Isolated limb perfusion in the management of locally advanced soft tissue sarcoma: a single center experience with long-term follow-up

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Abstract

Background Hyperthermic isolated limb perfusion (HILP) is an effective neoadjuvant treatment to avoid amputation in selected patients with locally-advanced extremity soft tissue sarcomas (STS).

Patients and Methods This retrospective study shows single-centre experience with HILP in patients with unresectable STS, candidates for amputation, treated at the University Hospital and at Veneto Institute of Oncology of Padua (Italy) between February 1989 and September 2013. Surgery was performed at least 6-8 weeks after HILP; before surgery, a magnetic resonance imaging (MRI) was used to evaluate tumor shrinkage and response as well as the structures (e.g. vessels, nerves) around the tumor.

Results A total of 117 patients were included; 55 patients (47.0%) achieved a pathological complete response and 35 patients (29.9%) a pathological partial response; there was no difference in response based on tumor presentation (primary *vs* local relapse; p=0.094). The overall limb sparing rate was 77.8% (91/117 patients).

Conclusions Our experience confirms that HILP is an effective treatment for non-resectable primary, recurrent or metastatic advanced limb STS that is associated with a high rate of limb sparing and durable local disease control.

Key words: perfusion, sarcoma, tumor necrosis factor

Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of malignant tumors. About 60% arise in limbs and more than 90% can be widely excised with limb preservation [1]. The current treatment of localized STS consists of limb-sparing surgery associated with pre- or post-operative radiation therapy [2]. However, in 5-10% of cases radically resection with adequate surgical margins cannot be achieved for disease extension or neurovascular involvement, unless compromising limb functionality or preservation. Consequently, these patients are suitable candidates for amputation, even though without a significant survival improvement [3, 4].

Thus, there is obvious motivation to include also chemotherapy in the treatment approach of patients with locally-advanced advanced disease in an effort to decrease the extent of the required surgical resection and, consequently, to promote better functional outcomes, in addition to improving metastasis-free and overall survival. In this way, an aggressive regimen of neoadjuvant systemic chemotherapy consisting of mesna, adriamycin, ifosfamide, and dacarbazine (MAID), associated with 44Gy external beam radiotherapy, followed by resection and post-operative chemotherapy with or without additional radiation has shown high rates of local and distant control, although it was associated with noteworthy toxicity. In fact, according to a recent report from the Massachussets General Hospital on 66 patients with high risk extremity and truncal sarcomas who were managed with this treatment regimen, 23 of them (32%) experienced pre-operative complications, while 31 (47%) reported post-operative complications [5].

Locoregional chemotherapy has been introduced to improve clinical response with the purpose of administering high drug dosages and containing systemic toxicity. For this reason, the blood supply of the affected limb must be isolated and an extra-corporeal circulation must be established for the optimal delivery of chemotherapeutic agents. HILP with tumor necrosis factor-alpha (TNF-α) and melphalan (L-PAM) represents an alternative to limb amputation for patients with locally advanced STS [6-8]. After the pioneering work by Lejeune and Lienard [9], a European multicenter study reported by Eggermont [10] included

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186 patients with unresectable STS treated with HILP with TNF-α and L-PAM before surgical resection. The results showed an overall response of 82% and a limb salvage rate of 82%. Later studies confirmed these results, reporting a limb salvage rate of 77-87% [11-14]. Currently, HILP with low-dose TNF-α plus L-PAM is an interesting local treatment option in Europe for patients with unresectable locally advanced limb STS. This study reports the experience of a single institution with HILP in patients with unresectable limb STS, who were otherwise candidates for amputation

Methods

This retrospective study included all locally advanced non-resectable patients with limb STS patients treated at the University Hospital and at Veneto Institute of Oncology of Padua (Italy) between February 1989 and September 2013. All patients were evaluated by a multidisciplinary sarcoma medical team and judged non-resectable on the basis of the following criteria: multifocal disease, recurrence in previously irradiated areas, deep local recurrences close to bones or infiltrating nerves, or any combination of these factors. In case of stage IV disease, HILP was offered when the patients had oligometastatic visceral involvement and limb disease was judged highly symptomatic. Exclusion criteria for HILP were relevant peripheral vascular disease, severe heart disease and coagulation disorders, concomitant chemo/radiotherapy or immunosuppressive therapy. The surgical technique used for HILP has been described in detail elsewhere [11]. In brief, 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 cannulas/catheter were inserted into the vessels, following 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 systemic leakage with a gamma probe placed over the heart and connected to a gamma counter for continuous monitoring and recording [15]. No additional cancer treatments were given in the interval between HILP and surgical resection. Surgery was performed at least 6-8 weeks after HILP and magnetic resonance imaging (MRI) was used to evaluate tumor shrinkage and the surrounding structures.

