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ORIGINAL ARTICLE – MELANOMAS

20 Years Experience of TNF-Based Isolated Limb Perfusion for In-Transit Melanoma Metastases: TNF Dose Matters

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ABSTRACT

Background. Approximately 5–8% of melanoma patients will develop in-transit metastases (IT-mets). Tumor necrosis factor-α (TNF) and melphalan-based isolated limb perfusion (TM-ILP) is an attractive treatment modality in melanoma patients with multiple IT-mets. This study reports on a 20 years experience and outlines the evolution and major changes since the introduction of TNF in ILP.

Methods. A total of 167 TM-ILPs were performed in 148 patients, between 1991 and 2009. TM-ILPs were performed at high doses of TNF (3–4 mg) from 1991 to 2004 ($n = 99$) and at low doses of TNF (1–2 mg) from 2004 to 2009 ($n = 68$) under mild hyperthermic conditions (38°C–39.5°C.). Melphalan doses were unchanged at 10–13 mg/l (leg and arm, respectively). Characteristics for the 167 ILPs were: 81 stage IIIB, 65 stage IIIC, and 21 stage IV disease.

Results. The overall response rate was 89% ($n = 148$). (Complete response [CR] = 61%; partial response [PR] = 28%). CR rates correlated with stage ($P = .001$) and with high-dose vs. low-dose TNF (70% vs. 49%; $P < .006$). High-dose TNF prolonged local control (median 16 months vs. 11 months; $P = .076$). Survival was not influenced by TNF dose. CR after ILP and number of lesions also correlated with local progression-free interval. Overall survival did correlate with stage of disease ($P < .001$), size of the lesions ($P = .001$), and a CR ($P < .001$).

Conclusions. This 2-decade single-center experience demonstrates that TM-ILP is a safe and effective treatment modality for melanoma patients with multiple IT-mets. Higher dose of TNF was associated with significantly higher CR rates and prolonged local control without an effect on overall survival.

Malignant melanoma incidence is rising rapidly. In 2008 there were approximately 62,000 new cases of primary melanoma in the United States, of which approximately 50% were extremity melanoma.[1] In 5–8% of cases, melanoma patients will develop in-transit metastasis (IT-mets). As regional recurrence often precedes systemic disease, amputative surgery is in general no longer practiced, although old series of radical surgery have demonstrated that some patients with IT-mets confined to the limb can be cured.[2,3] Simple surgical resection may suffice for incidental and low numbers of IT-mets, but in cases of rapid recurrences and multiple IT-mets, isolated limb perfusion (ILP) provides an attractive treatment option that can improve local control markedly and thereby quality of life.

ILP, developed by Creech et al., achieves a 20-fold higher concentration of chemotherapeutic drugs when compared with systemic therapy.[4,5] Melphalan-based ILP (M-ILP) has been the standard treatment and has been reported to achieve overall complete response (CR) rates in the range of about 50%.[6] In general large IT-mets showed a poor response and inhomogeneous uptake comparable with locally advanced soft tissue sarcomas (STS). The introduction of tumor necrosis factor-α (TNF) changed this situation dramatically. Large tumors now reacted very well to ILP.[7] This led to a successful multicenter trial in Europe and the approval of TNF-based ILP (TM-ILP) for irresectable extremity soft tissue sarcomas (STS).[8] Similar

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encouraging results were reported for the use of TNF in ILP for melanoma patients.[9] Preclinical and clinical studies suggested that a reduction of the dose of TNF to 1 mg for the arm and 2 mg for the leg might be as effective as the higher doses.[10–13] Therefore, we changed TNF doses from 4 to 2 mg for ILP of the leg and from 3 to 1 mg for an ILP of the arm starting in 2004. This study reports on our 20-year experience, analyzes the determinants of response and toxicity in patients with multiple melanoma IT-mets of the limb, and outlines the evolution and major changes since the introduction of TNF in ILP.

