Tumour response after hyperthermic isolated limb perfusion for locally advanced melanoma

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ABSTRACT

INTRODUCTION: The aim was to describe tumour response, complications, recurrence and survival after hyperthermic isolated limb perfusion (ILP) with melphalan or melphalan in combination with tumour necrosis factor-alpha in patients with melanoma metastases confined to an extremity.

MATERIAL AND METHODS: A total of 84 perfusions were performed (53 women, 31 men, median age 63 years) from 1993 to 2010. 95% of the perfusions were administered to the lower limbs and 5% to the upper limbs. The inclusion criteria were recurrent and/or clinically apparent cutaneous/subcutaneous extremity in-transit melanoma metastases.

RESULTS: The response rate after ILP was 85%; 42% had complete response (CR), 43% partial response (PR), 12% no change (NC) and 3% progression. Two- and five-year survival rates were 57% and 31%, respectively, and they were higher for patients with than without lymph node metastases. Time from ILP to recurrence was a median of seven months (range 1-37 months) for patients with CR or PR. Survival was longer for patients with CR or PR than for patients showing NC or progression. Several patients had mild or moderate local toxicity reactions, two patients developed severe local toxicity.

CONCLUSION: ILP induces tumour regression in the vast majority of patients. One patient, i.e. 1% of the group, died from surgical complications. Otherwise, ILP treatment had an acceptable morbidity in this group of very sick patients. We are convinced that the treatment should be offered to improve local disease control in patients with multiple and/or recurrent melanoma confined to an extremity if surgical excision is not possible.

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The annual incidence of melanoma is around 1,800 in Denmark with a population of about 5.5 million, and the incidence has shown a marked increase over past decades. Approximately 5-8% of the patients with high-risk primary melanoma (Breslow thickness > 1.5 mm) will develop in-transit metastases [1] which are defined as cutaneous or subcutaneous metastases at a distance of > 2 cm from the primary tumour, but not beyond the regional lymph nodes. They are difficult to treat surgically, and former use of amputation did not improve survival [2]. In an attempt to improve survival and save the patients from devastating amputations, ILP was introduced in 1958 [2-4].

Presence of regional lymph node metastases at the time of isolated limb perfusion (ILP) is a key prognostic factor and has a negative impact on survival [5]. The concept of ILP consists of isolation of an extremity with connection to an extracorporeal circulation. This allows regional administration of cytotoxic drugs at up to 25 times the systemically tolerable concentration [1, 5] with minimal systemic side effects. The drug of choice is melphalan (L-phenylalanine mustard) alone or together with tumour necrosis factor (TNF)-alpha [6]. TNF-alpha has a vasculotoxic effect, increases the uptake of melphalan and is especially useful in bulky tumours. ILP is usually performed under mild hyperthermic conditions with muscle and subcutaneous temperatures kept between 38 and 40 °C. True hyperthermia (42-43 °C) causes severe damage to normal tissues and only yields a marginally increased therapeutic effect and should therefore be avoided [7]. The combination of hyperthermia and cytostatic drugs has been shown to have a synergistic effect on the tumour response [1, 8-10].

The purpose of the present analysis was to study the clinical value of ILP in patients with locally advanced melanoma in an extremity. All patients were treated at the Department of Plastic Surgery, Copenhagen University Hospital (Rigshospitalet).

The study was approved by The Danish Data Protection Agency.

MATERIAL AND METHODS

Patients

Between 1993 and 2010, 84 patients (53 women and 31 men, with a median age of 63 years, range 20-82 years) were treated with ILP for locally advanced melanoma. The inclusion criteria were recurrent and/or clinically apparent, cutaneous or subcutaneous melanoma metastases distal to the regional lymph nodes on the limb (American Joint Committee on Cancer (AJCC) stage IIIA-C [11]). All patients were perfused for ≥ 30 minutes.

The number of visible metastases at the time of perfusion varied between one and ≥ 4 (**Table 1**). Some patients had regional lymph node metastases. The exact

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TABLE 1

Patients and isolated limb perfusion procedures.

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Patients (women/men)	84 (53/31)
Location of primary tumour: upper/lower extremity	4/80
No. metastases: 1-3/≥ 4	22/62
ILP procedures: axillary/iliac/femoral	4/75/5
Melphalan only/melphalan + TNF-alpha	76/8

ILP = isolated limb perfusion; TNF = tumour necrosis factor.

