Efficacy of high vs low dose TNF-isolated limb perfusion for locally advanced soft tissue sarcoma

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Accepted 8 January 2008

Abstract

Aims: The administration of a high dose of rTNF-α (3–4 mg) and Melphalan via isolated limb perfusion (ILP) for patients with locally advanced limb STS was shown to be effective. Reports that a low dose of TNF (1 mg) is as effective, led to the adoption of the low dose regimen as the treatment of choice. The purpose of this study was to compare two groups of patients with locally advanced limb STS, that was treated with high and low dose TNF-ILP, in terms of limb preservation.

Methods: Retrospective study of 41 patients who underwent ILP, with “high dose” (HD) and “low dose” (LD) TNF. ILP/TNF was performed on candidates to either amputation or significantly mutilating surgery without this treatment. In both groups, all patients, with the exception of three in each group, underwent resection of the residual tumor or tumor bed or limb 8–12 weeks after the procedure.

Results: In the HD group, marked tumor softening occurred within 48 h, and in tumors protruding through the skin, hemorrhagic necrosis was evident within 24 h. The overall response rate was 65.2%. Five patients achieved a CR and 10 had a PR; in five of these patients >90% necrosis of the tumor occurred. In eight patients, only minimal regression was observed (stabilization of disease). The rate of limb sparing was 69.5%. In the LD group, the overall response rate was 30.7%. CR was achieved in one patient. PR was observed in two. Two patients were lost to follow up. Of the remaining 15 patients, limb preservation was achieved in 53.3%.

Conclusion: Despite the retrospective comparison and possible selection bias, it is possible to raise the concern that at least some patients may benefit from a higher TNF dose perfusion in ILP for advanced limb STS.

Published by Elsevier Ltd.

Keywords: Isolated limb perfusion; ILP; TNF-α; Limb sarcoma

Introduction

The treatment of limb soft tissue sarcoma (STS) is multidisciplinary, based on resection of the tumor with its anatomic compartment, irradiation and combination chemotherapy.

The surgical approach to limb STS has changed during the last two decades. It has been proven that although up to 50% of patients will die of their disease,1 amputation and even microscopically incomplete resection does not change the overall survival, and the combination of limb-sparing surgery and adjuvant therapy, mainly radiation, can locally control the disease, to a level comparable with amputation.2,3 Nonetheless, amputation is unavoidable in 10–20% of these patients despite aggressive conventional therapy.

In cases of limb threatening STS, necessitating amputation or severely mutilating surgery, due to tumor fixation to neurovascular bundle or bone, isolated limb perfusion (ILP) with rHu-TNF-α combined with antiblastic treatment (mostly Melphalan or Doxorubicin), has been proved to increase limb preservation. Another indication is locoregional metastatic disease, not amenable to surgical treatment.

When ILP-TNF was first introduced by Liénard et al.,4 the dose of TNF was arbitrarily set on 3–4 mg, for upper and lower extremity, respectively. This dosage was deduced from studies in rats, defining the murine effective dose as 50 μg/kg, and calculated as 10 times the human tolerated systemic dose.5,6
Using HD TNF-based ILP, studies have demonstrated an overall response rate of up to 90% and limb preservation in 75–85% of patients. 7,8

Based on animal studies, suggesting an equal efficacy of lower TNF doses 9–11 and partly because of a concern of local toxicity and systemic side effects, the 3–4 mg TNF regimen was challenged. Reducing the dose also significantly lowered the high cost of the procedure, and many centers have moved to an LD protocol of 1 mg of TNF. 

In a phase II study, performed by Gutman et al., 7 35 patients with locally advanced STS, necessitating an amputation or mutilating surgery, underwent 41 ILPs with high dose TNF (3–4 mg) and Melphalan. Limb salvage was achieved in 85%. The overall response rate was 91%. Thirteen patients had a complete response and 19 had a PR; in five of these patients 90% necrosis of the tumor occurred.

After the conclusion of this study, performing isolated limb perfusions with TNF and Melphalan, has become an option for patients with limb-jeopardizing primary or recurrent STS. In the first years (1997–2000) the procedure was done with HD TNF, but around 2000, we moved to an LD protocol, as did other centers around the world. During these years (2000–2006) the clinical impression of the physicians caring for these patients was that the treatment seemed to be less effective.