PATIENTS AND METHODS

Patients

Between 1991 and 2009, 173 ILPs were performed in patients with extensive melanoma IT-mets in the limb. For 5 patients clinical data were insufficient because they came from abroad and did not have adequate follow-up in our center. One patient died 4 days after ILP without any leakage of TNF as a result of a myocardial infarction (mortality: 0.6%). There were 13 patients who underwent ILP twice because of recurrence. Also, 3 patients underwent 3 perfusions. As a result 167 ILPs in 148 patients were included for analysis (Fig. 1).

As a result of publications in literature indicating that in sarcoma patients a lower dose of TNF might be as effective as a high dose, we lowered the dose of TNF in 2004 in our center from 3–4 mg to 2 mg for a lower limb perfusion and from 3 to 1 mg for an upper limb perfusion.[11,14] High-dose TNF perfusions between 1991 and 2004 ($n = 99$) and low-dose TNF perfusions between 2004 and 2009 ($n = 68$) were compared. All demographic data, disease presentation, and ILP characteristics were retrieved from a prospectively maintained database.

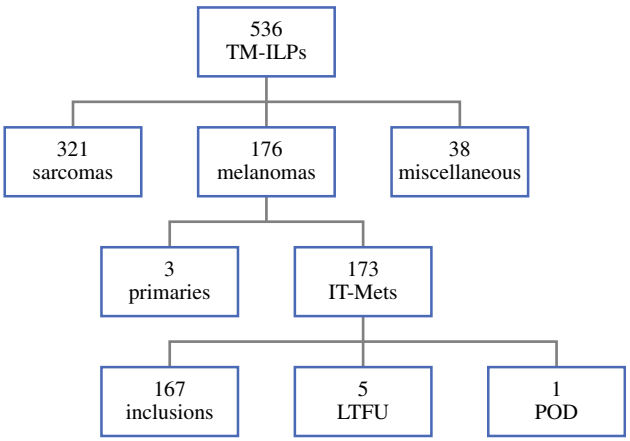

FIG. 1 Inclusion flow chart. *TM-ILP* TNF-based ILP, *IT-Mets* in-transit metastasis, *LTFU* lost through follow-up, *POD* perioperative death

Treatment

The technique of ILP with TNF and melphalan has been described previously.[15,16] Briefly, the procedure is performed with patients under general anesthesia. After heparinization, a targeted blood circuit is isolated by clamping and cannulation of the major artery and vein and connected to an oxygenated extracorporeal circuit. A tourniquet compresses collateral vessels and prevents leakage. Using a precordial scintillation probe to detect technetium-labeled albumen, leakage is monitored for the length of the procedure. The standard dose of TNF in the 1st decade was 3 mg for the arm and 4 mg for the leg. Currently, a dose of 1 mg in the arm or 2 mg in the leg of recombinant TNF-α (Boehringer Ingelheim GmbH, Ingelheim/Rhein, Germany) is injected as a bolus once the temperature of the limb reached 38°C. Subsequently, 13 mg/l (arm) or 10 mg/l (leg) melphalan (L-PAM, Alkeran, Burroughs Wellcome Ltd., London, UK) was administered 30 min after the limb temperature reached 38–39.5°C. The doses of melphalan were not changed during the last 2 decades and have been standardized for more than 40 years. After 90 min of perfusion, the limb is washed out with 1 l (arm) to 4 l (iliac perfusion) of physiological saline solution and 6% dextran (Macrodex Pharmacia, Uppsala, Sweden).