Table 1. Baseline patient characteristics

Characteristics	Patients (n=117) n (%)
Sex	
Male	55 (47.0)
Female	62 (53.0)
Age	
<50 years	42 (35.9)
≥50 years	75 (64.1)
Tumor location	
Upper limb	28 (23.9)
Lower limb	89 (76.1)
Tumor burden	
Unifocal	82 (70.1)
Multifocal	35 (29.0)
Presentation	
Primary	92 (78.6)
Recurrent	25 (21.4)
Tumor size	
<10 cm	60 (51.3)
≥10 cm	57 (48.7)
Distant metastases	17 (14.5)
Previous treatments	
Chemotherapy	6 (5.1)
Radiotherapy	9 (7.7)
Combination	3 (2.6)
Stage	
T1b	13 (11.1)
T2b	104 (88.8)
Grading	
I-II	12 (10.3)
III	105 (89.7)
Histotype	
Leiomyosarcoma	23 (19.7)
Liposarcoma	20 (17.1)
Malignant peripheral nerve sheath tumor	17 (14.5)
Pleomorphic sarcoma	16 (13.7)
Synovial sarcoma	14 (11.9)
Lymphangiosarcoma	7 (5.9)
Myxofibrosarcoma	4 (3.4)

Results

A total of 117 patients (55 men, 62 women, age 11–92 [median 53] years) were included in the study (see Table 1 for further details about the study population).

Surgical vascular access was obtained through the axillary vessels in 28 patients (23.9%), the femoral vessels in 67 patients (57.2%) and the external iliac vessels in 22 patients (18.8%). The median value for maximum temperature registered during the procedure was 40.5ºC (range

