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Fifty Tumor Necrosis Factor–Based Isolated Limb Perfusions for Limb Salvage in Patients Older Than 75 Years With Limb-Threatening Soft Tissue Sarcomas and Other Extremity Tumors

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Background: Isolated limb perfusion (ILP) with tumor necrosis factor (TNF) and melphalan is highly effective in treating limb-threatening soft tissue sarcoma (STS) and other bulky tumors. Because of fear of TNF-associated toxicity, ILP with TNF is not offered to older patients in some cancer centers, although especially in older patients, every attempt to avoid an amputation that may end their independence must be considered.

Methods: Out of 306 TNF-based ILPs, 50 ILPs were performed for limb salvage in 43 patients >75 years old (range, 75–91 years): 29 STS and 14 melanoma patients.

Results: In the STS patients, a response rate of 76% and a limb-salvage rate of 76% were achieved; in the melanoma patients, a 100% response rate and a 93% limb-salvage rate were achieved. Local toxicity was mild. The three postoperative deaths that occurred in the total series of 306 TNF-based ILPs in Rotterdam (<1%) occurred in patients >75 years old after leakage-free perfusions and were not related to TNF but to extremely high-risk profiles in these three patients.

Conclusions: Older patients should not be withheld a TNF-based ILP for limb salvage, because the procedure is safe and highly effective in these patients.

Isolated limb perfusion (ILP) is a technique of cancer treatment that delivers high doses of cytostatic drugs to a tumor-bearing extremity that is isolated from the systemic circulation and connected to a heart-lung machine.[1] By ILP, regional concentrations of chemotherapeutic agents 15 to 20 times higher than those reached after systemic administration can be achieved without systemic toxicity.[2] In the management of locally advanced soft tissue sarcoma (STS), limb salvage is a major challenge. In patients with multiple and/or bulky in-transit melanoma metastases, obtaining local control is a major challenge. In contrast to the inefficacy of ILP with melphalan alone in the management of irresectable extremity STS, with response rates of only 10% to 35%,[3,4] the introduction of tumor necrosis factor-α (TNF) in combination with melphalan in ILP has been reported in a European multicenter trial; it resulted in response rates >80% and limb-salvage rates >70% in STS.[5,6] These results led to the approval of TNF in Europe.[7] Also, in the management of in-transit metastases, TNF seems to improve complete response (CR) rates,[8] especially in patients with bulky tumors and in patients whose previous ILP with melphalan alone failed, as has been demonstrated by reports from the Surgery Branch of the National Cancer Institute in the United States.[9,10]

The incidence of STS increases rapidly above the age of 50 years. Approximately 18% of the patient population is above the age of 70 years.[4] The incidence of malignant melanoma has more than doubled over the last 20 years.[12] For both men and women, rates increased relatively more in the older age groups. As a consequence of these epidemiological features, we are confronted with a large group of elderly patients who might need a limb-saving procedure such as ILP. These pa-

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tients, especially, will be severely limited in their mobility and lose independence when amputation of a limb has to be performed. Therefore, especially in the elderly, every attempt to avoid amputation must be considered, and a TNF-based ILP must be considered despite the age of the patients. The perception that TNF-based ILP is a risky endeavor has been demonstrated to be false provided that leakage is monitored and well controlled.[13] But even in the event of significant leakage, we have demonstrated that with correct fluid management and postoperative care, patients do not develop major or life-threatening complications.[14] Therefore we do not think it is reasonable to consider age a limiting factor for patients to undergo a TNF-based ILP. Here we present our single Rotterdam institution experience in a large series of patients aged >75 years with irresectable STS or in-transit melanoma metastases of an extremity. These patients were all treated by ILP with high-dose TNF and melphalan.

PATIENTS AND METHODS

ILP Methodology

We have described the procedure of the current TNF-based ILP previously.[1,2] In brief, isolation of the blood circuit of a limb is achieved by clamping and cannulating the major artery and vein, connecting to an oxygenated extracorporeal circuit, ligating collateral vessels, and applying a tourniquet. Once isolation is secured, drugs can be injected into the perfusion circuit.