Given the paucity of data regarding the dose—response relations of TNF-ILP in locally advanced STS, we retrospectively examined the outcome of our procedures, in terms of histologic response, rate of limb salvage and limb recurrence.

Patients and methods

Patients

Between January 1997 and December 2006, 42 patients underwent 46 consecutive ILPs, for limb threatening STS. Their admission and follow-up files were retrospectively examined. No patient was excluded.

In the HD group, there were 14 male and 12 female patients, with an age range of 22–82 (mean, 51 years). Twenty-two patients had histologically proven STS, which was primary in 20 patients and recurrent in 6 (malignant fibrous histiocytoma [MFH] [9]; liposarcoma [6]; malignant schwannoma [1]; soft tissue chondrosarcoma [1]; extra-skeletal ewing sarcoma [1]; synovial [1]; clear cell [1]; spindle cell [1]; and leiomyosarcoma [1]). Three patients had large, locally invasive desmoid tumor and one had a non-HIV related Kaposi sarcoma.

In the LD group, there were 12 male and 5 female patients, with an age range of 22–72 (mean, 46 years). Thirteen patients had histologically proven STS, which was primary in 7 and recurrent in 10 (epithelioid [3]; liposarcoma [3]; spindle cell [2]; MFH [1]; synovial [1]; clear cell [1]; and leiomyosarcoma [1]). Two patients had locally invasive desmoid tumor and two had a non-HIV related Kaposi sarcoma.

Before being referred to ILP, two patients from the HD group received systemic chemotherapy. One was treated with combination of Adriamycin and Ifosfamide (AI) and one with systemic Adriamycin and intra-arterial Cisplatin. Six patients from the LD group received systemic chemotherapy before ILP. Four were treated with AI, one with Adriamycin and Dacarbazine and one with Interferon-γ (p < 0.05).

In the HD group, 6 tumors were located in the upper extremities and 20 in the lower. In all but three patients, STS was confined to the limb. These patients underwent a palliative limb-sparing procedure in the face of a stable systemic disease.

In the LD group, 6 tumors were located in the upper extremities and 11 in the lower. In all patients, the tumor was confined to the limb. In the HD group, 6 of the 26 patients were operated on, prior to the perfusion. One of them received radiation and two were treated with systemic chemotherapy (Adriamycin and Ifosphamide). In the latter LD group, 10 of the 17 patients underwent previous operations. Three patients were irradiated and six received systemic chemotherapy.

Procedures

The first 26 patients (1997–1999) underwent 29 ILPs with HD TNF (3–4 mg for upper and lower extremity, respectively) combined with Melphalan (1–1.5 mg/kg, for upper and lower extremity, respectively). Thereafter, 2000–2006, 17 patients underwent 17 perfusions with LD TNF (1 mg) combined with Melphalan (1–1.5 mg/kg, for upper and lower extremity, respectively).

Four patients underwent two ILPs each. In two patients from the HD group, who achieved definite partial response (PR), and in whom the tumor shrank significantly but not sufficiently to render it resectable, without endangering limb function, a second ILP-TNF was performed 5 and 8 weeks after the first. One patient from the HD group, suffered a significant systemic leak, and the procedure was terminated after 30 min, before the addition of Melphalan. This patient had a second ILP 5 weeks later. Another patient from the HD group was lost to follow up for 35 months. This patient returned with multiple local recurrences and underwent an LD ILP.

No patient from the LD group had more than one perfusion.

All patients, in both groups, were referred from the National Center for Bone and Soft Tissue Tumors, where they had been classified as absolute candidates for amputation or extensive mutilating surgery involving the neurovascular bundle, by the same orthopedic oncologist.