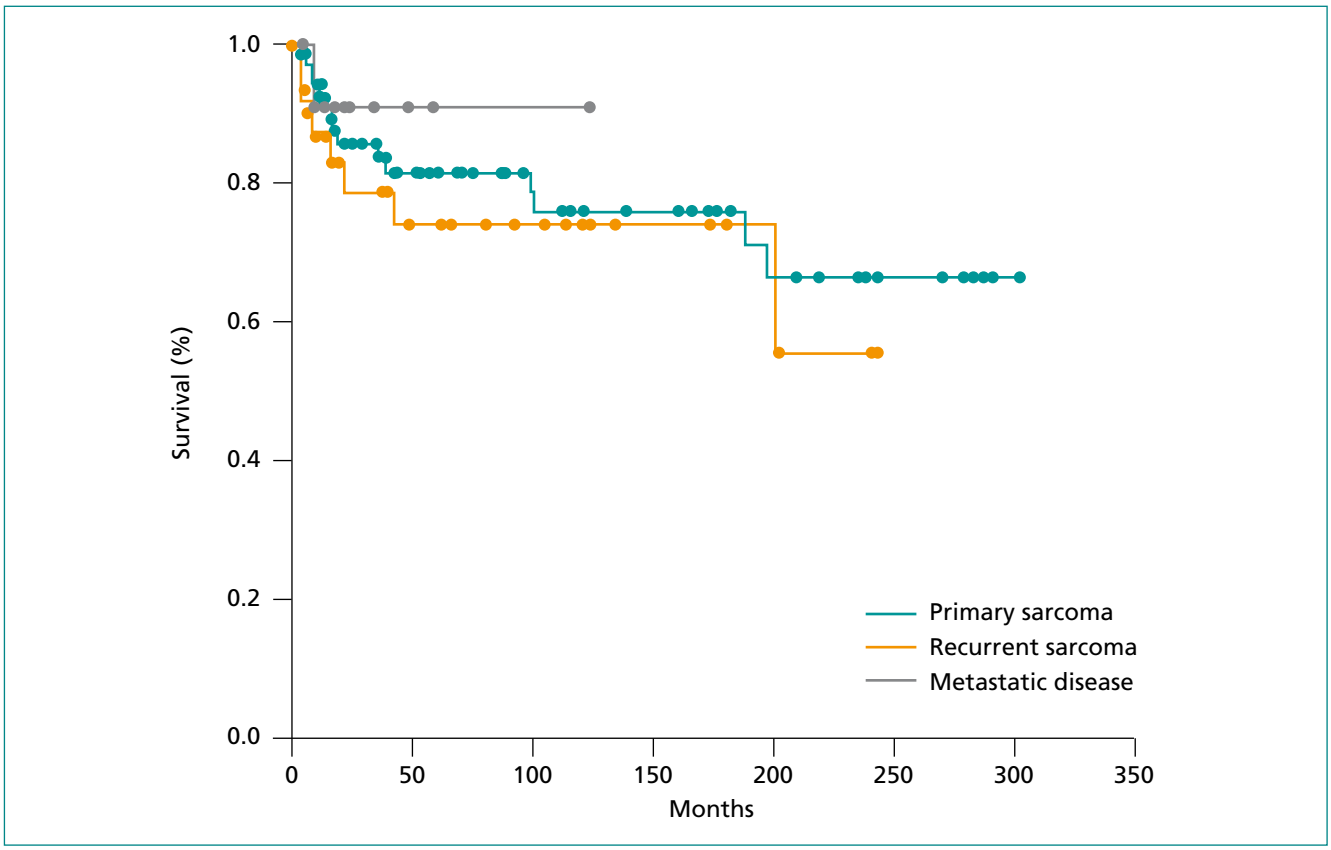

Fig. 1. Local-tumor progression-free survival.

39.2-43.0ºC). Median systemic leakage was 4.8% (range 0-8%).

After HILP 2 patients achieved a complete response (1.7%), 94 patients a partial response (80.3%) and 21 patients (18.0%) had stable disease. After surgical resection, 54 patients achieved a pathological complete response (46.1%), 36 patients a pathological partial response (30.4%) and there was no pathological change in 27 patients (23.5%). Limb-sparing surgery was performed in 91/117 patients (77.8%). Twenty-six patients (22.2%) required limb amputation: one patient was amputated due to locoregional toxicity after HILP; 17 patients were amputated because of poor response to HILP; and 8 patients, treated with HILP and surgical resection, required limb amputation for disease recurrence during follow-up.

Overall local-tumor progression-free survival (LPFS) was 80.6%.

In patients with primary and local recurrent disease, 5-year, 10-year and 15-year LPFS rates were respectively 81.6%, 76.0% and 71.2% (Figure 1). In patients with primary disease, 5-year, 10-year, 15-year overall survival rates were respectively 58.6%, 49.8% and 43.1%; corresponding values in patients with local recurrent disease were 64.5%, 51.7%, 44.3% (Figure 2). In stage IV patients, estimated 5-year overall survival was 7.1%.

Discussion

In Europe, after the approval of TNF-α by the European Agency for the Evaluation of Medicinal Products, TNF-α based HILP has become one of the most widely used treatment options for limb threatening STS [16-20]. The present study summarizes a single center experience with HILP over a 24-year period in patients with locally-advanced extremity STS. Our experience confirms that HILP is a highly active and effective treatment, in fact overall pathologic response rate in our 117 patients was 76.5% and the limb sparing rate was up to 77.8%. The procedure has proved to be safe (we reported 1 death due to systemic drug leakage and related fatal leucopoenia) and the locoregional toxicity profile was easily manageable in most patients.

The pathologic tumor response was complete in 53/115 (46.1%) resected patients and partial in 35/115 (30.4%). These results are comparable to previous series, where the overall response rate ranged from 63% to 96% [6-10, 12, 14], and open the question about the need of surgical resection after a complete clinical response following HILP. However, the discrepancy between the radiological and pathological complete response rate in our study (1.7% and 46.1%, respectively) underlies the impossibility to predict a pathological complete response after HILP and

