserve limb function and quality of life for patients with unresectable sarcomas of the extremities.

Hyperthermic Isolated Limb Perfusion for Extremity Sarcomas

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Background: *The treatment options available for extremity sarcomas are amputation or limb-sparing surgery with radiation, which may incur significant morbidity and body disfigurement. Hyperthermic isolated limb perfusion (HILP) may be an attractive option in extremity sarcomas for unresectable lesions to preserve limb function and maintain quality of life.*

Methods: *We report the outcomes of 5 patients who underwent HILP for unresectable primary or recurrent extremity sarcomas from 1994 to 2000 at our institution.*

Results: *All patients had initial complete clinical responses to HILP, and the limb was salvaged in 4 of the 5 patients. Complications included chronic lymphedema, neuropathic pain, and prolonged wound healing.*

Conclusions: *HILP with melphalan is a safe and effective treatment option for selected patients with locally advanced and unresectable extremity sarcomas. The response rates are high, with limb salvage occurring in most patients. Further studies of larger groups of patients are warranted.*

Background

Hyperthermic isolated limb perfusion (HILP) is a surgical procedure for regional intravascular delivery of heat and high doses of chemotherapeutic and biologic agents to an extremity. The procedure is utilized for locally advanced malignancies or recurrent cancer confined to the extremity. HILP is based on the cardiopulmonary bypass technique developed for cardiac surgery in the 1950s and used in oncologic surgery for regional delivery of high doses of drugs. This tech-

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nique exposes tumors to drug doses up to 20 times higher than the doses delivered using the systemic route, and it also minimizes the amount of drug entering the systemic circulation.

Isolated limb perfusion (ILP) was first performed and reported in 1958 by Creech and colleagues¹ in a patient with in-transit lower-extremity melanoma who had a complete response (CR) and died of unrelated causes 16 years later. Based on such experiences, ILP gradually became popularized and is currently an accepted treatment for patients with in-transit or locally advanced cutaneous extremity melanoma. In locally advanced melanoma, reports have described overall response rates of 50%-100% using various chemotherapeutic and biologic agents.²⁻⁴

The studies on the efficacy of HILP have been primarily in patients with cutaneous melanoma. The experience in other malignancies is more limited. Soft-tissue sarcoma is another tumor that has been treated with HILP. Of the approximately 6,000 new cases of soft-tissue sarcomas diagnosed per year, approximately 3,600 occur in the extremities. The treatment options available for extremity sarcomas are amputation or limb-sparing surgery with radiation. However, patients

may incur significant morbidity and body disfigurement. For locally advanced and unresectable primary sarcomas or recurrent tumors, options for limb salvage are limited. Limb perfusion may be an attractive option for unresectable lesions in order to preserve limb function and improve quality of life.

Methods

Five patients underwent therapeutic HILP for extremity sarcomas at our center from 1994 to 2000. Patients were considered for HILP if they had recurrent or unresectable primary disease. For the technique of the HILP, all patients underwent general anesthesia. Following isolation and cannulation of the external iliac, common femoral, or subclavian artery and vein, patients were given melphalan for limb perfusion at a dose of 1.2 mg/kg (lower extremity) or 0.8 mg/kg (upper extremity) at 40-40.5°C for 1 hour. By convention, the patients with melanoma were given melphalan for limb perfusion for 1 hour, and this was adapted for patients with sarcomas. Flow rates of 800-1,000 mL/min were achieved and adjusted to minimize leakage of the drug into the systemic circulation. After completion of the perfusion, the cannula was

Patient Characteristics and Outcomes After HILP With Melphalan for Extremity Sarcoma