Hyperthermic ILP with rHu-TNF and Melphalan

The technique has been previously described. 13 Briefly, the main artery and vein of the perfused limb were
dissected, and all collaterals ligated. The vessels were then cannulated and connected to a heart-lung machine. A membrane oxygenator and silicone tubing were used. A tourniquet (200–400 mmHg) or Esmark band was applied on the root of the limb to ascertain complete vascular isolation and to ensure that the entire tumor was within the perfused area and received adequate drug dosing. For below-knee or below-elbow lesions a pneumatic tourniquet was applied proximal to the blood vessel cannulation sites. For proximal lesions reaching the groin area or arm, the iliac or axillary vessels were cannulated and an Esmark band applied. For the lower limb, it was anchored at the anterior—superior iliac spine and pubic bone level with the aid of pins inserted into the pelvic bones. For the upper limb, it was anchored at the scapular and pectoral levels with the aid of pins. Patients with tumors extending beyond the inguinal and axillary lines, in which it was estimated that proximal vascular cannulation and/or Esmark band application could not be safely achieved, were excluded and ILP was not attempted. The temperature of the perfused limb was maintained at 39 °C during the entire procedure by both external heating and warming of the perfusate to 40 °C. Circuit priming was done with blood, Ringer’s lactated solution, and heparin. All patients, in both groups, underwent ILP at a flow rate of 110–400 mL/min in the upper limb and 110–650 mL/min. At the end of the procedure, the limb was thoroughly rinsed, the cannulas extracted, and the blood vessels repaired. Systemic leakage from the perfused limb was monitored continuously using 99Tc radiolabeled human serum albumin injected into the perfusate. Radioactivity above the precordial area was recorded using a Geiger counter. The perfusion parameters did not differ in between the two groups.

Drugs

rHu-TNF-α (Boehringer Ingelheim, Ingelheim/Rhein, Germany) was administered at a dose of 3 and 4 mg for the upper and lower limbs, respectively, as a bolus into the arterial line of the perfusate, in the first 29 procedures. Thereafter, the dosage was reduced to 1 mg for both the upper and lower limbs. Melphalan (Alkeran; Wellcome Bendix, London, United Kingdom) was administered at 1.0 and 1.5 mg/kg body weight for the upper and lower limbs, respectively, 30 min after TNF and the perfusion was continued for an additional 60 min. A higher dose is required for the lower limb given its significantly larger volume. Calculation of the Melphalan dose according to body weight was considered a reliable method with results similar to those achieved after limb volume measurement.13

Follow-up and definitive surgery

All patients were evaluated by a team of surgical oncologists performing the ILP, an orthopedic oncologist and a medical oncologist. Clinical assessment was performed 6–8 weeks after ILP. Limb toxicity was assessed according to Wieberdink et al.14

Patients with a clinical complete response (CR) were referred for surgical excision of the tumor bed for histologic confirmation in cases of a solitary lesion. In CR patients with multifocal lesions, multiple biopsies were performed. Patients with clinical partial regression in tumor size underwent excision of the remaining tumor. Altogether, four patients had more than one procedure. As described, in two patients from the HD group, with definite partial response that did not allow for limb salvage (based on imaging data), a second ILP/TNF was performed. One patient had a systemic leak, leading to ILP termination before the completion of the procedure and one had a multiple locoregional recurrence, and underwent a second, LD procedure.

Results

In the HD group, 29 perfusions were performed on 26 patients. In the LD group, 17 patients underwent the procedure.

Complications

During the perfusions, the average systemic leak rate was 2.25% (range 0–15%) in the HD group and 1.08% (range 0–4.5%) in the LD group (p > 0.05). In two patients in the HD group, the leak rate rose to 14% and 15% during the procedure. This increment was associated with hemodynamic changes and led to termination of the procedure. In one patient, this occurred 10 min before the end of the perfusion and led to a minimal shortening. This patient, aged 79, had a complicated post-operative course, characterized by a surgical site bleeding, aspiration pneumonia and severe sepsis, culminating in death, 50 days from ILP. Tumor response is unknown.

In the second patient, the procedure was terminated after the TNF and before the addition of Melphalan. This patient had an uneventful recovery, and underwent a second ILP shortly thereafter.

Length of hospitalization was 13.75 days (range 5–50) for the HD group and 13.5 days (range 4–62) for the LD group.

As mentioned, there was one procedure-related mortality in the HD group.