Drugs

Recombinant human TNF-α ($4.9–5.8 \times 10^7$ U/mg) was administered at doses of 2 to 4 mg in the perfusion circuit; recombinant human interferon-γ (IFNγ; .2 mg or 1.5×10^6 U/ampoule) was administered in the ILPs performed in the period 1991 to 1993 on days -2 and -1 subcutaneously and on day 0 into the perfusion circuit. Both TNF and IFNγ were obtained from Boehringer Ingelheim GmbH (Ingelheim/Rhein, Germany). Melphalan (L-phenylalanine mustard; Alkeran™; Burroughs Wellcome, London, UK) was obtained as a sterile powder (100 mg) that was dissolved aseptically by using solvent and diluent provided by Burroughs Wellcome (London, UK). Because of its efficacy and low regional toxicity profile, melphalan is the standard drug, most commonly used at a dose of 10 mg/L of perfused tissue for a leg and 13 mg/L for an arm. The perfusate is heated to 39°C to 40°C to achieve mild hyperthermia tissue temperatures in the limbs, to be kept stable at 39°C. Radiolabeled albumen is injected into the extracorporeal circuit so that leakage into the systemic circulation can be detected with a precordial scintillation probe.[15] Leakage monitoring is mandatory, especially now that high doses of TNF are used in the treatment of STS and melanomas. After 1.5 hours of perfusion, the limb is rinsed with an electrolyte solution, cannulas are removed, and the vessels are repaired. Classification of postoperative limb toxicity was performed according to Wieberdink et al.[16]: grade I, no reaction; grade II, slight erythema, edema, or both; grade III, considerable erythema and/or edema with some blistering, slightly disturbed motility permissible; grade IV, extensive epidermolysis and/or obvious damage to the deep tissues, causing definite functional disturbances; threatening or manifest compartmental syndrome; and grade V, reaction that may necessitate amputation.

Patients

At the Erasmus University Medical Center-Daniel den Hoed Cancer Center, 306 TNF-based ILPs were performed in STS patients (224 ILPs) and melanoma patients (82 ILPs) between 1991 and 2001. In 43 patients (14 men and 29 women) older than 75 years, 50 TNF-based ILPs were performed. Twelve patients also received .2 mg of IFNγ subcutaneously on the 2 days before the ILP as well as .2 mg of IFNγ in the perfusion circuit during ILP. All ILP and follow-up data in our institution are recorded prospectively in a database. Patient and ILP characteristics, treatment results, and follow-up data are listed in Table 1 for STS or other nonmelanoma limb-threatening tumors and in Table 2 for melanoma. The mean age of this selected group of patients was 79 years (range, 75–91 years). Twenty-nine patients with irresectable STS or other limb-threatening tumors of the leg (n = 19) or arm (n = 10) underwent 34 ILPs (Table 1). Nineteen were treated for primary tumors and 10 for recurrences. In this group, the median size of single tumors (n = 20) was 10 cm (range, 6–38 cm), and for multifocal tumors (n = 9) it was 5 cm (range, 1–20 cm). Two patients with Stewart-Treves syndrome had undergone three ILPs each. One patient underwent two perfusions. Fourteen patients with in-transit melanoma metastases (all lower extremity) underwent 16 ILPs (Table 2). Two patients underwent two ILPs.

RESULTS

Sarcomas and Nonmelanoma Limb-Threatening Tumors

In the STS group, all patients but two (postoperative deaths) were evaluated for response by magnetic resonance imaging (MRI) and histopathologic evaluation of the tumor resection specimen after response to the ILP.