TABLE 2

Post-operative complications following isolated limb perfusion according to the Wieberdink classification [12].

Grade	
I	No subjective or objective evidence of reaction
II	Slight erythema and/or oedema
III	Considerable erythema and/or oedema with some blistering Slightly disturbed motility permissible
IV	Extensive epidermolysis and/or obvious damage to the deep tissues causing definite functional disturbances Threatening or manifest compartmental syndrome
V	Reaction which may necessitate amputation

tumour volume was not determined, as tumour volume was only assessed by clinical examination. Preoperative evaluation included physical examination and imaging to exclude distant metastases (chest X-ray or computed tomography (CT); abdominal ultrasound or CT; brain CT; in the more recent years, also whole body fludeoxyglucose – positron emission tomography (FDG-PET /CT).

The patients were closely monitored for a minimum of 24 hours post-operatively, including assessment of local (Wieberdink's criteria, cf. **Table 2**, [12]) and systemic toxicity (WHO criteria [13]: body temperature, blood pressure and blood chemistry). Tumour response according to the WHO´s criteria was prospectively registered at an out-patient visit after four weeks: complete response (CR) was defined as full tumour regression, partial response (PR) as ≥ 50% regression, no change (NC) as 0-49% regression, and progression as an increase in the number or growth of limb metastases [13]. Seven patients were reperfused (five patients twice and two patients thrice). All reperfusions were carried out later than four weeks, when the out-patient clinical control was performed. The effects and complications and time to death in those seven patients were only registered once for each patient in the present analysis, i.e. after their first ILP perfusion.

The patients were followed in our department for a varying amount of time, depending on the clinical course. In a few patients, repeated ILP procedures were performed. Systemic chemotherapy may have been given to a few patients in the local hospital in which the patients were followed in their terminal phase, but this was not registered.

Survival was calculated from data attained from patient records and data prospectively registered in the Danish Melanoma Group database as well as from the Danish Register of Cause of Death.

Perfusion procedure

ILP was performed in general anaesthesia by a specialised team (anaesthesiologists, surgeons, nuclear medicine physicians and perfusion specialists).

The axillary, iliac, femoral or popliteal vessels were cannulated and clamped and then connected to a cardiopulmonary pump. The surrounding vessels were ligated and a tourniquet applied around the extremity to isolate the limb from the systemic circulation to prevent leakage. Leakage to the systemic circulation was monitored with a gamma probe over the precordial region. Ten MBq of ^{99m}Tc-labelled, autologous red blood cells or ^{99m}Tc-labelled human serum albumin was injected into the systemic circulation for background measurement; and 110 MBq of the same tracer was added to the perfusate. Because of a high risk of severe systemic toxicity, perfusion was terminated if an activity increase over the precordial region indicated leakage of ≥ 10% [14]. Melphalan alone was used in patients with multiple melanoma metastases, but given in combination with TNF-alpha in re-perfusions and to patients with bulky tumours. The latter because a low uptake of melphalan in large tumors can be improved 3-6 fold with the use of TNF-alpha [1, 5, 15, 16], which also has an antitumour effect [5, 14].

Subcutaneous and muscle tissue temperature was kept constant at 38-40 °C, and the temperature was continuously monitored by heat sensors. When the target temperature (> 38 °C) was achieved, the cytostatic drug(s) was added after heparinisation: A bolus of melphalan was injected into the extracorporeal circulation and circulated for 60 minutes, (until January 2002 calculated as 1 mg/kg bwt, from 2002 as 10 mg/l perfusate). TNF-alpha was injected before melphalan administration as a bolus into the extracorporeal circulation and circulated for 30 minutes. The TNF-alpha dose was 3 or 4 mg (upper or lower extremities). Before disconnecting the system, the agents were washed out with a physiological saline solution. If it had not been done previously, complete regional lymph node dissection was performed before ILP.

No patient had more than minor leakage (≤ 10%) during the perfusion. Twelve perfusions were terminated ahead of schedule (between 30-60 minutes) because of increasing leakage after 30 minutes.

Trial registration: not relevant.