Age	Sex	Histology	Reason for HILP	Site/Size	Response to HILP	Time to Recurrence After HILP (mos):		Site of Recurrence	Additional Treatment	Follow-up	Survival (mos) From HILP
						Local	Systemic				
51	M	Osteosarcoma	Recurrence	Left leg/ 5 × 15 cm	CR	3	23	Leg nodules; lung metastases	Below-knee amputation; lung resections	Alive/NED	45
62	F	Giant cell tendon sheath sarcoma	Recurrence and treated metastatic disease	Right thigh/ multiple SQ nodules	CR	—	13 27	Lungs; groin LN abdominal wall; cervical LN	Lung resections; chemotherapy, radiation therapy	Alive/PD	32
93	M	Angiosarcoma	Unresectable primary	Left arm/ 10 × 25 cm	CR	3	—	Left arm	Local excision	Alive/NED	6
39	M	Malignant fibrous histiocytoma	Recurrence	Left leg/ 6.5 × 3.5 cm	CR	—	—	—	—	Alive/NED	39
41	M	Malignant fibrous histiocytoma	Recurrence and metastatic disease, debulking of tumor	Left leg/ ulcerated 6 × 6 cm	CR	—	simultaneous	Lung, brain	Chemotherapy	Dead/PD	10

HILP = hyperthermic isolated limb perfusion
 SQ = subcutaneous
 LN = lymph node
 CR = complete clinical response
 NED = no evidence of disease
 PD = progressive disease

removed, and the artery and vein were repaired. Response to HILP was determined by physical examination and radiographic studies and was designated as CR if no clinical evidence of residual tumor was seen at 3 months following perfusion.

Results

HILP was performed in four men and one woman with the age range of 39 to 93 years (Table). HILP was used in 4 patients for recurrent cancers and in 1 patient for locally advanced primary tumor. Histologies included malignant fibrous histiocytoma (2 patients), angiosarcoma (1), osteosarcoma (1), and giant cell tendon sheath sarcoma (1). Four patients underwent lower-extremity HILP, and 1 had upper-extremity HILP (Figure). One patient underwent HILP with debulking of a large ulcerated lower-extremity sarcoma. All 5 patients had an initial CR to HILP. One patient remains without any evidence of disease at 39 months. Four patients developed disease that consisted of a local recurrence on the perfused extremity (1 patient), systemic disease only (2 patients), and both local and systemic disease (1 patient). Of the 2 patients with local recurrences, excision alone was used in 1 and a below-knee amputation in the other. Limb salvage was achieved in 4 of the 5 patients. Two patients with sys-

temic recurrent disease underwent lung resection and remain disease-free.

Four patients are alive at 6, 32, 39, and 45 months from the time of HILP: 3 with no evidence of disease and 1 with progressive disease. One patient died of his disease at 10 months from the time of HILP, but the extremity was free of recurrence at the time of death. Two patients had treatment-related complications: 1 patient developed chronic lymphedema and neuropathic pain after the perfusion, and 1 patient experienced prolonged wound healing at the resection site.

Conclusions

The treatment options available for extremity sarcomas are amputation or limb-sparing surgery with radiation. However, limb-sparing resection for sarcomas is not optimal if clear margins cannot be achieved in cases where there is evidence of neurovascular invasion or extensive soft-tissue involvement with no reconstruction alternative after resection. For patients with advanced primary sarcomas or recurrent tumors, amputation is usually considered the primary option. However, patients incur significant morbidity and body disfigurement with these procedures. Furthermore, amputations have not been shown to



A 93-year-old man with unresectable angiosarcoma of the right arm before (A, B) and after (C, D) hyperthermic isolated limb perfusion with melphalan. The patient had a complete clinical response to the treatment and preservation of upper-extremity limb function.

improve survival rates in patients with large, deep-seated tumors. Up to 85% of these patients undergoing major amputation for extremity sarcomas have progression of their disease with distant metastases.^{5,6} Therefore, patients who undergo amputation or major morbid surgical resections may develop distant metastatic disease in the near future. Functional limb preservation is a major goal in the management of extremity sarcomas and one that poses a considerable challenge. Even in the presence of metastases, patients may require local control since the lesions often multiply, grow, and ulcerate. HILP is an attractive option for unresectable lesions in order to preserve limb function and improve quality of life. In our series of 5 patients with unresectable or recurrent extremity sarcomas who underwent HILP with melphalan with or without partial resection, the initial responses were good, with all 5 patients having complete clinical disappearance of tumors and with limb salvage in 4 of the 5 patients.