Response and Toxicity

Clinical response was obtained 2–4 weeks and 8 weeks after ILP. Afterwards, follow-up was 3 monthly in the first 2 years after ILP and at longer intervals thereafter. Response rates were defined according to WHO criteria.[17] Toxicity after ILP was classified following Wieberdink et al.[18]

Statistical Evaluation

Overall survival (OS) and time to local or systemic progression (TLP/TSP) were defined as time between ILP and death, local progression, or systemic progression, respectively. The end of follow-up was defined as the last visit to the outpatient clinic. On January 1, 2011 the community death register was consulted to determine OS. Estimates were drawn using the Kaplan-Meier method.[19]

Prognostic value of baseline factor as used in previous literature was evaluated for 3 endpoints (TLP/TSP/OS) using Cox regression and was expressed in hazard ratios.[16,20–28] Prognostic value of the same factors for CR was determined using logistic regression and analogously

expressed in odds ratio. Multivariate analysis was performed with all factors that reached 10% significance in univariate analysis. A stepwise backward algorithm was used to exclude factors without significant prognostic value. To compare baseline factors within the 2 groups a *t* test was used. All tests were done at a significance level of 5%.

RESULTS

Patients

In total, 167 TM-ILP were analyzed in 148 subsequent patients. Median age of patients was 65 years (range, 25–93); 103 patients (70%) were female. Median follow-up was 20 months (range, 1–130). Disease staging was according to the AJCC staging system, which resulted in 81 cases (48%) with stage IIIB, 65 cases (39%) with stage IIIC, and stage IV in 21 cases (13%).[29] All demographic, disease presentation, and ILP characteristics are summarized in Table 1. Most remarkable evolutions on characteristics over time were a shift toward older patients ($P = .030$), shorter period between diagnosis and TM-ILP ($P = .001$), and smaller lesions ($P = .016$).

Treatment

Patients underwent ILP via the axillary ($n = 7$, 4%), iliac ($n = 85$, 51%), and femoral ($n = 75$, 45%) approach. A significant shift from an iliacal approach to a femoral approach was observed in the later years, ($P = .003$, Table 2). Hospital length of stay decreased for every perfusion type (Table 2).

Response Rate and Limb Function

An overall response rate of 89% ($n = 148$) was observed. In 102 cases (61%) a CR was recorded, 46 patients (28%) had a partial response (PR), and 19 (11%) had no change (NC). Patients treated with a high-dose TM-ILP had a CR rate of 70% compared with a CR rate of 49% for those treated with a low-dose TM-ILP ($P = .006$). A CR was significantly more often observed in patients with stage IIIB disease (77%) compared with patients with stage IIIC or IV disease, 49% vs. 38%, respectively (IIIB vs. IIIC, $P = .002$; IIIB vs. IV, $P = .003$; IIIC vs. IV, P 0.45). In multivariate analysis TNF dose, stage of disease, and age remained significant prognostic factors for CR (Table 3).

Limb function was assessed in all 148 patients, which resulted in perfect function in 118 cases (80%), loss of function without the necessity of using crutches in 15 cases (10%), and 4 cases (3%) of severe limb function loss necessitating crutches. In 2 patients (1.5%) an amputation was necessary because of post-ILP locoregional toxicity (Wieberdink grade V). In 8 patients (6%) an amputation was necessary because of uncontrollable ulcerating locoregional tumor recurrences ($n = 8$), In 1 patient an