RESULTS

Response rate: The positive response rate after four weeks was 85%, 12% had NC, and progression despite treatment was observed in 3%. In 76 cases, ILP was performed with melphalan alone, in eight cases a combination with TNF-alpha was used.

Complications within four weeks: One patient died from surgical complications (retroperitoneal haematoma) two days after ILP.

Local toxicity was mild in the majority of patients: No or slight (Wieberdink I and II, cf. Table 2) toxicity occurred in 44% and 43%, respectively, considerable toxicity in 11% (Wieberdink III), and severe toxicity only in 3%: Two patients developed compartment syndrome after ILP (Wieberdink IV), but recovered after surgical decompression. Other local complications included: seroma (1%), wound infections (18%), subcutaneous haematoma (2%) and deep venous thrombosis (1%). No patients showed clinical signs of systemic toxicity.

Limb function was assessed after four weeks. In general, the adverse events were mild and limited to the perfused extremity: oedema (32%), paraesthesia (13%), pain (7%) and hyper-pigmentation of the perfused limb (7%). None had loss of limb function.

Long-term follow-up: The median follow-up time was 65 months (range 21-218 months). A total of 47 patients died from melanoma, seven from other causes and four without registration of a specific cause of death. The remainder (26 patients) were still alive after five years (**Figure 1**).

Recurrence-free survival (**Table 3**) from the time of ILP was a median of seven months for patients with CR and PR. Survival (Table 3) was a median of 17 months with wide ranges (0-185 months), a little longer in responders, and much shorter but with fairly wide ranges in patients with NC or progression. The two- and five-year survival rates (Table 3) after ILP were 57% and 31%, respectively. Twenty-two patients died in the period between two and five years after ILP. Survival rates were markedly longer for patients without lymph node metastases than for patients with lymph node metastases.

FIGURE 1

Patient flow over five years.

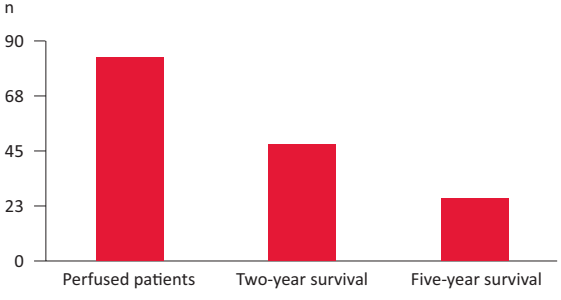


TABLE 3

Long-term outcome after isolated limb perfusion.

	Survival, months, median (range)						
	recurrence free	total	2-year survival, %	5-year survival, %	CR, %	PR, %	NC + PRO, %
All patients	5 (0-37)	17 (0-185)	57	31	42	43	15
CR	7 (3-37)	22 (8-51)	–	–	–	–	–
PR	7 (1-28)	21 (5-185)	–	–	–	–	–
NC or PRO	1 (0-4)	9 (0-40)	–	–		–	–
– LN MET	–	–	74	60	–	–	–
+ LN MET	–	–	37	30	–	–	–

CR = complete response; LN = lymph node; MET = metastasis; NC = no change; PR = partial response; PRO = tumour progression.

DISCUSSION

This analysis confirms previous reports showing a marked and comparable effect on local tumour control after ILP in patients with locally advanced melanoma in an extremity [5, 15]. An overview of existing ILP studies (mixed series) shows a CR rate of 40-76% and 44-90% in patients treated with melphalan only or melphalan and TNF-alpha combined, respectively [5].

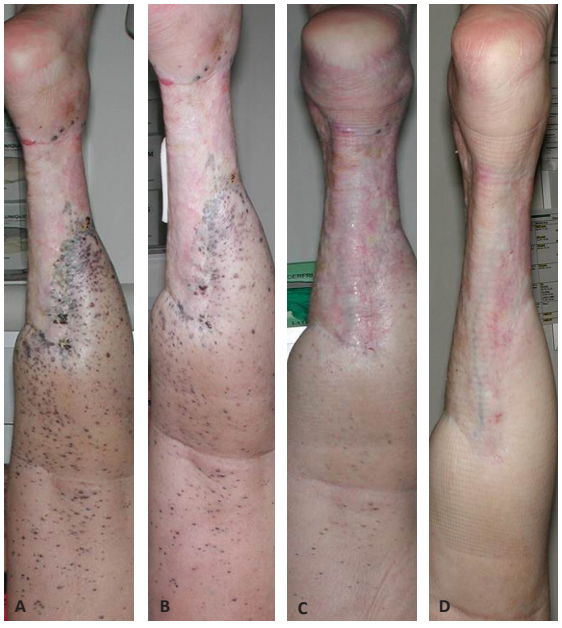
Survival and recurrence-free survival were comparable to those reported in other studies and longest in CR and shortest in patients with NC or progression. The presence of lymph node metastases was also associated with shorter survival [17].

