HHS Public Access

Author manuscript

Int J Hyperthermia. Author manuscript; available in PMC 2015 July 21.

Published in final edited form as:

Int J Hyperthermia. 2013 ; 29(1): 1–7. doi:10.3109/02656736.2012.740548.

Isolated Limb Infusion for Limb Salvage in Limb Threatening Extremity Sarcomas

Nasreen A. Vohra, MD[1], **Kiran K. Turaga, MD, MPH**[5], **Ricardo J. Gonzalez, MD**[1,3], **Anthony Conley, MD**[1,4], **Damon Reed, MD**[1], **Marilyn M. Bui, MD, PhD**[2], **David Cheong, MD**[1,3], **Douglas G. Letson, MD**[1,3], and **Jonathan S. Zager, MD**[1,3]

[1]Department of Sarcoma Oncology, Moffitt Cancer Center, Tampa, Florida

[2]Department of Anatomic Pathology, Moffitt Cancer Center, Tampa, Florida

[3]Department of Surgery, Morsani College of Medicine at the University of South Florida, Tampa, Florida

[4]Department of Oncologic Sciences, Morsani College of Medicine at the University of South Florida, Tampa, Florida

[5]Division of Surgical Oncology, Medical College of Wisconsin Clinical Cancer Center, Milwaukee, Wisconsin

Abstract

Background—Locally advanced, limb threatening soft tissue sarcomas (STS) pose a significant treatment challenge. We report our experience using isolated limb infusion (ILI) in patients with unresectable extremity STS.

Methods—Twenty-two patients with extremity STS underwent 26 ILIs with melphalan and dactinomycin. Patient characteristics, intra-operative parameters and toxicity were recorded. Outcome measures included limb-salvage and in-field response rates.

Results—Of the 19 lower and 7 upper extremity ILIs, Wieberdink grade III toxicity or less was observed in all. Median follow up was 11 months. Seventeen patients were evaluable at 3 months post ILI with an overall response rate of 42%. Four (24%) had complete response (CR), 3 (18%) partial response (PR), 3 (18%) stable disease (SD) and 7 (41%) progressive disease (PD). Twelve of 17 (71%) underwent successful limb preservation at a median of 9 months post ILI. Two (12%) were downstaged to resectable disease and remain NED after surgery at 30 and 22 months post ILI.

Conclusions—ILI is an attractive modality that provides regional disease control and limb preservation in patients with limb threatening sarcoma. Although short term results appear encouraging, long term follow up is needed to fully assess the role of ILI in unresectable extremity STS.

Corresponding Author: Jonathan S. Zager, MD, FACS, Director of Regional Therapies, Department of Cutaneous Oncology and Sarcoma, Moffitt Cancer Center, 12902 Magnolia Drive, SRB 4.24012, Tampa, FL 33612, Phone: 813-745-1085, Fax: 813-745-5725, jonathan.zager@moffitt.org.

Keywords

Isolated limb infusion; sarcomas; ILI; Soft tissue sarcoma; Melphalan; Unresectable extremity sarcoma

Introduction

Locally advanced (unresectable without an amputation or functionally debilitating surgery) extremity soft tissue sarcomas (STS) were routinely treated with amputations until several studies showed a high risk of progressive disease and distant metastasis and a lack of survival benefit [1-6]. Limb preservation for locally advanced sarcoma often requires radical resection and reconstruction which may result in significant morbidity, disfigurement, loss of function and compromised quality of life [7-9]. Although several studies have shown response rates in the range of 62-91% with the use of hyperthermic isolated limb perfusions (HILP) for soft tissue sarcomas of the extremity, only a few small studies using isolated limb infusion (ILI) (a well established treatment modality for recurrent melanoma on the extremities) have been described [10-19]. In this study we report our institutional experience on response rates and limb salvage rates in patients who undergo ILI for locally advanced limb threatening sarcomas of the extremity.