TABLE 1 Patient and tumor characteristics

	High-dose (1991–2004)	Low-dose (2004–2009)	Total (1991–2009)	*P* value
Sex				
Female	62 (71%)	41 (67%)	103 (70%)	.598
Male	25 (29%)	20 (33%)	45 (30%)	
Age				
<65 years	55 (56%)	26 (37%)	81 (49%)	.030
≥65 years	44 (44%)	42 (63%)	86 (51%)	
Location primary				
Arm	3 (3%)	2 (3%)	5 (3%)	.737
Leg	47 (54%)	40 (67%)	87 (59%)	
Foot	29 (34 %)	16 (26%)	45 (31%)	
Back	4 (5%)	2 (3%)	6 (4%)	
Unknown primary	3 (3%)	1 (1%)	4 (3%)	
Missing	1	–	1	
Breslow				
Median in mm (range)	2.89 (0.6–15.0)	3.00 (0.7–11.0)	2.97 (0.6–15.0)	.579
Missing	25 (29%)	12 (20%)	37 (25%)	
Primary to IT-mets				
≤1 year	30 (36%)	31 (52%)	61 (43%)	.052
>1 year	53 (64%)	28 (48%)	81 (57%)	
Missing	4	2	6	
Time between IT-mets and ILP				
≤6 months	41 (42%)	46 (69%)	87 (53%)	.001
>6 months	57 (58%)	21 (31%)	78 (47%)	
Missing	1	1	2	
Location				
Arm	4 (4%)	3 (4%)	7 (4%)	.906
Leg	95 (96%)	65 (96%)	160 (96%)	
Number of lesions				
<10	41 (41%)	37 (54%)	78 (47%)	.098
≥10	58 (59%)	31 (46%)	89 (53%)	
Size largest				
<40 mm	53 (53%)	49 (72%)	102 (61%)	.016
≥40 mm	46 (47%)	19 (28%)	65 (39%)	
AJCC stage				
IIIB	46 (47%)	35 (52%)	81 (48%)	.706
IIIC	39 (39%)	26 (38%)	65 (39%)	
IV	14 (14%)	7 (10%)	21 (13%)	
Prior treatment				
None	59 (60%)	56 (82%)	115 (69%)	.019
ILP	17 (17%)	8 (12%)	25 (15%)	
RTx	3 (3%)	2 (3%)	5 (3%)	
CTx	9 (9%)	–	9 (5%)	
Immuno	4 (4%	1 (2%)	5 (3%)	
Combination	7 (7%)	1 (2%)	8 (5%)	

ILP isolated limb perfusion, *RTx* radiotherapy, *Ctx* chemotherapy, *Immuno* immunotherapy

TABLE 2 Treatment characteristics

	High dose (1991–2004)			Low dose (2004–2009)			Total (1991–2009)			*P* value
Type of ILP										
Axillary	4 (4%)			3 (4%)			7 (4%)			.003
Iliacal	61 (62%)			24 (35%)			85 (51%)			
Femoral	34 (34%)			41 (60%)			75 (45%)			
	Ax	Il	Fem	Ax	Il	Fem	Ax	Il	Fem	
Dose (mg)										
Median melphalan	46	110	60	40	98	60	42	110	60	
Hospitalization										
Median days	14	11	10	5	8	6	10	10	8	

Ax axillar, *il* iliacal, *fem* femoral, *ILP* isolated limb perfusion, *TNF* tumor necrosis factor α

amputation was necessary for arthrosclerosis despite a CR. In case of amputation, median time span between first ILP and amputation was 17 months (mean 19, range 2–32).

Local Progression

Local progression after ILP occurred in 56% of cases (n = 93) after a median time of 13 months. Although not significant, a trend towards better local control could be observed in the high dose TM-ILP group. Median time to local progression (TLP) was 16 months after high dosed TM-ILPs while those treated after TNF dose reduction showed a median TLP of 11 months ($P = .076$, Fig. 2c). Patients with a CR after ILP had a significantly longer median TLP of 19 months, whereas a PR or NC resulted in a median TLP of 6 months ($P < .001$). Patients treated for ≥10 lesions had a shorter TLP compared with those with <10 lesions. (9 vs. 24 months, respectively, $P = .002$). CR after ILP and number of lesions remained significant prognostic factor for local progression in multivariate analysis (Table 3).

Systemic Disease

Patients treated with curative intent (stage IIIB and IIIC, $n = 146$) developed systemic disease (stage IV) in 79 cases (54%) with a median time to systemic progression (TSP) of 26 months. Patients with a CR had a median TSP of 39 months, whereas patients with PR or NC showed a median TSP of 11 months ($P < .001$). Female sex ($P < .001$), the size of the largest lesion ($P = .002$), and stage of disease ($P < .001$) were baseline factors reaching significance in univariate Cox regression analysis. Sex, size, stage of disease, and response to ILP remained significant prognostic factors for TSP in multivariate analysis. The dosage of TNF was not of influence on TSP ($P = .236$). Once patients developed systemic disease, median survival time was 7 months.