TABLE 1. *Characteristics of 29 patients with irresectable STS or other limb-threatening tumors at the time of ILP (n = 34) with TNF and melphalan*

Patient No.	Sex	Age (y)	Histology	Grade (1–3)	Site	No. Tumors	P/R	Type of ILP	Local toxicity (Wieberdink) (I–V)	Clinical response	Histological response (% necrosis)	Final outcome	Limb salvage	Dead (D) or alive (A)	Follow-up (mo)
1[a]	F	78	Angiosarcoma	2	Lo arm	>100	R	Brach	2	CR	ND	CR			
	F	80	Angiosarcoma	2	Lo arm	>100	RR	Axil	2	CR	ND	CR			
	F	82	Angiosarcoma	2	Lo arm	>100	RR	Axil	3	PR	ND	PR	Y	D	47
2	F	75	Liposarcoma	1	Lo arm	1	R	Brach	3	CR	ND	CR	Y	A	≥85
3	F	82	Leiomyosarcoma	2	Up arm	1	P	Brach	2	PR	>70	PR	Y	D	57
4	F	82	Mal Fibr Hist	3	Up leg	1	P	Iliac	3	NC	ND	NC	Y	D	6
5	F	83	Liposarcoma	3	Up leg	2	P	Iliac	2	PR	>90	PR	Y	A	≥55
6[a]	F	81	Mal Fibr Hist	2	Lo leg	4	R	Popl	2	NC	ND	NC			
	F	82	Mal Fibr Hist	2	Lo leg	6	RR	Fem	2	CR	ND	CR	N	D	22
7	F	78	Pleiomorfsarc	3	Fos popl	1	R	Iliac	2	NC	ND	NC	N	D	14
8[b]	M	91	Liposarcoma	3	Fos popl	1	P	Iliac	2	ND	ND	ND	Y	D	0
9	F	87	Leiomyosarcoma	2	Foot	1	R	Popl	2	NC	ND	NC	Y	D	8
10	M	76	Leiomyosarcoma	3	Lo arm	1	P	Brach	4	PR	90	PR	Y	A	≥43
11	M	75	Clear cell tumor	3	Up + lo leg	3	R	Iliac	3	CR	100	CR	Y	D	9
12	F	75	Mal Fibr Hist	2	Lo foot	1	R	Fem	3	NC	>90	PR	Y	D	3
13	M	83	Extraskeletal osteosarcoma	3	Up leg	1	P	Iliac	3	NC	90	PR	Y	D	9
14[b]	M	76	Squamous cell	NA	Lo arm	3	R	Axil	4	ND	ND	ND	Y	D	0
15	F	77	Leiomyosarcoma	3	Fos popl	1	P	Popl	2	PR	90	PR	Y	A	239
16[a]	F	77	Angiosarcoma	2	Lo Arm	30	P	Brach	3	CR	ND	CR			
	F	78	Angiosarcoma	2	Up + lo arm	20	R	Axil	2	CR	ND	CR			
	F	80	Angiosarcoma	2	Up + lo arm	>10	RR	Axil	1	CR	ND	CR	Y	A	≥46
17	F	83	Mal Fibr Hist	3	Lo leg	3	R	Popl	2	PR	<50	PR	N	D	26
18	F	76	Angiosarcoma	1	Lo arm	21	P	Brach	3	CR	100	CR	Y	A	≥21
19	M	83	Synoviosarcoma	2	Up leg	1	R	Iliac	2	CR	ND	CR	N	A	≥28
20	F	76	Schwannoma	3	Up leg	1	P	Iliac	-	NC	<50	NC	Y	A	≥26
21	M	79	Schwannoma	3	Lo arm	1	P	Brach	2	PR	<10	PR	Y	A	≥10
22	F	77	Kapos sarcoma	1	Lo leg	30	P	Fem	1	CR	100	CR	N	A	≥18
23	M	81	Mal Fibr Hist	3	Lo arm	1	P	Brach	1	NC	<50	NC	Y	A	≥17
24[b]	M	76	Undifferentiated carcinoma	2	Up leg	1	P	Iliac	2	CR	100	CR	N	D	0
25	M	75	Liposarcoma	3	Fos popl	1	P	Iliac	2	NC	>50	PR	N	A	≥11
26	M	81	Epitheloid sarcoma	3	Lo leg	1	P	Fem	1	PR	>90	PR	Y	A	≥8
27	F	78	Angiosarcoma	1	Total arm	>20	P	Axil	2	CR	ND	CR	Y	A	≥6
28	M	80	Squamous cell	NA	Hand	1	P	Brach	2	PR	ND	PR	Y	A	≥3
29	M	86	Mal Fibr Hist	3	Lo leg	1	P	Fem	2	PR	ND	PR	Y	A	≥3
Mean		79.5										CR 38%	22/29 = 76%		26.0
Median		78										PR 38%			18.0