Methods

Patient Selection

Institutional Review Board approval was obtained at Moffitt Cancer Center prior to performing this retrospective analysis. Patients who underwent ILI for locally advanced soft tissue sarcoma of the extremity from January 2008 to March 2012 were identified using a prospectively collected ILI database. Locally advanced/unresectable sarcomas in this series pertained to patients who have failed surgery and are not candidates or who have failed systemic chemotherapy and /or radiation. All patients who are deemed eligible for ILI have an informed discussion with the medical oncologist, radiation oncologist and surgical oncologist as well are discussed in our sarcoma multidisplinary tumor board regarding best treatment options for these patients. Most patients are heavily pretreated with extensive surgeries, systemic therapy and previous radiation with very little other options aside from amputation. In the current series the only other option for these patients at the time of discussion of ILI in the clinic was amputation, which was given as options to the patients when discussing risks, benefits and alternatives of the ILI. Repeat ILIs were and are offered to patients who have shown either a response to a melphalan based ILI in the past and then progressed or completely responded and recurred. We do not offer repeat ILIs to patients who do not show a response to a melphalan based ILI initially. No patient received more than 2 ILIs in this series.

Calculation of Limb Volume

Limb volume was calculated by taking circumferential limb measurements starting from the distal portion (hand or foot) of the extremity at 2 cm intervals. The most proximal measurement was taken at the level of the inferior edge of the tourniquet where such would

be applied during the actual procedure. 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 volume of the limb.

Dosing of Chemotherapeutic Agents

The dose of melphalan used 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. A corrected melphalan dose based on ideal body weight (cIBW) was used in all but 1 patient (96%). Dactinomycin was used at 100 μg/L limb volume for both upper and lower extremities. These doses were based on original descriptions of ILI by the Sydney Melanoma Unit [12,20,21]. Chemotherapy consisting of appropriately dosed melphalan and dactinomycin admixed with 400 ml heparinized normal saline.

Technique of Isolated Limb Infusion

The ILI procedures were performed as described previously [20,21]. Briefly, high-flow 5F to 6F arterial and venous catheters were inserted under fluoroscopic guidance via a femoral artery and vein approach in the contralateral extremity and positioned with their tips in the involved extremity at a previously marked site distal to the tourniquet. The extremity was prewarmed with liquid warming blankets (Kimberly Clark®). 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 chemotherapy into systemic circulation. Two subcutaneous temperature probes were placed in the proximal and distal aspects of the involved extremity. Once temperatures of 37°C or greater were achieved, the tourniquet was inflated to 250mmHg (upper extremity (UE)) or 350mmHg (lower extremity (LE)), 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 one-way valves or 3-way stopcocks for unidirectional flow. The chemotherapy was rapidly infused in 5 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 until the effluent was clear. The flush/effluent was manually extracted from the venous catheter and discarded. Heparinization was reversed with protamine. Catheters were removed when the activated clotting time was at or near baseline.

Postoperative Care and Toxicity

Postoperatively, patients were monitored in the intensive care unit for 24 hours for serial neurovascular checks after which they were transferred to the surgical ward. The serum creatinine phosphokinase (CPK) level was measured twice daily while patients were in the hospital. Patients were discharged once CPK levels peaked (usually postoperative day 4 for lower extremity and 2 for upper extremity) and started to decline. Patients who developed grade IV CTCAE serologic toxicity (CPK levels >1000 IU/L) were treated with intravenous hydration using 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 [22]. Limb toxicity was determined by close physical examination throughout the hospitalization and assessed again at visits 2, 6, and 12 weeks postoperatively using the scale shown in Table I proposed by Wieberdink et al [23]. Severe acute limb toxicity was defined as Wieberdink grade IV or higher.

Outcome Measures

Response rates were measured using the modified Response Evaluation Criteria in Solid Tumors on cross-sectional imaging at 3 months postoperatively and every 3 months thereafter [24]. For cutaneous lesions modified RECIST and serial caliper measurements were used to evaluate response to treatment.

Statistical Analysis

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

Results

Demographic Characteristics

As shown in Table II, twenty-two patients who underwent a total of 26 ILIs for soft tissue sarcomas of the extremity from January 2008 to March 2012 were identified using the ILI database at Moffitt Cancer Center. The median age was 71 years (range, 19-93 years); 14 (64%) were women. Of the 22 patients, 4 (18%) underwent repeat infusions. Seven (30%) of the 26 infusions were in the UE. ILI was aborted in one patient due to occlusion of the brachial artery secondary to compression resulting from the tumor. Table III demonstrates the ten different histologic subtypes that were encountered in the 22 patients: 9 (41%) patients had undifferentiated pleomorphic sarcoma, 4 (18%) had high grade myxofibrosarcoma, 2 each (9% each) had Kaposi's sarcoma, and synovial sarcoma whereas 1 each (4.5% each) had epithelioid sarcoma, leiomyosarcoma, angiosarcoma, alveolar rhabdomyosarcoma and fibrohistiocytic sarcoma.