Survival

The overall actuarial 3-year, 5-year, and 10-year survival rates after ILP were 40% (±4%), 26% (±4%), and 13% (±3%), respectively; median OS was 24 months. CR after perfusion resulted in a prolonged median OS of 44 months, while patients with PR or NC had a median survival of 11 months (Fig. 2a, $P < .001$). When data were stratified for stage of disease, 5-year survival was 42% for stage IIIB disease, 15% for stage IIIC disease, and 0% for stage IV disease (Fig. 2b, $P = .001$). In univariate regression analysis, female sex ($P < .001$), age ($P = .004$), a primary on the limb ($P = .009$), Breslow thickness ($P = .003$), small size of IT-mets ($P < .001$), and long interval between diagnosis of IT-mets and perfusion ($P = .003$) appeared to be other favorable prognostic factors correlated with prolonged survival. In multivariate analysis age, small size, lower stage of disease, and complete response after ILP remained significant prognostic factors for prolonged survival. Analogously to time to systemic progression, dose of TNF was not associated with OS ($P = .272$, Fig. 2d). All hazard ratios are summarized in Table 3.

Body Mass Index

Patients with a body mass index (BMI) > 30 had a CR rate of 63% ($n = 19$), which is similar to the CR rate of 60% for those with a BMI of ≤30 ($P = .78$). Median TLP was 13 months for patients with a BMI ≤ 30, while patients with a BMI > 30 had a median TLP of 12 months ($P = .82$). In univariate analysis, BMI as prognostic baseline factor did not reach significance for clinical outcome, nor for TLP, TSP, or OS.

Leakage and Toxicity

Local toxicity was not observed (Wieberdink I) in 31 cases (18%), slight (Wieberdink II) in 93 cases (56%),

TABLE 3 Analysis of prognostic factors for CR, local progression, systemic disease, and OS

Variable	CR		Local progression		Systemic disease		Overall survival	
	Univariate OR (*P*)	Multivariate OR (*P*)	Univariate HR (*P*)	Multivariate HR (*P*)	Univariate HR (*P*)	Multivariate HR (*P*)	Univariate HR (*P*)	Multivariate HR (*P*)
Sex								
Female[a] vs. male	0.56 (.088)	–	1.01 (.951)	–	**2.48 (<.001)**	**1.83 (.022)**	**1.97 (<.001)**	–
Age								
<65 vs. ≥65 years	**0.51 (.039)**	**0.49 (.047)**	1.36 (.147)	–	1.27 (.296)	**–**	**1.71 (.004)**	**1.52 (.031)**
BMI								
≤30[a] vs. >30	1.16 (.725)	–	1.04 (.886)	–	1.06 (.851)	–	1.22 (.403)	–
Location of primary	0.82 (.562)	–	0.88 (.561)	–	1.50 (.094)	–	**1.68 (.009)**	–
Limb[a] vs. acra vs. else	0.71 (.590)		0.73 (.534)		2.79 (.053)		**2.30 (.030)**	
Breslow thickness (in mm.)	0.93 (.347)	–	1.04 (.344)	–	1.08 (.189)	–	**1.12 (.003)**	–
Interval prim vs. IT-mets								
≤1[a] vs. > 1 year	0.96 (.893)	–	0.80 (.298)	–	1.47 (.111)	–	0.90 (.548)	–
Location of lesions	1.11 (.770)	–	1.06 (.809)	–	1.37 (.327)	–	1.24 (.330)	–
Total[a] vs. lower vs. upper	0.57 (.266)		0.94 (.846)		0.94 (.826)		1.37 (.285)	
Number of lesion								
<10[a] vs. ≥10 lesions	0.87 (.666)	–	**1.77 (.002)**	**1.84 (.005)**	0.92 (.697)	–	0.86 (.418)	–
Size of largest lesion								
<4[a] vs. ≥4 cm	0.75 (.380)	–	0.79 (.288)	–	**2.01 (.002)**	**1.76 (.023)**	**2.19 (<.001)**	**2.16 (<.001)**
AJCC stage of disease	**0.30 (.001)**	**0.23 (<.001)**	1.47 (.075)	–	**2.74 (<.001)**	**1.95 (.010)**	**2.32 (<.001)**	**1.64 (.020)**
IIIB[a] vs. IIIC vs. IV	**0.19 (.001)**	**0.13 (<.001)**	0.71 (.430)				**4.46 (<.001)**	**2.58 (.002)**
Prior ILP	1.35 (.463)	–	1.05 (.855)	–	0.87 (.628)	–	0.72 (.156)	
no[a] vs. yes								
Interval IT-mets vs. ILP	1.72 (.094)	–	1.02 (.925)	–	**0.62 (.041)**	–	**0.57 (.003)**	–
≤6[a] vs. > 6 months								
Period of ILP								
1991–2004[a] vs. 2004–2009 (high[a] vs. low)	**2.44 (.006)**	**2.57 (.010)**	0.70 (.084)		1.36 (.236)	–	0.81 (.280)	
CR achieved								
No[a] vs. yes	NA	NA	**0.34 (<.001)**	**0.32 (<.001)**	**0.46 (.001)**	**0.53 (.018)**	**0.29 (<.001)**	**0.35 (<.001)**

