Isolated Limb Infusion as a Limb Salvage Strategy for Locally Advanced Extremity Sarcoma

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BACKGROUND: Treatment-resistant, locally advanced soft tissue sarcomas often require amputation for complete tumor extirpation. Isolated limb infusion (ILI) selectively delivers high-dose chemotherapy to the extremity in an attempt to achieve limb salvage. The aim of this study was to report perioperative and oncologic outcomes after ILI in patients with extremity soft tissue sarcomas.

STUDY DESIGN: From 1994 to 2016, 77 patients underwent 84 ILIs at a total of 5 institutions. Melphalan and actinomycin D were circulated for 30 minutes after complete tourniquet occlusion of the limb, then actively washed out to prevent systemic exposure.

RESULTS: The procedure was performed in an upper extremity on 19 patients (21 infusions) and in a lower extremity on 58 patients (63 infusions). The 3-month overall response rate (ORR) for the entire cohort was 58%, and there was a statistically significant difference ($p = 0.03$) between upper (37%) and lower extremity (66%) ORR. With median follow-up of 20.6 months (range 0.6 to 146.1 months), the overall limb salvage rate was 77.9%. For those who underwent amputation due to progression of disease, the median time to amputation was 4.5 months. With a median follow-up of 20.6 months, the median overall survival for the entire cohort was 44.3 months. The distant metastatic-free survival was longer for responders than nonresponders ($p = 0.01$), though the disease-specific survival was not different for the same groups ($p = 0.2$).

CONCLUSIONS: Isolated limb infusion for extremity soft tissue sarcoma results in an objective response for half of the patients who are otherwise facing amputation, and offers prolonged limb salvage for the vast majority of patients. The procedure is well tolerated without serious complications. (J Am Coll Surg 2017;224:635–642. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Regional chemotherapy was developed as a strategy to treat patients with in-transit melanoma as a way to deliver chemotherapy to disease without systemic toxicity. The initial procedure described was hyperthermic isolated limb perfusion (HILP) with open cannulation of the vessels at the proximal aspect of the extremity and a high-flow oxygenated perfusion,[1-4] but more recent efforts have focused on isolated limb infusion (ILI).[5-11] This

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Abbreviations and Acronyms

CPK = creatine phosphate
DMFS = distant metastatic-free survival
HILP = hyperthermic isolated limb perfusion
ILI = isolated limb infusion
LRFS = local recurrence-free survival
NED = no evidence of disease
ORR = overall response rate
OS = overall survival

technique involves the instillation of chemotherapy through percutaneously placed arterial and venous catheters in an extremity, with tourniquet occlusion of the extremity proximal to the catheter tips. The chemotherapy is circulated for 30 minutes, then washed out from the limb before restoring systemic circulation. The less invasive approach of ILI, in which the catheters can be placed percutaneously by radiographic guidance, was recently shown to have equivalent outcomes when retrospectively compared with HILP.[12]

Patients with locally advanced extremity soft tissue sarcoma have limited therapeutic options. In the absence of distant metastatic disease, amputation has been the standard treatment, reserving systemic chemotherapy for those patients who progress. Historically, amputation was standard for resectable high-grade extremity sarcoma as well, but chemotherapy and radiation therapy are now standard surgical adjuncts, making limb salvage the standard of care.[13-16] Regional chemotherapy has been proposed as a limb salvage strategy for patients with locally advanced sarcoma. Initial reports using the HILP technique described limb salvage rates of 80%. The technique of ILI was initially described for sarcoma patients in the neoadjuvant setting, and an 85% to 100% objective response rate was reported for patients who underwent resection after infusion,[5,6] with 65% obtaining a complete response in 1 study.[6] Three recent reports of ILI as a treatment strategy apart from surgical resection report objective response rates ranging from 42% to 79%.[9,10,17]

Despite encouraging results from these limited reports, long-term outcomes have not been reported for regional chemotherapy using ILI in patients with locally advanced extremity sarcoma. There is concern that without a complete response in the extremity, distant disease may flourish, resulting in decreased overall or distant metastatic-free survival (DMFS) for these patients compared with amputation. The purpose of this report was to describe the long-term outcomes from several high volume centers of ILI for patients with locally advanced extremity sarcoma.

METHODS

After obtaining IRB approval, data were collected from 5 centers to complete a retrospective analysis of patients who underwent ILI for locally advanced soft tissue sarcoma from 1994 to 2016. Data collected included demographic details, sarcoma histologic subtype, procedure details, postoperative course with toxicity, 3-month response to treatment, and long-term oncologic outcomes.

Preoperative assessment

Patients were considered candidates for ILI if they had a locally advanced extremity sarcoma, no objective evidence of vascular disease in the affected extremity, and no evidence of distant metastatic disease on imaging studies. Before surgery, limb volume was calculated with either circumferential measurements of the extremity at 1- to 2-cm intervals or by volume displacement. Volume measurements were used to determine the dose of chemotherapeutic agents, which included a combination of actinomycin (range 3.5 to 13.6 mg/L limb volume) and melphalan (range 46.1 to 142.9 μg/L limb volume).

Intraoperative isolated limb infusion procedure

Under fluoroscopic guidance, arterial and venous catheters were placed from the contralateral groin or brachium into the affected limb, with catheter tips positioned distal to the level of the tourniquet to ensure adequate isolation of the extremity. Patients were transported to the operating room and general anesthesia was induced. The extremities were warmed with either external warming blankets, warming pads, or heating lamps. Temperature probes were placed in the subcutaneous tissue and a tourniquet was placed proximal to all disease in the extremity. Unfractionated heparin was given intravenously to achieve an activated clotting time greater than 400 seconds. The tourniquet was inflated (250 mmHg upper extremity, 350 mmHg lower extremity) when the temperature of the extremity reached 37°C, and 60 mg of papaverine was given through the arterial catheter.

Arterial and venous catheters were connected to a closed circuit with 1-way valves or 3-way stopcocks to ensure flow in 1 direction. Chemotherapy was infused through the arterial catheter over a 5-minute period and then circulated for 30 minutes manually using a 20- to 30-mL syringe connected in line to the closed circuit (Fig. 1). The blood of the extremity was then drained through the venous catheter by infusing saline into the extremity and displacing the chemo-laden blood until the effluent was clear. Heparinization was reversed using protamine to reach an activated clotting time back to baseline. Catheters were removed and manual pressure—with or