Local toxicity was assessed, according to Wieberdink, before patient discharge and 6–8 weeks later, as the patient was admitted for primary tumor resection (23 in the HD; 11 in the LD) or in the outpatient clinic (4 HD; 5 LD). In the HD group, significant toxicity, considered as grade 3 or more, occurred in five patients, as compared to two patients in the LD group. There was no toxicity-related limb loss in this group. Two patients in the LD group lost their limb. One developed grade 5 toxicity with myonecrosis that necessitated an above knee amputation. The other had a compartment syndrome that did not respond to fasciotomy. An above elbow amputation was performed.

Please cite this article in press as: Nachmany I et al., Efficacy of high vs low dose TNF-isolated limb perfusion for locally advanced soft tissue sarcoma, Eur J Surg Oncol (2008), doi:10.1016/j.ejso.2008.01.007
Vascular complications occurred in four patients who had HD treatment. One was re-operated on, and had a segmental artery resection and reanastomosis, with limb survival. Three patients underwent failed vascular intervention, culminating in one above knee, one below-knee, and one finger amputation. In the patient with BKA, the primary tumor was in the thigh. It was resected later; therefore the response rate in this patient is known. In the LD regimen, there was no significant vascular event.

The post-operative limb loss rate in the HD group was 7.7%, compared with 11.7% in the LD group.

Response to ILP

In the HD group, response data are available in 23 patients (one died 50 days after the procedure, before response assessment was done; one underwent amputation above the tumor due to a vascular complication and one, who was referred from another hospital, was lost to follow up). Of these 23, 5 had complete response, 5 had near total (more than 90% necrosis) and 5 showed a partial response. The overall response rate was 65.2%. Stable disease (necrosis of ≤50%) was found in eight.

Of the 17 patients who underwent LD TNF-ILPs, 4 were either amputated or lost to follow up and their data on tumor viability are missing. In the remaining 13 patients, only one had a CR, one near total and two PR. The overall response rate was 30.7%. Both the overall and the good response (CR + near total) were significantly higher in patients who had an HD ILP, though these results were lower than our previous prospective study on 35 patients with HD TNF7 (Table 1).

Long-term follow-up

In the former group of HD TNF (1997–2000), 21 patients (23 minus 2 who lost their limb in the post-operative course) were followed for a mean of 58.5 months (nearly 5 years).

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<th>Pathologic response rate of our previous study with high dose TNF and the current study</th>
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<tr>
<td>Phase II high dose study6 (N = 35)</td>
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<tr>
<td>Complete response (100%)</td>
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<tr>
<td>Near total response (&gt;90%)</td>
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<td>Partial response (50–90%)</td>
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<td>CR + near total</td>
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<tr>
<td>Overall response</td>
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<td>Stable disease (&lt;50%)</td>
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*P-Value relates to the presented study.

During follow-up, eight suffered a local recurrence. Five had undergone limb amputation and three, conservative resection. Together with the two who lost their limb in the immediate post-operative course, seven underwent an amputation. Therefore the overall limb salvage rate was 76%.

The mean follow-up in the LD group was 29.8 months. Of the 17 patients, 2 were lost during follow-up.

Altogether, seven patients lost their limb — two in the immediate post-operative course, two during the definitive resection, due to inability to preserve vital structures, and three during follow-up, secondary to tumor recurrence. The overall limb salvage rate was 53.3% (p-value = NS) (Table 2).

Time to recurrence

The average follow-up of the first, high dose group was 58 months (range 1.6–118). In the latter low dose group, the average follow-up time was 29.8 months (range 8–63).

During these time frames, there was a trend for a faster local recurrence in the LD group (average 8.18 vs 28 months), but this did not reach statistic significance.

Discussion

Amputation in patients with advanced limb STS has no benefit over conservative treatment, in terms of survival prolongation. In the face of locally advanced STS, TNF-ILP has been established as a neoadjuvant therapy prior to limb-sparing surgery and as a significant treatment modality in case of multiple locoregional metastases.

The traditional dose of TNF has changed from the arbitrarily set 3–4 mg (so called “high dose”, based on in vitro and animal studies), to a lower dose regimen of 1 mg. This shift is based both on the concern of local and systemic toxicity and the impression that the low dose is as effective. Cost considerations may have been another driving force.

