Repeated Isolated Limb Infusion as Limb Salvage Therapy for Recurrent Unresectable Extremity Sarcoma

Leah E. Hendrick[1], David Portnoy[3], Michael Neel[4], Martin D. Fleming[1,2] and Jeremiah L. Deneve DO[1,2]*

[1]Department of Surgery, University of Tennessee Health Science Center, USA

[2]Department of Surgical Oncology, University of Tennessee Health Science Center, USA

[3]Department of West Cancer Center, University of Tennessee Health Science Center, USA

[4]Ortho Memphis, Memphis, TN, USA

Abstract

Introduction: Recurrent Soft Tissue Sarcoma (STS) of the extremity remains a difficult challenge. Isolated Limb Infusion (ILI) is a treatment option for patients with unrespectable extremity STS who would otherwise require amputation. We present a case of recurrent extremity sarcoma managed with ILI as a limb-salvage alternative to amputation.

Methods: We present a case of recurrent extremity sarcoma managed with repeated ILI and a brief review of the literature.

Case Report: A 34 year old male presented in July 2013 as a referral for forequarter amputation for management of unresectable recurrent left upper extremity sarcoma. At initial presentation in 2011, the tumor involved the median nerve. Neoadjuvant radiation was administered and a microscopic margin positive resection of a single left forearm lesion was performed. The patient developed multifocal recurrence in 2013 with lesions involving the initial left forearm site, the left upper extremity along the biceps tendon, a left clavicular lesion and left axillary lymphadenopathy. CT imaging of the chest demonstrated no evidence of distant disease. Resection of the multiple recurrences was performed followed by ILI. A partial response to ILI was initially observed. Additional disease developed 9 months after ILI and repeat ILI was performed. Forequarter amputation was ultimately required for local control of additional multifocal recurrence, 16 months after initial ILI. Distant disease eventually developed to which the patient succumbed in late 2015.

Conclusion: Management of recurrent extremity STS remains a difficult challenge. Repeated ILI offers an alternative to amputation for selected patients while maintaining function and quality of life.

Keywords: Sarcoma; Isolated Limb Infusion; Weiberdink; Recurrence; Amputation

Background

Soft Tissue Sarcomas (STS) are a heterogenous group of malignancies with distinct clinical and pathologic features [1]. STS are relatively rare, accounting for only 1% of adult malignancies with an estimated 11,900 people diagnosed annually in the United States [2]. More than 50 different subtypes have been identified with undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma and malignant peripheral nerve sheath tumors being most common [3]. These tumors may arise from the extremity, head/neck and truncal region and retroperitoneum or chest wall. Several prognostic factors such as tumor stage, size, grade and anatomic location have been demonstrated to have an impact on overall survival [4-6] with margin of resection, histology and the use of radiation also affecting local disease control [7-9]. Surgery is the standard treatment for primary extremity STS. A microscopic negative margin resection may be difficult in situations of abutment or involvement of critical neurovascular structures. In these situations, Radiation Therapy (RT) may be administered as either neoadjuvant therapy or in the adjuvant setting. Positive margins after surgical resection are associated with an increased risk of local recurrence [10,11]. Re-resection to negative margins is preferred, but may not be possible, especially in situations of critical nerve or vascular involvement or when resection may result in loss of function or significant impairment of the involved extremity. Postoperative RT is recommended and has been demonstrated to improve the local control of patients with positive surgical margins [12,13]. Despite appropriate aggressive

Table 1: Wieberdink Toxicity.

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

Table 2: Treatment and Outcome Data for ILI Therapy for Advanced Extremity STS.

Author	Year	N	Modality	Chemo	FU (mo)	ORR (%)	CR/PR/SD (%)	Limb Preservation (%)
Hegazy [24]	2007	40	ILI	Doxorubicin	15	85	-/85/-	83
Moncrieff [37]	2008	21	ILI	Melphalan Actin D	28	90	57/33/10	76
Turaga [33]	2011	12	ILI	Melphalan Actin D	8.6	78	14/64/-	78
Vohra [38]	2013	26	ILI	Melphalan Actin D	11	42	24/18/18	71

Figure 1: Recurrent left forearm lesion.