CR complete response, *OS* overall survival, *ILP* isolated limb perfusion, *TNF* tumor necrosis factor α, *NA* not applicable

[a] Reference group

Bold values reached significance ($P < 0.05$)

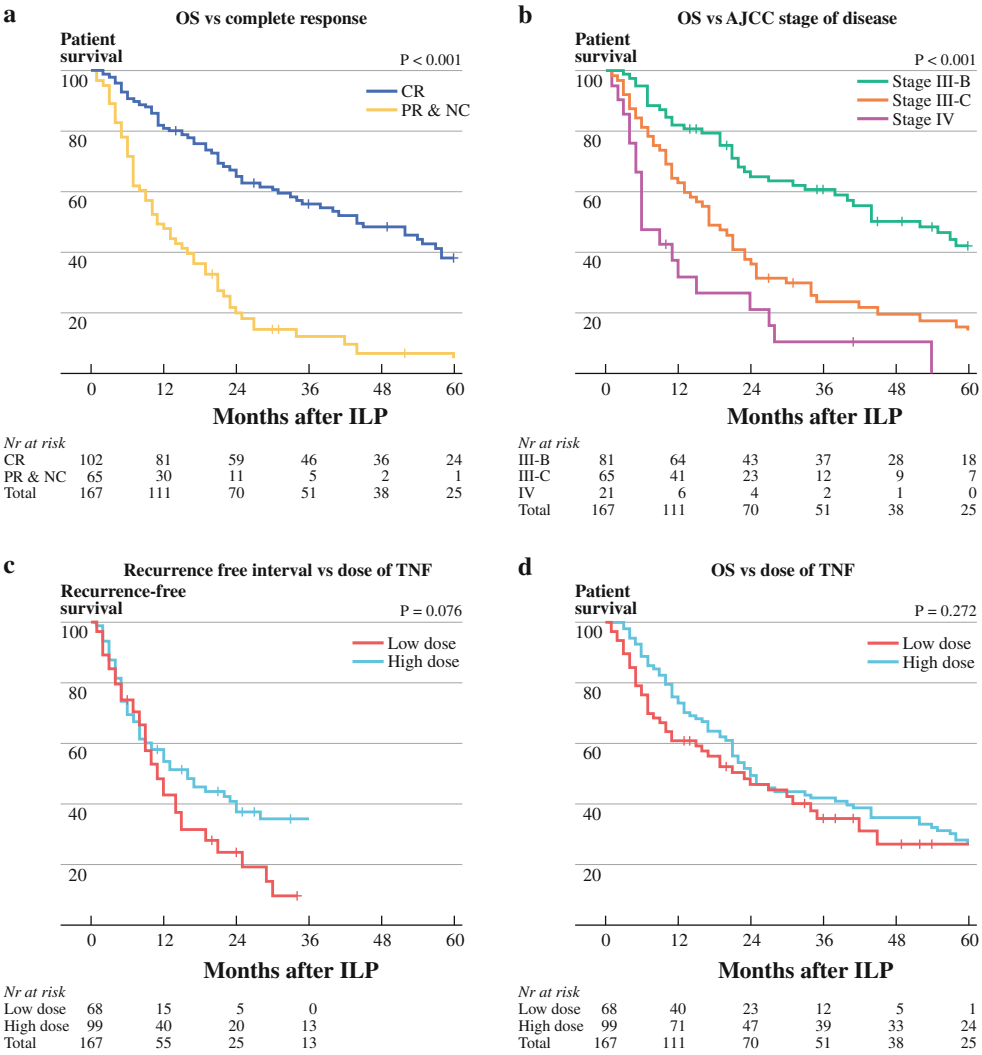

FIG. 2 **a** OS vs. complete response. **b** OS vs. AJCC stage of disease. **c** Recurrence-free interval vs. dose of TNF. **d** OS vs. dose of TNF. *OS* overall survival, *CR* complete response, *PR* partial response, *NC* no change, *TNF* tumor necrosis factor α, *ILP* isolated limb perfusion

considerable (Wieberdink III) in 38 cases (23%), and severe (Wieberdink IV) in 3 cases (2%). Amputation due to perfusion reaction was necessitated for 2 patients (1%), one after 2 months, the other after 6 months. The dose of TNF could not be identified as significant predictor for local toxicity ($P = .524$).

There was no or minor leakage (≤10%) in 160 ILPs (96%), median leakage was 0% (mean, 1.34; range, 0–25). Leakage was >10% in 7 patients of which 1 patient with 12% systemic leakage had a myocardial infarction 2 days after ILP; after referral to a cardiac department this patient was stabilized, had no further complications, and was discharged from hospital after 8 days. There were 2 other patients who experienced transient hypotension treated with vasopressors. Also, 1 patient had a grade IV leucopenia that lasted for 1 day, which did not need any intervention. There were 3 patients who did not experience any inconvenience of the >10% systemic leakage.

DISCUSSION