Intraoperative Parameters

As depicted in Table IV, limb volume, melphalan and dactinomycin doses are significantly higher in patients undergoing lower extremity ILI. Melphalan dose was corrected for ideal body weight in all but one patient who had his ILI prior to the implementation of cIBW in all ILI patients at our institution. Although a significantly greater degree of hypoxia (median PaO_2 at 30 minutes, 9 mm Hg in LE vs 17 mm Hg in UE, p = .02) is achieved in the LE, UE ILIs were noted to have significantly higher acidosis and base deficit (median pH at 30 minutes, 7.08 in UE vs 7.2 in LE, p = .03, base excess -15.3 mEq in UE vs -7.1 mEq in LE, p = .006). Papaverine was used in all patients. Median ischemia time was 51 minutes (range, 46-73). The median limb temperature at 30 minutes (39.5 °C) was 1°C higher than the median initial limb temperature (38.5 °C).

Postoperative Parameters and Toxicity

Median peak CPK values for LE ILIs were higher than those of UE ILIs however the difference was not statistically significant. CPK was noted to peak earlier in the postoperative period in patients with UE ILIs however the length of stay did not differ significantly in the two groups (median postoperative day to CPK peak, 2 days vs 4.5 days, p = .02 median LOS, 5.5 days vs 6 days, p = NS) (table 4). Toxicity as measured using the Wieberdink scale described in Table I was similar in both groups. Majority of the patients had grade I or II toxicity with only 23 % of the patients exhibiting grade III toxicity. No grade III toxicity was seen in any of the upper limb infusions. More importantly no grade IV or V limb toxicity was seen after any of the 26 infusions. Three patients were noted to have deep venous thrombosis during their postoperative follow up requiring systemic anticoagulation. Two of these were in the UE, one associated with placement of a percutaneously inserted central catheter and one in the arm that was infused. The patient with the lower limb DVT was also noted to have a pulmonary embolus discovered on routine imaging studies 3 months after ILI.

Outcome Measures

Response Rates—All patients included in the outcome analysis had at least a follow up of 3 or more months. Among the 17 evaluable patients who underwent a total of 21 infusions the median duration of follow up was 11 months (range, 3-33 months) whereas the median follow up after each ILI was 9 months (range, 3-33 months). This difference in follow up exists because the patients who underwent repeat ILIs had their follow up separated for each infusion. We chose 3 months post ILI as the first time point to evaluate for response using RECIST criteria which is consistent with previous reports on the use of ILI and determining response. At 3 months the overall response rate as shown in Table V was 42% (18% complete response [CR], 24% partial response [PR]) per infusion and 42% per patient (24% CR, 18% PR). Three patients (18%) had stable disease (SD) while 7 (41%) had progressive disease (PD). When evaluating responses stratified by extremity as shown in Table VI, the overall response rate was 45% in the lower limb infusions and 33% in the upper extremity with no statistical difference between the two. In addition no correlation was observed between histologic subtype of the sarcoma and response rates. Of the 4 patients undergoing repeat ILI there was 1 (25%) each with a CR, PR, SD and PD.

Limb Salvage Rates and Conversion to Resectability—Of the 17 patients with a minimum of 3-month follow up, 12 (71%) had successful limb preservation with a median limb preservation time of 9 months (range, 3-28 months). 6 (33%) patients in the intention to treat population (those who had one or more ILI's or who had an attempt at an ILI) eventually required amputations. 5 patients required amputations for progressive disease after their ILIs whereas one patient required an amputation after an aborted infusion secondary to occlusion of the brachial artery from compression by the tumor. Three patients had below the knee amputations, 1 had above the knee amputation, 1 hip disarticulation, and 1 above elbow amputation with a median time to amputation of 5 months (range, 3-8 months). Two patients (12%) underwent resection of the sarcoma in the lower extremity after ILI down staged their disease to resectable resulting in no evidence of disease (NED). Both of these patients remain NED to date at 30 and 22 months post ILI.

