

with melphalan alone; complete remission was achieved in 91% and 52%, respectively [23]. Therefore, TNF, IFN and melphalan may prove to be an important drug combination in isolated perfusion for the treatment of local recurrence and in-transit metastases from a malignant melanoma of the extremity.

It should be realised that perfusion with TNF, IFN and melphalan carries a greater risk than perfusion with melphalan alone. The procedure not only requires a good surgical technique, but also expert postoperative care at the intensive care unit. It is not yet clear whether the higher remission rates after perfusion with TNF, IFN and melphalan, compared with melphalan alone, will also result in a lower incidence of local recurrence.

For the time being, the first choice of treatment for patients with in-transit metastases from a malignant melanoma of an extremity, is hyperthermic regional perfusion, with a combination of TNF, IFN and melphalan.

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PII: S0959-8049(96)00123-2

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INTRODUCTION

THE VIEWPOINT of a dermatologist on malignant melanoma is, of course, different from that of a surgeon. In Germany, and in many other European countries, dermatologists do not only establish the primary diagnosis of cutaneous melanoma, but they additionally perform treatments and follow-up investigations in melanoma patients. The follow-up programme of the German Dermatological Society suggests at least 10 years of follow-up in melanoma patients, and clinical investigations are performed every 3 to 6 months. Therefore, the long-term effects of the treatments, which include cures, relapses as

well as side-effects, can be observed. This is the reason why dermatologists are well-informed on the long-term benefits of treatments and on their long-term toxicity.

Surgeons are, at least in Germany, more sporadically involved in melanoma treatment and follow-up. They are mainly involved in operations like lymph node dissections, surgical removal of metastases and hyperthermic limb perfusions. Surgeons tend to stress the immediate effects of their treatments, particularly, the complete removal of all recognisable tumour masses. Moreover, surgeons can sometimes be fascinated by major and complicated operations.

Isolated limb perfusion fits this setting; it is a major operation [1], and with the placement of catheters, the use of the pump-oxygenators, and the heating of the perfusate, it is a rather sophisticated technique [2]. Reviewing the reports on isolated limb perfusion in the literature, one can get the impression that the fascination in the surgical procedure and its technical implications may have contributed to the attractiveness of isolated limb perfusion among surgeons.

Isolated limb perfusion was introduced into melanoma therapy in 1957 by Creech and Krementz in New Orleans, Louisiana, U.S.A., and more than 1000 patients have been treated alone in this department [3]. Many departments of surgery in the United States, Australia and Europe introduced this therapeutic measure into melanoma therapy, but isolated limb perfusion has not become a standard treatment modality in melanoma. The present review tries to give an explanation why this fascinating approach favoured by many surgeons has not developed into a standard therapy in malignant melanoma.

THE CURRENT ROLE OF ISOLATED LIMB PERFUSION IN GERMANY

To explore the role of a treatment modality in cutaneous melanoma, the data of a melanoma registry may be a useful tool. Since 1983, the Central Malignant Melanoma Registry was established by the German Dermatological Society and by the end of 1995, 26686 patients had been registered by this institution [4]. Primary treatment modalities were documented in all patients and documentations of the follow-up and further treatments are available in more than 50% of these patients. Treatment with isolated limb perfusion has only been registered in 205 patients (0.7%). Of these, 121 treatments were performed in primary melanoma of the extremities and 84 treatments in patients with stage IIIa and IIIab disease. These results indicate that isolated limb perfusion is not an established therapeutic measure in melanoma treatment in Germany.

PROPOSED INDICATIONS FOR ISOLATED LIMB PERFUSION

The first patient treated with isolated limb perfusion was a melanoma patient stage IIIA with numerous satellite metastases at the left lower limb [2]. Currently, locoregional metastasis remains the main indication of isolated limb perfusion. Many reports have been published on series of treated patients in different departments of surgery. However, almost no controlled multicentre trials have been performed. The majority of patients treated had stages IIIA and IIIAB melanoma.

Many reports from single centres claim that the survival rates of treated patients have been increased after isolated limb perfusion [3, 5–9]. However, in these reports, only comparisons with historical controls were made. It is widely accepted today, that comparison with a historical control is not a valid basis for therapeutic decisions. The analysis of the data of the Central Malignant Melanoma Registry in Germany has shown that the prognosis of melanoma patients improved continuously with time, even without any significant change in therapy. The main reason for this improvement were changes in the prognostic factors of melanoma patients [4, 10].