Up arm, upper arm; Lo arm, lower arm; Up leg, upper leg; Lo leg, lower leg; Fos Popl, fossa poplitea; Fem, femoral ILP; Popl, popliteal ILP; Axil, axilar ILP; Brach, brachial ILP; P, primary; R, recurrence; RR, re-recurrence; CR, complete response; PR, partial response; NC, no change; NA, not applicable; ND, not determined; ILP, isolated limb perfusion; Mal Fibr Hist, malignant fibrous histiocytoma. Overall Response rate is 76% (CR 38%, PR 38%).

[a] These have undergone multiple perfusions.

[b] Patient died after surgery.

CRs were defined as clinical MRI-proven CRs, which were not operated on a second time, and clinical MRI-proven partial responses (PRs) that, after resection, were demonstrated to be 100% necrotic and were classified as histopathologic CRs. PRs were defined as tumors that underwent shrinkage of >50% or, in case of <50% clinical shrinkage, revealed a >50% necrosis on resection. The overall response rate (CR plus PR) was 76%, consisting of 38% CR and 38% PR. No change, defined as <50% tumor shrinkage and <50% necrosis, was seen in 18% of the patients. None of the patients had disease progression within 3 months of the ILP (Table 1).

In the soft tissue patient population, 31% of patients had multiple sarcomas and were not candidates for resections after ILP. In the patients with a single sarcoma, resection was made possible by the induction treatment with ILP and was performed in 16 of 20 patients at a median of 2.5 months after ILP. ILP and surgical treatment resulted in limb salvage in 22 (76%) of 29 patients after a median follow-up of 18 months. Amputation was performed in 7 of 29 patients. In three patients (all with multiple sarcomas in the extremity), repeated ILP was performed after a median of 20 months (range, 13–24 months) after prior ILP. In the sarcoma group, despite

TABLE 2. *Characteristics of 14 patients with in-transit melanoma metastases at the time of ILP (n = 16) with TNF and melphalan*

Patient No.	Sex	Age (y)	Site	No. Tumor	Type of ILP	Local toxicity (Wieberdink) (I–V)	Final outcome	Dead (D) or alive (A)	Follow-up (mo)
1[a]	F	78	Lo leg	>20	Fem	2	CR		
	F	80	Tot leg	>100	Iliac	2	CR	A	≥132
2	F	76	Tot leg	>100	Iliac	2	CR	D	10
3	F	75	Lo leg	>10	Popl	3	CR	D	4
4[ab]	F	82	Lo leg	>20	Popl	2	PR		
	F	83	Lo leg	>100	Iliac	3	CR	D	44
5	F	77	Lo leg	>10	Iliac	2	PR	D	11
6	F	76	Tot leg	>50	Iliac	2	CR	D	45
7	F	75	Lo leg	>50	Iliac	1	CR	D	21
8	F	76	Lo leg	<10	Popl	2	CR	D	16
9	F	80	Tot leg	>10	Iliac	2	CR	A	≥46
10	F	78	Lo leg	>10	Fem	2	CR	A	≥40
11	F	79	Foot	>50	Fem	2	CR	A	≥17
12	F	82	Lo leg	>20	Fem	3	PR	A	≥3
13	M	77	Lo leg	>20	Iliac	3	PR	A	≥3
14	F	91	Lo leg	>100	Fem	2	CR	A	≥3
Mean		78.7					CR 75%		27.0
Median		78					PR 25%		16

Abbreviations: Lo leg, lower leg; tot leg, total leg; Fem, femoral ILP; Popl, popliteal ILP; CR, complete response; PR, partial response; ILP, isolated limb perfusion; TNF, tumor necrosis factor. Overall Response rate is 100% (CR 75%, PR 25%).

[a] Patients who have undergone multiple perfusions (n = 2).

[b] This patient underwent an above-knee amputation of the limb because of arteriosclerosis more than 1 year after the last perfusion.

multiple tumors being present in 31% of the sarcoma patient population, local recurrence–free survival at 2 years was 50%. Despite the median age of 78 years, 50% of all patients were still alive at 4 years.