Discussion

Treatment of patients with locally advanced extremity STS presents a unique challenge to the oncologist. Surgeons are often faced with situations whereby they have to strike a balance between optimal oncologic outcomes and limb function [25]. Although an amputation is sometimes the only way to achieve a margin negative resection, we know that even with an amputation and good local control, ultimately there is not a significant survival benefit [7,26]. Regional therapy with ILI is an attractive and acceptable alternative therapy for disease control and limb preservation in patients with unresectable locally advanced or recurrent soft tissue sarcomas of the extremity that are otherwise facing an amputation due to no other therapeutic options available [27]. All of the patients in this study were facing amputation, most were heavily treated with radiation and/or systemic chemotherapy with progression of their local/regional disease, or were not candidates for systemic chemotherapy due to comorbidities that preclude use of systemic chemotherapy prior to referral to the surgical–oncologist. Their cases were discussed at our sarcoma multidisciplinary tumor board and were offered ILI since no other therapeutic options were available, including chemotherapy, radiation or aggressive surgical resections. The purpose of the current study was to report on a single institution series of the use of ILI for unresectable sarcomas of the extremities as a limb preserving option.

There have been three previously published studies reporting the use of ILI for STS of the extremity with encouraging results [12-14]. While this study contains some of the patients reported in the multicenter experience by Turaga et al, the current study is a single institution experience that has a longer follow up and more patients with the diagnosis of limb threatening sarcomas[13]. In comparing our outcomes to the published studies, we find our overall response and limb preservation rates to be somewhat lower. Moncrieff et al reported their experience with ILI for STS at the Sydney Melanoma Unit on 21 patients with an overall response rate of 90% (CR 57%, PR 33%) [12]. In contrast we have a response rate of 42% with a 24% CR and 18% PR. There are several possible reasons to explain these observed differences. Firstly, 67% of the patients in the Moncrieff study underwent preoperative ILI, whereas 82% of our patients undergoing ILI had previous attempts at resection and most were treated with other modalities [12]. In addition over 80% of our patient population had recurrent tumors compared to only 33% in the Moncrieff study [12]. The difference in outcomes may be related to differences in the patient population being treated with a majority of our patients being heavily pretreated with multimodality therapy. Secondly we used Melphalan dose corrected for ideal body weight. We know that this dose correction leads to lower toxicity in melanoma patients with equivalent CR and slightly lower PR; however the impact of this correction on response rates for sarcoma is unknown [28-30]. The multicenter study by Turaga et al showed a 75% response rate (CR 17%, PR 58%) for STS [13]. The high response rate in the Turaga et al study may be related to a small number of patients in the soft tissue sarcoma group but more importantly a short follow up duration overestimating the true treatment effect with the current study having longer median follow up than the Turaga study [13].

With multiple studies showing that hyperthermic isolated limb perfusion (HILP) has a response rate of 62-91% it seems logical to compare outcomes and toxicity of the two

different techniques [10,11,15]. While ILI is a minimally invasive technique of delivering regional chemotherapy with minimal morbidity, HILP is an invasive, complex, labor intensive technique requiring cannulation and clamping of the main artery and vein of the diseased extremity with infusion of chemotherapy using an oxygenated extracorporeal circuit [31]. In our study we did not observe grade IV or V limb toxicity while studies using HILP describe a significant limb toxicity rate of 10-50% based on the chemotherapeutic agent used [10,11,15]. In addition systemic toxicity is rare in patients undergoing ILI in contrast to HILP [27]. Moreover the technical/operative ease of repeating an ILI in a patient who has manifested a good partial response is far superior to that of a repeat HILP making ILI a more attractive option for repeat regional therapy.

Clearly comparing HILP and ILI in a randomized fashion would allow us to answer which technique is superior however such a clinical trial would be quite difficult to perform given the rarity of this disease, the various different histologic subtypes with different disease biology and the complexity of fair randomization based on disease burden.

ILI has been used in the neoadjuvant setting. Hegazy and colleagues reported the use of ILI in the neoadjuvant setting whereby patient underwent preoperative ILI with doxorubicin followed by external beam radiation 3 to 7 days after ILI. 85% of the patients had some response to treatment rendering them resectable [14]. With a median follow up of 15 months, there were 4 (13%) local recurrences; two were managed with reoperation, one with amputation and one with chemotherapy [14]. Although our study was not specifically looking at the use of ILI in the neoadjuvant setting, it is important to mention that 2 patients with lower extremity sarcomas who may have otherwise been treated with an amputation were downstaged to resectable disease. Both rendered disease free after undergoing resection and remain so at 30 and 22 months post ILI. These results certainly point towards exploring an expanding role of ILI to include neoadjuvant therapy.