There are only a few critical studies on the effects of isolated limb perfusion. Already, in 1985, Storm and Morton reported on the treatment results in a series of patients with locoregional advanced metastases in whom an 81% response rate

was achieved. However, despite locoregional disease control, the median survival rate was only 15 months owing to the development of distant metastases. They stated: "Thus, although limb perfusion can be a safe and highly effective means of achieving locoregional disease control, there appears to be little survival benefit. Therefore, perfusion should be reserved for palliative treatment of selected patients with locally advanced melanoma" [11].

To our knowledge, there is only one controlled trial in recurrent melanoma of the extremities [12]. In this trial, surgical excision of metastases alone was compared to surgery plus regional perfusion. The median tumour-free survival was significantly improved, but the overall survival was not significantly different in both groups. One of 33 patients in the perfusion group died due to treatment-related toxicity. The authors stated: "Regional hyperthermic perfusion after surgery of recurrent malignant melanoma should only be recommended in prospective and controlled trials, until its value has been proven in several randomised studies" [12].

In summary, it remains an open question whether hyperthermic limb perfusion is beneficial in extended locoregional metastasis of melanomas on the extremities when compared to other current treatment modalities.

DRUGS AND TECHNICAL APPROACHES UTILISED IN HYPERTHERMIC LIMB PERFUSION

The first attempts to treat melanoma patients by isolated limb perfusion were made using the alkylating agent melphalan (L-phenylalanine mustard). This drug was chosen as an antineoplastic agent because phenylalanine was known to have a key role in melanin synthesis. Melphalan has become the standard agent for isolated limb perfusion in melanoma patients. Many other drugs and drug combinations have been tried in order to improve the efficacy and to reduce the toxicity. For example, dacarbazine, which was found to be the most successful systemic agent in melanoma treatment, was used in high concentrations in isolated limb perfusion. However, dacarbazine is a prodrug and requires liver activation before it becomes cytotoxically active. This may be the explanation of why dacarbazine was ineffective in most studies with isolated limb perfusion [13, 14].

Cisplatin is another drug that has been applied in isolated limb perfusion [15–19]. More recent trials failed to demonstrate a superiority of cisplatin or any other drug over melphalan. Thompson and Gianoutsos concluded from their studies and from a review of the literature that neither cisplatin nor any other drug or drug combination so far used for ILP in melanoma patients achieved results that were clearly superior to those achieved with melphalan [20].

Possibly, the introduction of the cytokine tumour necrosis factor- α and Interferon- γ in combination with melphalan may improve the effectiveness of isolated limb perfusion. A level of 90% complete remission and a level of 10% partial remission have been originally described with this regimen [21–24]. Other groups, however, have failed to reproduce these favourable results by applying the combination of INF- α , INF- γ and melphalan [25]. Prospective randomised trials in order to compare the three-drug regimen with INF- α , INF- γ and melphalan to a standard melphalan-alone perfusion are currently in progress [26].

Furthermore, the best technical approach to perform isolated limb perfusion is still under debate. Different oxygenators have been used in isolated limb perfusion and mem-

brane-oxygenators seemed to be superior to the widely used bubble-oxygenators [27]. Therefore, Huber and colleagues proposed that membrane-oxygenators must be adopted as a new standard in isolated hyperthermic extremity perfusion [28]. Additionally, the role of hyperthermia in isolated limb perfusion is still an unsolved question. It seems that hyperthermia improves the results of isolated limb perfusion [29, 30]. Mild hyperthermia (39–40°C) in isolated limb perfusion was not superior to normothermic conditions (37–38°C) [31]. Many reports confirmed that the toxicity greatly depends on the tissue temperatures in isolated limb perfusion, and the toxicity clearly increases with increasing hyperthermia [32, 33]. The temperature in isolated limb perfusion with maximum efficacy and minimum toxicity is still to be defined. Interestingly, there are centres that have turned to a normothermic, low-flow hypoxic isolated limb perfusion with melphalan [33]. This has also been called isolated limb infusion. This procedure is technically much less complicated than isolated limb perfusion and it does not require an extracorporeal circuit [33].

TOXICITY

The toxicity in isolated limb perfusion is considerable, particularly after hyperthermic conditions. Mild oedema and erythema are always observed in patients who undergo hyperthermic perfusion, but this is, as a rule, transient. Vein thrombosis occurs in up to 10% of the patients treated. Peripheral neuropathy is observed in the deep peroneal nerve in 3–4% of the patients treated. Compartment syndromes occur often and several groups always perform fasciotomy after perfusion to prevent compression syndrome and to avoid late fibrosis [1]. The main local and systemic complications after hypothermic isolated limb perfusion are listed in Table 1. The values derive from two series of patients treated in the Regina Elena Cancer Institute in Rome and the National Tumour Institute in Milan [30].