Patients With Multiple or Bulky Melanoma In-Transit Metastases

In the melanoma patients, an overall response rate of 100% was achieved; this consisted of 75% CR and 25% PR. Therefore, all patients responded, and no stable disease or disease progression was observed. This resulted in a 93% limb salvage at a median follow-up of 16 months. The single amputation in this group (patient 4; Table 2) was not tumor related but was caused by severe arteriosclerosis more than 14 months after the last ILP. Two patients underwent a second perfusion 19 and 25 months after the first ILP. Both resulted in a CR after the repeated ILP. In the melanoma patients, no postoperative deaths occurred. Local progression–free survival in the melanoma population was almost 1 year. Despite the median age of 78 years, 33% of all patients were still alive at 5 years.

Local Toxicity

In 96% of the perfusions, only mild to moderate (Wieberdink grade I–III) local toxicity was observed. In none of the patients did an amputation have to be performed because of TNF- or melphalan-related toxicity after ILP. Only in the patient with a large ulcerating undifferentiated carcinoma metastasis in the upper leg, which became completely necrotic after the ILP and subsequently became infected, did a post-ILP amputation have to be undertaken, because the metastasis was the source of (eventually fatal) sepsis.

Leakage Control and Systemic Toxicity

Leakage Control

The median leakage rate was 0% (range, 0%–20%) in the 50 ILPs described in this series. In the sarcoma group of 34 ILPs, there were 26 ILPs with 0% leakage, 5 with <7% leakage, and 3 with significant leakage of 19%, 20%, and 20%. In the melanoma group of 16 ILPs, there were 10 ILPs with 0% leakage and 3 with <5% leakage. There were three ILPs with significant leakage of 10%, 12%, and 13%. None of these six patients with 10% to 20% leakage experienced grade 3 or 4 hypotension or any other form of grade 3 or 4 toxicity.

Systemic Toxicity

Most patients went through a slightly hyperdynamic postoperative period, which usually lasted 2 to 6 hours, with slightly increased heart rates and temperatures as a reaction to the circulating TNF immediately after the ILP. No major toxicity was observed in the immediate postoperative phase in any of the 43 older patients.

One patient with a history of multiple myocardial infarction and angina pectoris (patient 19; Table 1) developed a postoperative myocardial infarction. The ILP was associated with a leakage rate of 3%, and the postoperative course was associated with grade 2 hypotension.

Except in the patient (patient 8; Table 1) who developed a thrombosis of the mesenteric artery 3 days after the ILP and in the patient (patient 24; Table 1) who developed septic shock because of infection of the massive necrosis of a large ulcerated tumor mass 10 days after the ILP, no grade 2, 3, or 4 toxicity was observed with respect to liver function, renal function, or shock-like symptoms. Temporary mild fever (World Health Organization grade II or III) occurred after 32 of the 50 perfusions.

Complications

In the total series of 306 TNF-based ILPs performed between 1991 and 2001 in the Daniel den Hoed Cancer Center, three patients died from postoperative complications. All three patients were >75 years old. Two patients with a high-risk cardiovascular status and history died because of cardiovascular complications: a 91-year-old patient (patient 8; Table 1) developed a thrombosis of the mesenteric artery 3 days after the ILP, with a fatal outcome. A 76-year-old patient (patient 14; Table 1) with a history of prior cerebrovascular accidents died from a massive cerebrovascular accident on day 3 after an uneventful and leakage-free ILP. A cardiovascular complication also occurred in an 83-year-old patient (patient 19; Table 1). This patient had a history of multiple myocardial infarctions and angina pectoris and developed a postoperative myocardial infarction after yet another well-controlled ILP with a leakage rate of 3% and no significant postoperative hypotension. The third patient who died in the postoperative phase (patient 24; Table 1) developed immediate and total necrosis of a very large ulcerating undifferentiated carcinoma metastasis in the upper leg. This necrotic mass became infected, and the patient developed septic shock. Despite an amputation and optimal medical management, the patient died of sepsis.