HILP with melphalan and TNF has been used with good success in European countries. TNF is not available for use here in the United States and therefore was not included as a drug in the ILI regimen. A randomized study of HILP with TNF and Melphalan was published by Bonvalot et al. using 4 different doses of TNF in the effluent [32]. In this study there was no difference in response rates but regional toxicity was significantly lower in the lower TNF dose (1mg).

It should be noted that there may be some degree of systemic toxicity in patients who undergo HILP. Some of this in the literature can be related to the dose of TNF used (only available for use in European centers) as well as some melphalan leak and that regional toxicity might be abrogated with the use of milder hyperthermia. However, systemic toxicity of ILI is almost never seen due to no leak detected from total pneumatic tourniquet occlusion of the extremity. Regional toxicities have been shown to be greater on an individual study by study basis for HILP than for ILI in extremity sarcomas. These results have been detailed very nicely in a recent review of ILI and HILP for sarcomas and melanomas by Moller et al in 2008 [29].

There are several limitations to our study. This is a retrospective review with a small number of patients and a short follow up interval. Although the results are encouraging longer follow up will help determine the durability of these responses. However, these results certainly warrant further investigation into the use of this low morbidity procedure for the treatment of locally advanced soft tissue sarcomas. With the advent of novel chemotherapeutic agents and pathway-specific targeted agents, it is possible that in the near future this procedure could be optimized to achieve even better outcomes with minimal morbidity [33].

Acknowledgments

Angela Reagan, CIM and Susan Sharpe, MALS provided invaluable support in the drafting and preparation of the manuscript.

References

1. Brennan MF. Soft tissue sarcoma: advances in understanding and management. The surgeon : journal of the Royal Colleges of Surgeons of Edinburgh and Ireland. 2005; 3:216–223. [PubMed: 16076008]
2. Rooser B, Gustafson P, Rydholm A. Is there no influence of local control on the rate of metastases in high-grade soft tissue sarcoma? Cancer. 1990; 65:1727–1729. [PubMed: 2317756]
3. Williard WC, Hajdu SI, Casper ES, Brennan MF. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. Annals of surgery. 1992; 215:269–275. [PubMed: 1543400]
4. Stotter A. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. Annals of surgery. 1992; 216:615–616. [PubMed: 1444656]
5. Gustafson P, Rooser B, Rydholm A. Is local recurrence of minor importance for metastases in soft tissue sarcoma? Cancer. 1991; 67:2083–2086. [PubMed: 2004326]
6. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Annals of surgery. 1982; 196:305–315. [PubMed: 7114936]
7. Paredes T, Pereira M, Moreira H, et al. Quality of life of sarcoma patients from diagnosis to treatments: predictors and longitudinal trajectories. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2011; 15:492–499. [PubMed: 21306951]
8. Ferrone ML, Raut CP. Modern surgical therapy: limb salvage and the role of amputation for extremity soft-tissue sarcomas. Surgical oncology clinics of North America. 2012; 21:201–213. [PubMed: 22365515]
9. Davidge KM, Wunder J, Tomlinson G, et al. Function and health status outcomes following soft tissue reconstruction for limb preservation in extremity soft tissue sarcoma. Annals of surgical oncology. 2010; 17:1052–1062. [PubMed: 20107912]
10. Deroose JP, Eggermont AM, van Geel AN, et al. Long-term results of tumor necrosis factor alpha- and melphalan-based isolated limb perfusion in locally advanced extremity soft tissue sarcomas. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011; 29:4036–4044. [PubMed: 21931039]
11. Grunhagen DJ, de Wilt JH, Graveland WJ, et al. Outcome and prognostic factor analysis of 217 consecutive isolated limb perfusions with tumor necrosis factoralpha and melphalan for limb-threatening soft tissue sarcoma. Cancer. 2006; 106:1776–1784. [PubMed: 16541435]
12. Moncrieff MD, Kroon HM, Kam PC, et al. Isolated limb infusion for advanced soft tissue sarcoma of the extremity. Annals of surgical oncology. 2008; 15:2749–2756. [PubMed: 18648882]
13. Turaga KK, Beasley GM, Kane JM 3rd, et al. Limb preservation with isolated limb infusion for locally advanced nonmelanoma cutaneous and soft-tissue malignant neoplasms. Archives of surgery (Chicago, Ill : 1960). 2011; 146:870–875.