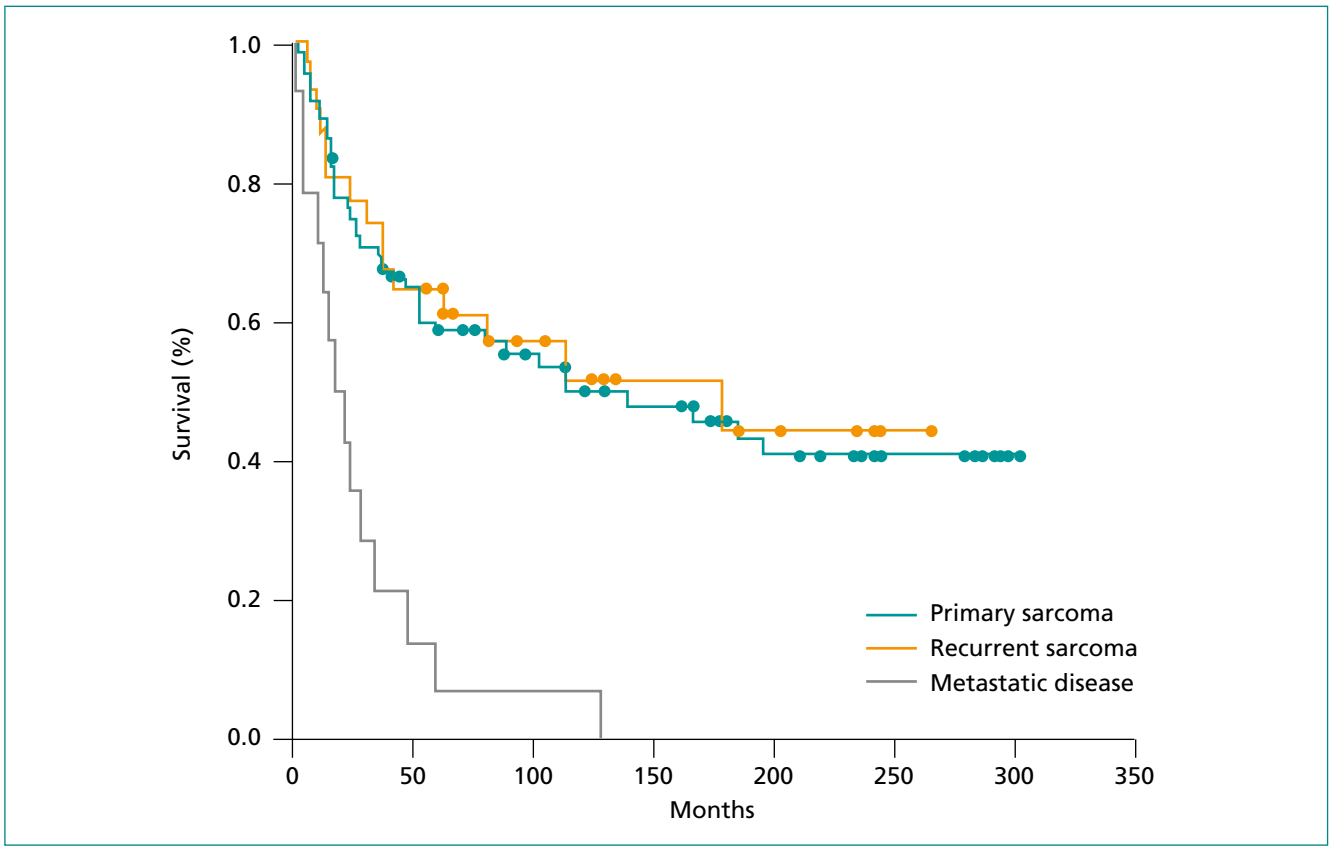

Fig. 2. Overall survival.

to identify the patients who could avoid a surgical resection. Moreover, especially in patients with a large tumor volume, surgical resection is beneficial in order to remove all the necrotic tissue and avoid possible sovrainfections. Therefore, HILP should be used in a neo-adjuvant setting to allow patients to undergo limb- and function-sparing tumor resection with the possibility of long-term local control.

Nevertheless, especially in patient with locally-advanced and multifocal disease, HILP could be also considered a definitive treatment particularly when a complete or near complete response is achieved. In this context, the recent availability of less invasive and promising locoregional treatments, such as isolated limb infusion (ILI) and electrochemotherapy (ECT), may open new possibilities in the multimodal management of these complex disease [21, 22]. For example, in order to spare patients from the morbidity of surgical resection, the residual disease after HILP could be easily managed by one of the recently minimally invasive technique, such as ILI and ECT. However, the risk of distant metastasis remains a major concern, and this risk is related to tumor grade and size. HILP cannot prevent the development of distant disease and new treatment strategies, for example the integration of locoregional treatments with systemic chemotherapy, should be explored in well-designed clinical trials; in the meanwhile, a very close follow-up of this subgroup of patients is crucial in order to early detect systemic disease progression.

In conclusion, our experience confirms that HILP is an effective treatment that confers a substantial limb-sparing effect and provides durable local disease control in patients with advanced limb STS, including those with primary, recurrent and also metastatic disease, when a rapid palliation is needed.