Acute complications were frequent, but mostly mild or moderate, they were local, related to surgical or cytotoxic effects, and they occurred in the first weeks after ILP. One patient died shortly after operation from a retroperitoneal haematoma, probably a complication to the cannulation procedure. In two patients, a post-operative fasciotomy was needed. The fairly high number of complications must be considered in relation to the very serious prognosis in these patients who have a history of multiple, loco-regional metastases of melanoma. Chronic, local complications included lymphoedema, paraesthesia and pain. Lymphoedema is believed to be mainly related to lymph node dissection, especially in the groin [18].

Our analysis shows – as the first in the Nordic countries – that ILP appears to have a very convincing effect on local tumour regression already after four weeks, even despite of the fact that the onset of anti-tumour effect is rather slow in many or most cases, in particular for TNF-alpha, and in spite of the fact that the effect of the treatment increases over the following 3-6 months, as shown in **Figure 2**. The tumour reduction may there-

FIGURE 2

Two and a half years after isolated limb perfusion (ILP), no metastases were visible in the perfused limb. Gradual reduction of pigmentation and softening of the metastases were observed in the first 18 months before ILP. **A.** Before ILP. **B.** Three months after ILP. **C.** 18 months after ILP. **D.** Two and a half years after ILP.



fore be underestimated in this study with only a four-week evaluation period of tumour response. On the other hand, in a few patients, disease progression may have counterbalanced a delayed onset of an anti-tumour effect.

Without a control group, the effect on survival cannot be evaluated. We observed a longer survival in patients without lymph node metastases, and survival was also related to the four-week tumour reduction after ILP, which confirms the findings of previous studies [17].

ILP is a technically demanding intervention that must be performed in institutions with a high level of cross-disciplinary expertise. Due to a lack of controlled studies, the effect on survival cannot be evaluated. However, the outstanding antitumor effect (Figure 2), i.e. 50-100% local tumour reduction in the vast majority of patients, may be hypothesised to lead to improved quality of life and possibly to prolonged survival.

Limitations of the study

The lack of an evaluation of the tumour response later than at four weeks is an obvious limitation, and the evaluation only included a clinical assessment, which is subject to considerable bias. However, the classification of tumour reduction of less than 50% as "no change" should be a safe limitation for uncertain changes being mis-classified as "partial regression". We therefore believe that a reduction in tumor load in these patients with an otherwise progressive malignant disease can hardly be questioned. The analysis of survival demonstrates the serious disease in these patients, but is otherwise of limited value since there was no control group, and since further treatment included repeated ILP (later than four weeks after the first ILP) in seven patients. Systemic chemotherapy may possibly have been given, but this was not systematically recorded. Other limitations include new imaging techniques during the study to exclude distant metastases, lack of objective tumour volume determination and change in the melphalan dose in the middle of the period. We do not believe that those factors have had a major impact on the outcome of the study.

Future perspectives

Other methods than ILP are currently under investigation, including intra-lesional chemoablation, radiation therapy and topical immunotherapy diathermy, cryotherapy and CO_2 laser ablation, and/or systemic chemo- or immunotherapy [19]. So far, ILP appears to be the best validated therapy for this patient group.

CONCLUSION

Tumour regression was induced already after four weeks in the far majority of patients treated with ILP for localized melanoma metastasis in one extremity. One patient, i.e. 1% of the group, died, and this was probably due to surgical complications. Otherwise, ILP treatment had an acceptable morbidity for this group of very ill patients. We are convinced that the treatment should be considered to improve local disease control in patients with multiple and/or recurrent melanoma confined to an extremity if surgical excision is not possible. The procedure must be performed in institutions with cross-disciplinary expertise.

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