14. Hegazy MA, Kotb SZ, Sakr H, et al. Preoperative isolated limb infusion of Doxorubicin and external irradiation for limb-threatening soft tissue sarcomas. Annals of surgical oncology. 2007; 14:568–576. [PubMed: 17094027]
15. Wray CJ, Benjamin RS, Hunt KK, et al. Isolated limb perfusion for unresectable extremity sarcoma: results of 2 single-institution phase 2 trials. Cancer. 2011; 117:3235–3241. [PubMed: 21246524]
16. Bonvalot S, Rimareix F, Causeret S, et al. Hyperthermic isolated limb perfusion in locally advanced soft tissue sarcoma and progressive desmoid-type fibromatosis with TNF 1 mg and melphalan (T1-M HILP) is safe and efficient. Annals of surgical oncology. 2009; 16:3350–3357. [PubMed: 19830495]
17. Kroon HM, Moncrieff M, Kam PC, Thompson JF. Outcomes following isolated limb infusion for melanoma. A 14-year experience Annals of surgical oncology. 2008; 15:3003–3013. [PubMed: 18509706]
18. Beasley GM, Ross MI, Tyler DS. Future directions in regional treatment strategies for melanoma and sarcoma. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2008; 24:301–309.
19. Beasley GM, Caudle A, Petersen RP, et al. A multi-institutional experience of isolated limb infusion: defining response and toxicity in the US. Journal of the American College of Surgeons. 2009; 208:706–715. discussion 715-707. [PubMed: 19476821]
20. Thompson JF, Kam PC, Waugh RC, Harman CR. Isolated limb infusion with cytotoxic agents: a simple alternative to isolated limb perfusion. Seminars in surgical oncology. 1998; 14:238–247. [PubMed: 9548607]
21. Thompson JF, Kam PC. Isolated limb infusion for melanoma: a simple but effective alternative to isolated limb perfusion. Journal of surgical oncology. 2004; 88:1–3. [PubMed: 15384062]
22. Nation Cancer Institute. Cancer Therapy Evaluation P: Common terminology criteria for adverse events (CTCAE) v 4.0. Bethesda, Md: National Institute of Health; 2009.
23. 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. European journal of cancer & clinical oncology. 1982; 18:905–910. [PubMed: 6891640]
24. van Persijn van Meerten EL, Gelderblom H, Bloem JL. RECIST revised: implications for the radiologist. A review article on the modified RECIST guideline. European radiology. 2010; 20:1456–1467. [PubMed: 20033179]
25. Demetri GD, Antonia S, Benjamin RS, et al. Soft tissue sarcoma. Journal of the National Comprehensive Cancer Network : JNCCN. 2010; 8:630–674. [PubMed: 20581298]
26. Dagan R, Indelicato DJ, McGee L, et al. The significance of a marginal excision after preoperative radiation therapy for soft tissue sarcoma of the extremity. Cancer. 2011
27. Deneve JL, Zager JS. Isolated regional therapy for advanced extremity soft tissue sarcomas. Surgical oncology clinics of North America. 2012; 21:287–299. [PubMed: 22365520]
28. Kam PC, Thompson JF. Isolated limb infusion with melphalan and actinomycin D in melanoma patients: factors predictive of acute regional toxicity. Expert opinion on drug metabolism & toxicology. 2010; 6:1039–1045. [PubMed: 20604735]
29. Moller MG, Lewis JM, Dessureault S, Zager JS. Toxicities associated with hyperthermic isolated limb perfusion and isolated limb infusion in the treatment of melanoma and sarcoma. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2008; 24:275–289.
30. Santillan AA, Delman KA, Beasley GM, et al. Predictive factors of regional toxicity and serum creatine phosphokinase levels after isolated limb infusion for melanoma: a multi-institutional analysis. Annals of surgical oncology. 2009; 16:2570–2578. [PubMed: 19543771]
31. Schraffordt Koops H, Oldhoff J, Oosterhuis JW, Beekhuis H. Isolated regional perfusion in malignant melanoma of the extremities. World journal of surgery. 1987; 11:527–533. [PubMed: 3630197]
32. Bonvalot S, Laplanche A, Lejeune F, et al. Limb salvage with isolated perfusion for soft tissue sarcoma: could less TNF-alpha be better? Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2005; 16:1061–1068. [PubMed: 15930042]

33. Riedel RF. Targeted agents for sarcoma: is individualized therapy possible in such a diverse tumor type? Seminars in oncology. 2011; 38(Suppl 3):S30–42. [PubMed: 22055970]

