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Isolated limb perfusion for the management limb threatening soft tissue sarcomas: The role of histological type on clinical outcomes

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Abstract

Background: Hyperthermic isolated limb perfusion (HILP) is an effective neoadjuvant treatment to avoid amputation in patients with locally advanced extremity soft tissue sarcomas (STS). We aimed to investigate whether STS histological type plays a role in predicting clinical outcomes.

Methods: This study reports a retrospective analysis of 125 patients with limb threatening STS (liposarcoma, n = 41; malignant peripheral nerve sheath tumor, n = 20; leiomyosarcoma, n = 20; miscellany, n = 44), who underwent HILP from 1990 through 2015 at our institution. The following endpoints were evaluated: tumor response (assessed by radiological imaging and histology), limb sparing rate, local progression-free survival (LPFS) and overall survival (OS).

Results: On average, overall (complete + partial) tumor response was significantly greater in patients affected with liposarcoma as compared to those with other histotypes (radiological response rate: 38/41, 92.7% vs 66/84, 78.6%, P-value: 0.048; mean histological necrosis: 83.6% vs 52.9%, P < 0.0001). Limb sparing rate was also higher among patients with liposarcoma as compared to other histotypes (39/41, 95.1% vs 62/84, 73.8%, P-value: 0.005). As regards survival, LPFS was similar across tumor types, whereas OS resulted significantly worse in patients with limb leiomyosarcoma (log-rank P-value: 0.009).

Conclusions: HILP is a very effective treatment modality for limb threatening STS. In our series, liposarcoma appears to be the histological type most sensitive to HILP in terms of tumor response and thus limb sparing, which might help clinicians in the patient selection process.

Keywords: Liposarcoma; Tumor necrosis factor; Melphalan; Hyperthermia; Perfusion

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Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of rare malignancies that include more than 50 different histological types, the most frequent in adults being liposarcoma.[1] Surgery in combination with radiotherapy (RT) is the mainstay of treatment of STS.[2] However, some locally advanced limb STS cannot be excised with adequate margins and preservation of functionality, which makes these patients candidates for amputation, a procedure that however does not appear to impact on survival.[3–5] Tumor necrosis factor (TNF) plus melphalan based hyperthermic isolated limb perfusion (HILP) represents an effective alternative treatment to limb amputation,[6] low-dose TNF plus melphalan (L-PAM) being generally considered the gold standard schedule.[7,8]

Although a number of studies demonstrated that HILP is an effective therapeutic strategy for limb preservation in locally advanced STS,[9–15] to the best of our knowledge only a few reports investigated the effect of tumor histotype on clinical outcomes, with special regard to tumor response and limb salvage rates.[8,16–18]

Therefore, we aimed to fill this gap of the international literature by reviewing the clinical records of patients with limb threatening STS treated with neoadjuvant HILP at our institution.

Patients and methods

Patients and criteria of non-resectability

Between 1990 and 2015, 125 HILP were performed for extremity STS at our institution. Baseline patient characteristics are presented in Table 1. All patients were evaluated by a multidisciplinary sarcoma medical team and considered unsuitable for radical resection according to the following criteria: multifocal disease, multiple recurrences, recurrence in previously irradiated areas, tumor infiltration of bones or nerves, or a combination of the previous factors. On the other side, exclusion criteria for HILP were peripheral arterial disease, severe heart disease and coagulation disorders, and concomitant chemo/radiotherapy or immuno-suppressive therapy. Ethical approval is not required for this study.

Hypertermic isolated limb perfusion

The surgical technique for HILP has been described in detail elsewhere.[10,12,19] In brief, under general anesthesia the main artery and vein of the affected limb were isolated and encircled with tourniquets. After systemic heparinization, the tourniquets were tightened as arterial and venous catheters were inserted into the vessels, after a transverse incision. Subsequently, they were connected to the extracorporeal circuit. An Esmarch tourniquet was placed at the root of the limb in order to collapse collateral vessels and to prevent systemic drug leakage. 99m Tc-Albumin was injected into the circuit to measure the perfusate-to-systemic circulation leakage with a gamma probe placed over the heart and connected to a gamma counter for continuous monitoring and recording.[19,20] The HILP consisted of a 90-min (1988–2003) or 60-min (2004–2014) perfusion. Three (arm) to 4 (leg) mg of TNF (1999–2003) or 1 mg (2004–2014) of TNF were combined with 8.5 mg/L/limb volume of doxorubicin (1988–2003) or with 13 mg per liter of leg volume or 10 mg per liter of arm volume of melphalan (L-PAM) (2004–2014).[7] The flow rate during perfusion was set at 470 ml/min and 700 ml/min for the upper and lower limb, respectively. In all patients, the maximum temperature during the procedure was set at 40–41 °C (borderline true hyperthermia) because true hyperthermia (>41–43 °C) is associated with unacceptable locoregional toxicity.[13,21,22] At the end of HILP the limb was washed.

No additional cancer treatment was given in the interval between HILP and surgical resection. Surgery was

Table 1
General features of cases included.

Histotype	Number	%	Sex	Mean age (range)	Arm
All	125	100	M:F = 53:72	52.4 (18–82)	U:L = 19/106
Liposarcoma	41	33	M:F = 19:22	51,6 (21–84)	U:L = 7/34
Myxoid	31	24,8	M:F = 11:20	47,5 (21–79)	U:L = 5/26
Pleomorphic	10	8	M:F = 8:2	53,6 (27–84)	U:L = 2/8
Leiomyosarcoma	20	16	M:F = 7/13	55,9 (19–79)	U:L = 2/18
MPSNT	20	16	M:F = 12/8	41,3 (18–72)	U:L = 4/16
Others	44	35	M:F = 18/26	53,8 (17–81)	U:L = 6/38
PUS	18	14.4	M:F = 9/9	61,7 (43–81)	U:L = 1/17
RMS	10	8	M:F = 6/4	44,8 (20–70)	U:L = 0/10
Angiosarcoma	5	4	M:F = 1/4	61,1 (46–75)	U:L = 3/2
EMC	4	3.2	M:F = 1/3	51,5 (23–67)	U:L = 0/4
CCS	2	1.6	M:F = 1/1	49 (34–64)	U:L = 1/1
Desmoid Tumor	2	1.6	M:F = 0/2	23 (17–30)	U:L = 1/1
eHAE	2	1.6	M:F = 1/1	65 (61–69)	U:L = 0/2
OS	1	0.8	M:F = 1/0	64	U:L = 0/1

U: upper; L: lower; MPSNT: malignant peripheral nerve sheat tumors; PUS: pleomorphic undifferentiated sarcoma; RMS: Rhabdomyosarcoma; EMC: extraskeletal myxoyd condrosarcoma; CCS: clear cell sarcoma; eHAE: haemangioperycitoma; OS: osteogenic sarcoma.

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