With an overall response (OR) rate of 89% and a CR rate of 61%, the present study demonstrates that TM-ILP is a successful treatment modality in obtaining local control of the limb in patients with melanoma in-transit metastases. Local and systemic toxicity is limited, which emphasizes the safety of this procedure. The reduction of the dose of TNF was associated with a lower CR rate.

The introduction of TNF ushered in a new era for ILP in Europe. The present study reported on the evolution observed over the past 2 decades. The most remarkable change was the dose reduction of TNF based on several previous studies describing comparable response rates with reduced local toxicity.[10,11,13,14] In the present series, a CR was more often observed in the period of high dose TM-ILPs. In multivariate analysis this difference remained significant.

The lowering of the dose of TNF not only led to inferior clinical response, but to an inferior local control as well. This was emphasized by the fact that there were no cases of maintained local control after 3 years in the low-dose TNF group (Fig. 2c). There was no significant correlation between the dose of TNF and systemic progression or OS. These findings fit in the concept of a locoregional treatment having locoregional benefit only. In our opinion, CR after TM-ILP occurs in patients with the more favorable biology, which allows a similar effect after low-dose perfusions.[16] Patients with more unfavorable biology might experience more often a CR and prolonged local control after high-dose perfusion compared with low-dose perfusion. However, systemic development and overall survival are dictated by the biology of the tumor, which explains that despite lower response rates and inferior local control low-dose perfusions show similar TSP and OS. This is illustrated in Fig. 2c and d.