We have previously presented our experience with 35 patients suffering from limb threatening STS.7 Isolated limb perfusion with high dose TNF and Melphalan, in the context of a phase II study, achieved an overall response rate of 91% and limb salvage in 85% of patients.

Very few studies have addressed the issue of TNF optimal dosage. In most, the effectiveness of the reduced
dose was not studied directly. However, both preclinical9 and clinical studies12,15–17 suggested that TNF dose reduction to 1 mg is as effective.

Rossi et al. studied the effect of ILP with low dose TNF combined with Doxorubicin in 20 patients with limb threatening STS. Eleven patients achieved histologic response of over 90% necrosis. Limb-sparing surgery was possible in 17.

In a retrospective non-randomized study of 64 ILPs performed with reduced TNF dose and compared to the “classic” high dose regimen, Grünhagen et al. show that both in melanoma and non-melanoma patients (most of them with STS), overall response rates are not affected by TNF dose reduction.17

The only prospective study on different TNF doses was performed by Bonvalot et al.12 This group randomized 100 patients with locally advanced limb STS considered non-resectable (for either multifocality or fixation/invasion to the neurovascular bundle and/or bone) to undergo ILP with constant dose of Melphalan and escalating doses of 0.5 mg, 1 mg, 2 mg and 3 or 4 mg of TNF. The main end point of objective tumor response on MRI was equivalent in the four TNF doses (68%, 56%, 72% and 64% in the 0.5 mg, 1 mg, 2 mg and 3 or 4 mg arms, respectively). The rates of conservative surgery, which is the final issue, were equivalent in the four groups.

Although these studies support dose reduction, the absence of high volume, multicenter prospective studies, addressing the issue, leave the dose question still open. Here we describe retrospectively our experience with high and low TNF-ILP for patients with limb threatening locally advanced STS.

Our current study, on 26 patients treated with HD TNF, vs 17 undergoing LD perfusion, cannot, by itself, prove our clinical impression that HD TNF-ILP is superior in terms of limb preservation. Nonetheless, it may show a tendency to better results with the HD perfusion.

The overall response rate and good response rate (>90% tumor necrosis) were higher in the high dose group (43.5% vs 15.4% and 65.2% vs 30.7%, respectively; p < 0.05 for both).

However, this study has several significant limitations regarding its ability to address the question of optimal TNF dosage. It is a retrospective analysis of patients treated as part of a clinical routine. A considerable drawback is the patient referral intent that may cause a substantial selection bias. During the first years, when the HD protocol was practiced, ILP was the first procedure performed on the vast majority of patients. Later, many patients were referred after failing local or systemic treatment (58% vs 23%; p < 0.025). This may influence both response rate and the sensitivity of the limb to local toxicity. It seems natural that tumors resisting different treatment modalities would have lower response rate and higher local recurrence, after “second-line” ILP. Since TNF mechanism of action is through tumor vasculature, relative resistance after radiation and surgery may be expected. This no doubt weakens our hypothesis that the reduced dose is responsible for the lower response rate.

Second, we observed a higher rate of local toxicity in the low dose group. This may also be explained by previous limb manipulation rendering the limb more susceptible to drug toxicity.

In spite of these limitations, this study demonstrated a higher response rate in patients treated with high dose TNF. This superior pathologic response did not translate into better limb salvage rate or lower local recurrence, though non-statistically significant trend was demonstrated. An important factor is the length of follow-up, which was more than three times longer in the high dose group (28 vs 8 months). The local recurrence rate is unfortunately expected to rise with time, in the latter LD group, and the recurrence rate differences may reach statistical significance.

Conclusion

The optimal TNF dose was never tested according to the highest standards of evidence-based medicine, and according to most authors is not expected to be. The accumulated data12,15–17 support the dose reduction practiced by most centers performing ILP. Given the described reservations it is possible to raise the concern that at least some patients may benefit from a higher dose perfusion. One such scenario is the case of a patient undergoing a second ILP, after partial response.

Conflict of interest

The authors have no conflict of interest.

References