This list of complications shows that toxicity in isolated limb perfusion is not negligible. Major life threatening complications may occur and treatment-related deaths are reported within nearly every large series. The side-effects reported in Table 1 were documented by two different centres, which also used, in part, different drugs and different strategies. However, the percentages of side-effects are in good agreement between the two institutions. Therefore, this list of

complications may be regarded as relatively representative [30]. The rate of amputation and death caused by perfusion were of the same magnitude as in another large meta-analysis of postperfusional toxicity in 2899 patients [34].

DISCUSSION

In reviewing the literature on isolated limb perfusion, there is a striking disproportion between the large number of patients treated in single centres in uncontrolled trials and the few treated in prospective randomised trials. This may be for various reasons. Firstly, a possible explanation may be that therapeutic limb perfusion was established in 1957, at a time when no tradition in prospective randomised control trials existed. If the isolated limb perfusion technique was to be established today, a much more critical approach would have been chosen. The safety of this procedure would have to be demonstrated in comparison to currently available treatment modalities. Secondly, the most effective regimen would have to be defined, and, thirdly, the efficacy would have to be proven in comparison to currently established treatment regimens. Unfortunately, these objectives are only in part or not at all fulfilled for isolated limb perfusion.

Isolated limb perfusion has been mainly applied to patients with locoregional recurrences (stage IIIA and IIIAB). This is the group in which complete response rates of 80% and more can be obtained with this treatment. The major problem in this group is the development of distant metastases. Isolated limb perfusion has obviously no effects on the development of disseminated disease. Furthermore, only part of all reports evaluated the percentage of local disease control. In the majority of cases with complete remission after isolated limb perfusion, recurrences have been observed. Probably, isolated limb perfusion should be reserved for palliative treatment of selected patients with locally advanced melanoma [11]. At least in an adjuvant trial after excision of locoregional metastases, no survival benefit could be observed in patients with additional isolated limb perfusion [12].

Complete remission is the magic word used by surgeons in evaluating isolated limb perfusion. Undoubtedly, a complete remission is also an encouraging event for the patient. However, the majority of patients with stage IIIA and stage IIIAB disease relapse, locally or with disseminated disease. Therefore, two different objectives should become the magic formula in isolated limb perfusion: long-term regional disease control and overall survival. Evaluations of the results of hyperthermic limb perfusion should mainly address these two criteria.

Melanoma treatment has clearly changed since isolated limb perfusion was first established. Thirty years ago many melanomas were only diagnosed in the metastatic stages. Krementz and colleagues, who introduced isolated limb perfusion, mentioned that this had been a therapeutic measure to prevent amputation [2]. However, amputation is now a very rare strategy in melanoma treatment, and having worked in this field since the beginning of the 1980s, I cannot recall a single case of amputation due to metastatic melanoma. I do recall, one case of an arm amputation due to a previous isolated limb perfusion in a well-known surgical centre.

Today, many treatment options are available for therapy of regional metastases. Their development is normally diagnosed at an early stage. If there are only a few lesions, surgical excision will be the primary treatment approach. If there are many metastatic lesions, combinations of surgical excision,

Table 1. Local and systemic complications after hyperthermic isolated limb perfusion [30]

Complications	%
Oedema	24–25
Erythema	18–19
Deep phlebitis	9
Burns	4–6
Peripheral neuropathy	3–4
Amputation	1.3–2
Articular block	1
Arterial obstruction	1–2
Embolism	0.5–1
Bone marrow depletion	3–5
Arterial rupture	0–0.5
Postoperative death	0–0.5

Nd-YAG or CO₂-laser-therapy and systemic treatments can be applied. Interestingly, according to my experience, the response to systemic treatment is greater for regional metastases than in disseminated metastases. If the patient is tumour-free after excision of all regional metastases, an adjuvant treatment with interferon-alpha will normally be given. These are the current treatment modalities to which isolated limb perfusion should be compared to define its role.

In conclusion, isolated limb perfusion's role in the treatment of stage IIIA and IIIB melanoma has still to be defined. In limited disease, surgery alone or in combination with adjuvant systemic treatment modalities may be equally effective or even superior to isolated limb perfusion. In extensive disease, the combination of systemic treatment with tumour reduction by surgery or laser surgery may be as effective as isolated limb perfusion. Probably, a role for isolated limb perfusion may be defined in the palliative treatment of regional bulky disease on an extremity.

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