Figure 2: Recurrent left upper arm lesion.

multimodality therapy, local recurrence is common, affecting up to 7-24% of cases [11,14,15]. Management of recurrent STS is a challenge as often times many patients have undergone neoadjuvant therapy prior to surgical resection. Local recurrence for those who may not have undergone preoperative therapy may be associated with a better prognosis than for those treated with a combined multimodality initial approach [16]. Little is known about the effect of local recurrence on overall outcome. It is generally thought that local recurrence of STS is associated with a poor prognosis and has a negative impact on distant metastasis and survival [17]. Historically, local recurrences were managed with extremity amputation [18]. Amputation offers definitive local control but does so often at the expense of patient function with the potential for significant morbidity and negative impact on quality of life. Furthermore, amputation does not have an impact on distant metastasis or overall outcome [19-21]. For this reason many suggest that attempts to surgically manage local recurrence a second time should be more aggressive than the initial treatment approach. Re-resection of extremity STS recurrence is the preferred treatment option if possible, as well as the repeated use of irradiation for those who received radiation during initial management. Both of these treatment approaches, however, are associated with a high-risk of treatment-related morbidity and may negatively affect extremity function. Selecting the most appropriate therapy that allows a patient to maintain function and quality of life without negatively affecting long-term outcome is important. The regional administration of chemotherapy in the form

of hyperthermic isolated limb perfusion (HILP) or Isolated Limb Infusion (ILI) allows treatment of the recurrent disease while sparing the need for amputation and maintaining extremity function and quality of life. Both procedures can be performed as either primary treatment of recurrent disease or as adjuvant treatment combined with resection and irradiation. We present a case of multifocal recurrent extremity STS managed with resection and repeated ILI as an alternative to amputation. A brief review of the literature focusing on the management of locally recurrent STS of the extremity with ILI is discussed.

Case Presentation

A 34 year old male presented in July 2013 as a referral for forequarter amputation for management of unresectable recurrent left upper extremity sarcoma. At the time of his initial presentation, the tumor was found to involve the median nerve. Neoadjuvant radiation therapy was administered and a microscopic margin positive resection was performed in 2011 of a single left forearm lesion. The following year, the patient developed left axillary lymphadenopathy. Excisional biopsy was performed which demonstrated metastatic high-grade sarcoma. He was treated with Adriamycin and iphosphamide. The patient developed multifocal recurrence in 2013 with lesions involving in the left forearm at the site of initial resection (Figure 1), the left upper extremity along the biceps tendon (Figure 2), a left clavicular lesion (Figure 3) and left axillary lymphadenopathy. CT imaging of the chest demonstrated no evidence of distant disease.

Figure 3: Recurrent left clavicular lesion.

Figure 4: Forequarter amputation.

Forequarter amputation was recommended for local control of the multifocal recurrence, which the patient subsequently declined. He was referred for evaluation for palliative ILI.

Resection of the proximal disease was performed including the left clavicular and bicep lesions as well as left axillary lymph node dissection. The forearm lesion was deemed unresectable because of median nerve involvement and left in situ. At the same operation, following resection left upper extremity ILI was performed using melphalan and Actinomycin D. Final pathology demonstrated high-grade sarcoma with negative margins from the left clavicular and biceps lesions. The left axillary lymph node dissection revealed metastatic high-grade sarcoma involving 2 of 27 lymph nodes. Postoperatively, the patient was monitored in the intensive care unit, where serial Creatinine Phosphokinase (CPK) levels were followed. After the CPK peaked and began to trend down to normal, he was discharged home (postoperative day 3). He tolerated ILI well with no serious side effects (Weiberdink I-II). Four months post-ILI, a partial clinical response of the left forearm lesion was observed with a notable decrease in size. Approximately 9 months after initial ILI, a new left shoulder mass developed and the left forearm lesion began to increase in size. Amputation versus resection and repeated ILI were presented as treatment option. Repeat resection of the left shoulder disease was performed followed by repeated ILI to manage the left forearm lesion.

Disease rapidly recurred involving the left shoulder girdle 3 months after repeated resection/repeat ILI and forequarter amputation was eventually performed in November 2014, 16 months after initial ILI (Figure 4). Repeated ILI and resection spared a functionally debilitating forequarter amputation for almost a year and a half. The high grade STS continued to progress, however, and CT imaging of the chest in May 2015 demonstrated multiple pulmonary metastases. The patient eventually died of disease progression in late 2015.