References

1. Cormier JN, Pollock RE. Soft tissue sarcoma. Ca Cancer J Clin 2004;54:94-109.
2. Stojadinovic A, Leung DH, Hoos A, et al. Analysis of the prognostic significance of microscopic margins in 2084 localized primary adult soft tissue sarcomas. Ann Surg 2002;235:424-34.
3. Williard WC, Hajdu SI, Casper ES, Brennan MF. Comparison of amputation with limb sparing operations for adult soft tissue sarcoma of the extremity. Ann Surg 1992;3:269-75.
4. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospec-

tive randomized evaluations of (1) limb sparring surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 1982;196:305-15.
5. Look Hong NJ, Hornicek FJ, Harmon DC, et al. Neoadjuvant chemoradiotherapy for patients with high-risk extremity and truncal sarcomas: a 10-year single institution retrospective study. Eur J Cancer 2013 Mar;49(4):875-83.
6. Taeger G, Grabellus F, Podleska LE, et al. Effectiveness of regional chemotherapy with TNF-alpha/melphalan in advanced soft tissue sarcoma of the extremities. Int J Hyperthermia 2008;24:193-203.
7. Bhangu A, Broom L, Nepogodiev D, et al. Outcomes of isolated limb perfusion in the treatment of extremity soft tissue sarcoma: a systematic review. Eur J Surg Oncol 2013;311-9.
8. Seinen JM, Hoekstra HJ. Isolated limb perfusion of soft tissue sarcomas: a comprehensive review of literature. Cancer Treat Rev 2013;39:569-77.
9. Lienard D, Ewalenko P, Delmotte JJ, et al. High-dose recombinant tumor necrosis factor alpha in combination with interferon gamma and melphalan in isolation perfusion of the limb for melanoma and sarcoma. J Clin Oncol 1992;10:52-60.
10. Eggermont AM, Schraffordt Koops H, Klausner JM, et al. Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas. The cumulative multicenter European experience. Ann Surg 1996;224:756-64.
11. Rossi CR, Foletto M, Di Filippo F, et al. Soft tissue limb sarcomas: Italian clinical trials with hyperthermic antiblastic perfusion. Cancer 1999;86:1742-9.
12. Lejeune FJ, Pujol N, Lienard, et al. Limb salvage by neoadjuvant isolated perfusion with TNFalpha and melphalan for non-resectable soft tissue sarcoma of the extremities. Eur J Surg Oncol 2000;26:669-78.
13. Rossi CR, Foletto M, Mocellin S, et al. Hypertermic isolated perfusion with low-dose TNFalpha and doxorubicin in patients with locally advanced soft tissue sarcomas. J Chemother 2004;16:58-61.
14. Bonvalot S, Laplanche A, Lejeune F, et al. Limb salvage with isolated perfusion for soft tissue sarcoma: could less TNF-alpha be better? Ann Oncol 2005;16:1061-8.
15. Casara D, Rubello D, Pilati P, et al. Optimized procedure of real-time systemic leakage monitoring during isolated limb perfusion using a hand held gamma probe and 99m Tc-HSA. Nucl Med Commun 2004;25:61-6.
16. Eggermont AM, ten Hagen TL. Isolated limb perfusion for extremity soft-tissue sarcoma, in-transit metastases, and other unresectable tumors: credits, debits, and future perspectives. Curr Oncol Rep 2001;3:359-67.
17. Schraffordt Koops H, Eggermont AM, Lienard D, et al. Hypertermic isolated limb perfusion for the treatment of soft tissue sarcoma. Semin Surg Oncol 1998;14:210-4.
18. Smith HG, Cartwright J, Wilkinson MJ, et al. Isolated limb perfusion with melphalan and tumour necrosis factor α for in-transit melanoma and soft tissue sarcoma. Ann Surg Oncol 2015 Sep 8 (Epub head of print).
19. Jakob J, Tunn PU, Hayes AJ, et al. Oncological outcome of primary non-metastatic soft tissue sarcoma treated by neoadjuvant isolated limb perfusion and tumor resection. J Surg Oncol 2014;109:786-90.
20. Rastrelli M, Tropea S, Basso U, et al. Soft tissue limb and trunk sarcomas: diagnosis, treatment and follow-up. Anticancer Res 2014;34:5251-62.
21. Vohra NA, Turaga KK, Gonzalez RJ, et al. The use of isolated limb infusion in limb threatening extremity sarcomas. Int J Hyperthermia 2013;29(1):1-7.
22. Campana LG, Bianchi G, Mocellin S, et al. Electrochemotherapy treatment of locally advanced and metastatic soft tissue sarcomas: results of a non-comparative phase II study. World J Surg 2014;38:813-22.