Table I

Wieberdink 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 compartment syndromes
V	Reaction that may necessitate amputation

Table II

Demographic characteristics of patients undergoing isolated limb infusion

Variable	Overall	Upper Extremity (N=7)	Lower extremity (N=19)
Number of infusions	26	7	19
Number of patients	22	6	16
Patients with Single ILI	17	4	13
Patients with Repeat ILI	4	1	3
Aborted ILI	1	1	0
Age, median, range, years	71 (19-93)	79(54-93)	69(55-71)
Female gender (% of total)	14 (64%)	4 (18%)	10 (45%)

Abbreviations: ILI, isolated limb infusion

Table III

Histologic Subtype of Sarcoma in patients undergoing isolated limb infusion

Histologic Subtype	Number (%)
Undifferentiated pleomorphic sarcoma	9 (41%)
Myxoinflammatory fibroblastic sarcoma	4 (18%)
Synovial sarcoma	2 (9%)
Kaposis sarcoma	2 (9%)
Epithelioid sarcoma	1 (4.5%)
Leiomyosarcoma	1 (4.5%)
Angiosarcoma	1 (4.5%)
Alveolar rhabdomyosarcoma	1 (4.5%)
Fibrohistiocytic sarcoma	1 (4.5%)

Table IV

Intraoperative and postoperative parameters for patients undergoing isolated limb infusions

Variable	Overall (N=26)	Upper Extremity (N=7)	Lower extremity (N=19)	P-value
Limb volume, median, range, L	6.54 (1.4-11)	2.4 (1.4-3.0)	7.1 (6.5-10.3)	0.003
Melphalan dose, median, range, mg	34 (20-44)	19 (11.5-27)	38 (20-65)	0.002
Dactinomycin dose, median, range, mg	650 (140-900)	233 (140-300)	695 (320-900)	0.001
Melphalan dose adjusted for Ideal Body Weight, %	96	100	95	NS
Papaverine use intraoperatively, %	100%	100%	100%	NS
Initial Limb Temp, ° Centigrade	38.5 (37.1-39.8)	38.5 (38.5-39.8)	38.5 (37.1-39.4)	NS
Temp at 30 minutes, ° Centigrade	39.5 (37.8-40.6)	39.7 (39.4-40.2)	39.4 (37.8-40.6)	NS
Perfusate blood gas at 30 minutes				
PaO2, median, range, mm Hg	10 (5-38)	15(7-38)	9(5-10)	0.02
pH, median, range	7.2 (6.97-7.28)	7.08(7.06-7.25)	7.2(6.97-7.28)	0.03
Base excess, median, range, mEq	-10 (-17, -3.8)	-15.3(-16.5, -7.9)	-7.1(-17, -3.8)	0.006
Ischemia time, minutes, range	51 (46-73)	53.5(44-60)	50.5(47-73)	NS
Peak CPK, median, range, U/mL	455 (82-1058)	131 (69-184)	607 (93-1135)	NS
Day of CPK peak, median, range	4 (2-4.5)	2 (1.5-4)	4.5 (3-5.5)	0.02
Wieberdink toxicity				NS
Grade I-II	18 (69%)	6 (86%)	12 (63%)	
Grade III	6 (23%)	0 (0%)	6 (37%)	
Length of stay, days, range	6 (5-10)	5.5 (5-7)	6 (5-10)	NS

Abbreviations: CPK, Creatinine phosphokinase; NS, not significant

Table V

Response rates for patients undergoing isolated limb infusions

Evaluable patients at 3 months post ILI	Per infusion (%) N=21	Per patient (%) N=17
Overall response	42	42
Complete response	18	24
Partial response	24	18
Stable disease	14	18
Progressive disease	43	41
Resected to NED	9	12

Abbreviation: ILI, Isolated Limb Infusion

Table VI

Response rates for patients undergoing isolated limb infusions stratified by extremity *

Evaluable patients at 3 months post ILI	Upper Extremity (%) N= 3	Lower Extremity (%) N = 14
Overall response	33	45
Complete response	33	17
Partial response	0	28
Stable disease	33	11
Progressive disease	33	44

* No significant difference seen between ORR and CR for Upper Extremity vs Lower Extremity

Abbreviation: ILI, Isolated Limb Infusion; ORR, Overall Response Rate; CR, Complete Response