Discussion

This case highlights some of the difficulties experienced in managing patients with local recurrence of extremity STS. As in this case presented, involvement of critical neurovascular structures may limit treatment options and/or resectability and have a negative impact on local control. The development of multifocal or distant disease, which may occur synchronously at the time of recurrence, affects treatment planning and recommendation. Obtaining local control in the setting of distant disease certainly becomes more challenging. Often, treatment efforts focus on distant metastases and the local disease process is left untreated unless symptomatic. How to appropriately manage multifocal recurrence and/or symptomatic
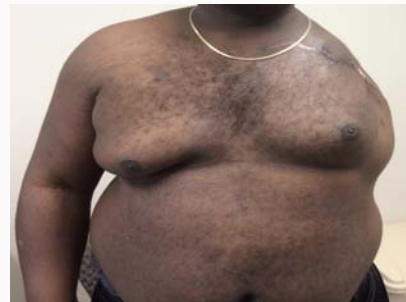
local recurrence is difficult. For patients with bulky recurrent tumors involving critical neurovascular structures, selecting an appropriate therapy that provides local control without compromising quality of life, limb function or long-term outcome is a challenge. Amputation, as previously mentioned, provides definitive local control, but at the expense of loss of function and does nothing to address neither distant disease nor does it impact overall survival [19,22]. There has been a growing trend over the last several decades toward limb-preservation therapies when treating these complicated patients. Regional delivery of chemotherapy can be used as an adjunct to surgical resection with radiation therapy for advanced STS of the extremity. Furthermore, regional therapy offers the potential for local control, especially in situations of unresectable, isolated recurrent disease or recurrent disease in the presence of distant metastasis. Two techniques, HILP and ILI, allow the regional administration of chemotherapy, delivering drug concentrations 15 to 25 times higher than systemic dosages without the systemic side effects [23]. There are numerous potential indications for regional therapy for STS, most notably: multifocal primary tumors [24] recurrent disease [25] those undergoing prior resection with irradiation [26] bulky primary tumors [27,28] or high-grade tumors [27]. Elderly patients [29] and those with distant metastasis treated in a palliative setting [30] have been shown to gain a benefit in local control and limb-salvage rates using these techniques. HILP was initially described in the 1950s for treating melanoma patients with regional in-transit disease and was the first regional chemoperfusion therapy to demonstrate an improvement in limb-salvage rates in patients with unresectable extremity STS [23] HILP is an invasive technique and requires an extracorporeal bypass circuit [31]. ILI is a less invasive approach for administering regional chemotherapy, which was first described in the 1990's by the Sydney Melanoma Unit for the treatment of in-transit metastases for melanoma [32]. ILI is technically a less complex procedure with overall response rates close to those observed with conventional HILP.

Procedural Details

ILI is performed under hyperthermic, nonoxygenated conditions using percutaneously placed catheters. High-flow 5Fr to 6Fr arterial and 6Fr to 8Fr venous catheters are inserted by way of an uninvolved lower extremity and advanced fluoroscopically into the involved extremity. This may be done pre-operatively by interventional radiology or intraoperatively by vascular surgery after the induction of general anesthesia. Heparin is administered to achieve full systemic anticoagulation with a target activated clotting time greater than or equal to 350 seconds. The catheters are connected to an infusion circuit that consists of a heat exchanger and bubble excluder. Once subcutaneous temperatures of greater than 37°C are achieved, a

pneumatic tourniquet is placed on the proximal aspect of the limb to be infused, isolating the limb from the systemic circulation. Papavarine (60 mg) is injected into the arterial catheter and chemoperfusion is initiated. The cytotoxic agents, often melphalan and acitnomycin D, are administered and circulated for 30 minutes. After infusion is complete, the limb is manually flushed with one liter of isotonic crystalloid solution, heparinization is reversed with protamine and the catheters are removed when the ACT is at or near baseline. Patients are monitored daily for regional toxicity with serial Creatine Phosphokinase (CPK) measurements and discharged home when CPK levels peak and fall back towards baseline, generally within 4 to 6 days [33].

Toxicity of ILI

ILI is generally well tolerated with mild side effects and systemic toxicity is uncommon. Rhabdomyolysis, as measured by serum CPK, may be encountered in patients undergoing ILI, therefore patients are monitored in the hospital for several days post-treatment. CPK levels often rise greater than 1000 IU/L and require daily blood urea nitrogen and creatinine level monitoring to avoid myoglobin-induced renal failure. Aggressive hydration with isotonic saline and maintenance of urine output greater than 0.5 mL/kg/hr may reduce the risk of renal failure caused by myoglobinuria [34]. Patients with CPK levels greater than 1000 IU/L are hydrated and given corticosteroids to decrease muscle edema and inflammation and are monitored until CPK levels fall towards baseline.