The dose reduction of TNF in ILP for melanoma patients was mainly based on data in sarcoma patients. Our group published in 2005 a mixed series of sarcoma and melanoma patients with only 16 melanoma patients who received low-dose TNF.[14] Rossi et al. described a series of 20 low-dose perfusions in melanoma patients.[13] The low numbers of patients might explain why these studies did not find the correlation between dose of TNF and CR rate and local control. Our series is one of the largest in the world with a mature follow-up, and therefore the outcome might be different compared with our previous, smaller series.

There is no consensus in the literature about the benefit of using TNF in ILP for IT-mets in melanoma patients. Cornett et al. performed the only randomized controlled trial so far in which they report an increased local and systemic toxicity without any beneficial effect in clinical response (CR rate 26% for TM-ILP vs. CR rate 25% for M-ILP).[30] This study was subject of several criticisms, so their conclusions should be read with caution.[31] First of all, they reported complete response rate after 3 months, which is an uncommon endpoint since a substantial proportion of patients reach CR between 3 and 6 months. Secondly, there was very little data provided concerning differences between patients and tumor characteristics between both arms. Thirdly, the true indication for TNF-based ILP, bulky disease was not analyzed.

Alexander et al. reported recently the long-term follow-up results of a mixed TM-ILP and M-ILP series.[20] They did not identify a significant correlation between the addition of TNF to M-ILP and infield progression, which might be explained by the lower number of patients included in this study. The reported CR rate of 69% is slightly higher compared with ours in a more favorable patient population (68% stage IIIA disease in their group vs. 48% in the present study). Rossi et al. reported a CR rate of 60% for TM-ILP and 42% for M-ILP, which was a significant difference ($P = .05$).[32] With the correlation between CR rate and local control on one hand and the dose of TNF on the other, the present study emphasizes the important role of TNF in ILP for melanoma patients.

Certainly in bulky disease TNF is of additional value. Melphalan uptake is very low in large tumors, which can be improved by a 3- to 6-fold with the use of TNF.[33] Consequently, we consider TM-ILP indicated for patients with bulky disease and those resistant for M-ILP. When disease load is limited, melphalan-only based ILP might be effective in achieving local control.[34,35] In cases of small lesions restricted to the distal parts of the limb, isolated limb infusion with melphalan can be of value.[36] Literature suggests that reduction of duration of TM-ILP has no influence on either clinical response or local control.[37] However, these results are achieved in soft tissue sarcoma patients and should be investigated in an IT-mets melanoma study population.

A variety of treatment modalities for IT-mets have been used with various successes. If lesions are limited in number and size, simple surgical excision is the preferred treatment modality. Smaller lesions too numerous for excision were treated with carbon dioxide laser therapy, intralesional injections, and electrochemotherapy, but all with poor clinical response rates.[38–44] After decades of failing to identify effective systemic therapy, there are promising results achieved with PLX4032 and ipilimumab in patients with stage III and IV disease. PLX4032 (vemurafenib) provides a rather limited PFS of only 5.5 months in irresectable stage III–IV disease and ipilimumab a response rate of only about 10%, so the role of ILP remains established while that of these new drugs in the treatment for IT-mets is still unclear.[45–47]

TNF increases the efficacy of ILP. We demonstrated that high doses of TNF are correlated with higher CR rates and superior local control in patients with high tumor burden and those having failed previous therapy. Since the main objective of TM-ILP in melanoma patients is obtaining local control, rather than improving survival, high-dose TNF perfusions seem preferable to low-dose TNF perfusions.

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