The results of early published reports on HILP for extremity sarcomas are difficult to discern due to significant variables in the studies, including drug agent, dosage, treatment strategies with use of concomitant surgery, radiation, and systemic chemotherapy. In 1975, Stehlin et al⁷ published one of the first series on ILP (no hyperthermia) for extremity sarcomas using a combined approach with radiation and local excision. They showed that this could be performed with low morbidity and mortality. Soon thereafter, Kremenz and colleagues⁸ reported the response rates of 113 patients who underwent ILP with chemotherapy with or without excisional surgery. In 54 patients who underwent ILP alone, the early response rate was 83%, but beyond 3 months, CR and PR were only 11% and 22%, respectively. In early studies in sarcoma patients,^{8,9} the overall response rates were fairly low — approximately 20%-35%, with 11% CR. However, more recent studies¹⁰⁻¹³ show improved responses, with up to 37% CR and 57% PR and with limb salvage rates of 80%-90%.

Various chemotherapeutic agents have been used to improve response rates. Melphalan is the standard drug used in limb perfusion for melanoma patients and was used in the past for extremity sarcomas with disappointing results.⁹ Doxorubicin (Adriamycin) showed somewhat improved response rates when used with melphalan.² In another study,¹⁴ there was a 57% conversion rate from unresectable to resectable tumors with HILP using doxorubicin alone with a local recurrence rate of 15% in those patients who underwent limb-sparing surgery. Limb perfusion with cisplatin in one series of 4 patients showed promising results,¹⁵ with CR or PR in 3 patients.

More recent advances in HILP have involved newer biologic agents such as tumor necrosis factor (TNF) with its potential antiangiogenic properties.^{11,16} Eggermont et al¹⁶ published one of the largest series of HILP for soft-tissue sarcomas using TNF and melphalan. Of 246 patients, pathologic CRs were seen in 28% and PRs in 47%. At a median follow-up of greater than 3 years, the limb salvage rate was 71%. TNF is now approved in Europe for ILP of extremity soft-tissue sarcomas. However, in the United States, TNF is currently available only as part of a study trial. Interferon gamma has also been used in addition to TNF and melphalan and appears to add no further benefit.^{11,17,18}

Sarcomas are tumors of mesenchymal origin with a wide range of histologic features. Response to limb perfusion may be better in certain histologies of sarcomas than others. In one study,¹⁹ all of the 5 patients with angiosarcoma had a CR after HILP. In our series, 1 patient with angiosarcoma had a significant response, with complete regression of a 10 × 25-cm upper-extremity tumor.

Bone sarcomas also respond to limb perfusion. Limb-sparing surgery was possible in 70% of patients with unresectable bone sarcoma patients.²⁰ One patient in our series underwent HILP for osteosarcoma and had a good response initially but required a below-knee amputation for multiple local recurrences.

The most common side effects after limb perfusion are regional skin toxicity ranging from erythema and edema, blistering, and complete necrosis of the extremity requiring amputation. Other complications include ankle stiffness, muscle atrophy,²¹ 5% incidence of deep vein thrombosis,²² and 5%-8% long-term peripheral neuropathy and myopathy.²³ In our series, 1 patient developed significant morbidity of peripheral neuropathy. Systemic toxicity occurs as a result of perfusate leak. Most perfusions can be performed with less than a 10% leak rate. Toxicity from systemic leak is a significant concern with TNF, which can cause vasodilation, hypotension, and leaky capillary syndrome. However, the systemic side effects (eg, neutropenia) with melphalan at low systemic drug levels are minimal and well tolerated.

In our series of patients, HILP with melphalan was a safe and effective treatment option for locally advanced extremity sarcomas. The response rates were high, with limb salvage achieved in most patients. Amputation or major disfiguring surgical resections can be avoided so those patients may have improved quality of life. Further studies are warranted in larger groups of patients.

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