Regional toxicity is more commonly observed with ILI than systemic toxicity. A commonly used classification system characterizing acute tissue reactions was first reported by Wieberdink and has standardized regional toxicity reporting for patients undergoing ILI therapy (Table 1) [35]. Acute regional toxicity-related symptoms are typically observed within the first 72 to 96 hours after ILI [32,36]. Common reactions to therapy include mild erythema, edema and pain (Wieberdink II-III). Mild to moderate blistering is frequently seen up to several days' post-ILI therapy. The development of compartment syndrome progressing to the need for amputation has been reported but is generally uncommon. Long-term toxicity is infrequently reported and may include parathesias or permanent nerve dysfunction.

Results of ILI

The outcome for patients undergoing regional therapy with ILI for extremity STS is generally favorable. Most patients experience at least a partial response to therapy which is assessed generally 3 months after ILI treatment. Disease responses are assessed by a combination of physical examination and cross-sectional imaging andare characterized as: complete response, partial response, stable disease and no response. Overall response rates are similar for those undergoing ILI or HILP but HILP is thought to produce more complete responders than ILI. Tumor response rates range from 79% to 90% for patients with advanced extremity STS that undergo ILI who were previously only considered for amputation [24,33,37]. The outcome for patients treated with ILI for extremity STS is listed in (Table 2). Hegazy and colleagues first reported on 40 patients with unresectable extremity STS who were treated with ILI using doxorubicin [24]. All patients were felt to be unresectable at initial diagnosis, and amputation was considered as the only viable treatment option. ILI was performed pre-operatively with doxorubicin (0.7 mg/kg for upper extremity or 1.4 mg/kg for lower extremity) followed by external beam radiotherapy (started 3-7

days after ILI) for a total dose of 35 Gy in ten fractions. An objective clinical tumor response was observed in 85% of patients and the sarcoma was rendered resectable in most cases. With a median follow up of 15 months, a limb salvage rate of 82.5% was achieved using this multimodality treatment regimen. Turaga and colleagues reported similar results in 2011 with a series of 22 patients with non-melanoma cutaneous metastases managed with ILI for limb threatening disease [33]. Fourteen of the 22 patients (64%) underwent ILI for STS. Overall end points included limb preservation and clinical tumor response. Two patients underwent repeat ILI (1-Kaposi sarcoma, 1-pleomorphic high-grade sarcoma). The response rate for patients with STS was 75% (17% complete response and 58% partial response) per patient and 78% (14% complete response and 64% partial response) per infusion. Vohra and colleagues reported on a series of 26 ILI procedures (19-lower extremity, 7-upper extremity) in 22 patients with locally advanced, unresectable STS [38]. The authors' primary end points were in-field response and limb-salvage rates. Seventeen patients were evaluable at 3 months of follow up. No grade IV Wieberdink toxicity was observed. Four (24%) had a complete response, 3 (18%) partial response, 3 (18%) stable disease and 7 (41%) had disease progression. Twelve of the 17 evaluable patients were able to undergo successful limb-salvage. Importantly, 2 (12%) were able to undergo resection after ILI and remain free of disease afterwards for 22 and 30 months, respectively. In addition to tumor response, the use of ILI may spare these complex patients the potential morbidity and need for amputation. ILI limb-salvage rates are similar to those observed with HILP. Four of the larger ILI series for STS document limb-preservation rates in the range of 71% to 83% [24,33,38] Local or regional recurrence after ILI has been reported and can occur in 42% to 48% depending on the prior treatment [24,37]. Repeat ILI in these instances, offers additional treatment of the tumor and local control, even in the presence of distant disease.

Conclusion

Local recurrence of extremity STS remains a challenging problem to treat. Resection and irradiation for recurrence are preferred therapies but often at the cost of significant treatment-related morbidity. Amputation provides excellent local control but may negatively affect patient quality of life without providing any impact on survival. Limb-salvage techniques using regional chemotherapy in the form of HILP or ILI are attractive alternatives to amputation and may be useful adjuncts to resection and irradiation. ILI, in particular, is well tolerated with favorable response rates, is repeatable and can be performed in the setting of distant disease. Patients with recurrent extremity STS should be referred for multidisciplinary consultation both for clinical trial consideration and to optimize treatment planning and potential for long-term outcome.

Abbreviations

CPK: Creatine Phosphokinase

HILP: Hypertheric Isolated Limb Perfusion

ILI: Isolated Limb Infusion

RT: Radiation Therapy

STS: Soft Tissue Sarcoma

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