DISCUSSION

In elderly people, amputation of a limb has a major effect on their independence and daily activities. However, older patients with irresectable STS or recurrent melanoma of the extremities are often subjected to amputation because the risk of an ILP is considered to be too high. Here we demonstrated that ILP is very efficient in achieving limb salvage and local tumor control in elderly patients, with acceptable morbidity and mortality. In the face of imminent amputation or unacceptable loss of control over locoregional tumor growth in melanoma patients, we have not turned down any patient above the age of 75 years for a TNF-based ILP. Thus, we have accepted the considerable risk associated with this position. Here we report on the largest single-institution experience with the efficacy and risks of TNF-based ILP in elderly patients. Out of 306 TNF-based ILPs, 50 ILPs were performed in this patient population with the goal of avoiding amputation, which more than in any other age group determines the independence and quality of how these patients can continue their lives.

Until several years ago, TNF was thought be inapplicable in a clinical setting because of its severe toxicity when administered systemically. However, in an isolated perfusion setting, it can be used very safely and is extremely efficient in inducing tumor responses when combined with cytostatic agents. We have demonstrated that this extremely potent synergy is based on the selective vasodestruction of the tumor-associated vasculature,[5,17] as well as on the greatly enhanced uptake of melphalan or any other chemotherapeutic drug in the tumor when combined with TNF in the ILP setting.[18,19]

Safe administration of TNF is guaranteed because we use continuous leakage monitoring and adequate hydration of patients. These components are both essential in the management of possible TNF-related toxic side effects.[10] The median leakage during ILP was <0% (range, 0%–20%). Even in cases with leakage, this can be managed very well. We previously described a series of patients with leakage from 12% to 65%. No fatal complications occurred, and only a few shocks were observed, which could be managed without intubation and with little need for vasopressor support.[11] Also in case of leakage, adequate hydration turned out to be the key in the treatment of TNF-related toxicity.

Also, in this group of older patients, ILP can be performed safely, without severe toxicity and morbidity. In this patient group, with a mean age of 79 years, the overall perioperative mortality was low, and the local toxicity was Wieberdink grade II or III in the vast majority of patients. Vrouenraets et al.[20] recently reported on regional toxicity after ILP with TNF and demonstrated that increasing age was not correlated with more severe toxicity. The median hospital stay in this patient population of elderly patients after ILP was approximately 2 weeks. In the postoperative period, most patients were completely mobilized and left the hospital without severe functional impairment.

The response rates and limb salvage percentages were comparable to those in ILP studies in younger STS patients.[1] In melanoma patients, the locally advanced bulky tumors, in particular, may cause such pain, hemorrhage, or vascular compression that amputation of the affected limb sometimes has to be considered. ILP with TNF and melphalan is an effective method to achieve local tumor control and thereby is of great antimorbidity value. It is regarded as the treatment of choice in bulky cases of melanoma or treatment failures after ILP with melphalan alone. The 3 deaths reported in this series are the only 3 postoperative deaths that we encountered in the 306 patients treated with TNF-based ILP in Rotterdam between 1991 and 2001, and this reflects the risks that have been accepted in this patient population. Two patients had extensive cardiovascular disease. The third patient died from sepsis caused by the infection of a totally necrotic massive tumor, which was confirmed to be a histopathologic CR, in the upper leg after ILP. The fact that this rapid tumor had penetrated the skin and was ulcerating should have kept us from performing the perfusion, because there was no way that infection of this necrotic mass could have been prevented. The fact that the complications occurred after leakage-free ILPs further underlines the point that the complications were due to patient-specific risks and not to uncontrolled elements of the ILP. We want to emphasize, however, that adequate experience with the procedure and the status of reference centers for TNF-based ILP are a prerequisite to deal successfully with these patients.

This series of older patients with limb-threatening sarcomas or multiple in-transit melanoma metastases demonstrates the safe and efficient use of TNF-based ILP. It results in high response rates and, thereby, high limb-salvage rates and very good local tumor control rates in both the sarcoma and the melanoma patients. Older patients should be offered and not be withheld a TNF-based ILP for limb salvage.

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