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Current Controversies in Cancer

Is Isolated Limb Perfusion of Metastatic Malignant Melanoma of the Extremity Worthwhile?

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INTRODUCTION

THE PRINCIPLE of regional perfusion using cytostatic drugs stems from a study performed by Klopp and colleagues in 1950 [1]. These authors found that pain was alleviated and that tumour volume decreased after small doses of nitrogen mustard (chlormethine) were injected into the regional arterial blood flow. The best results were obtained when venous return from the treatment area was blocked. In 1959, Creech and colleagues [2] combined this procedure with extracorporeal circulation using a pump oxygenator.

In 1960, Stehlin and colleagues [3] reported on 116 regional perfusions performed at the MD Anderson Hospital in Houston, Texas, U.S.A. The majority of patients had a tumour of an extremity, while the remainder had a tumour in the pelvic region or in the head and neck region. Luck [4] discovered that melphalan (L-phenylalanine mustard) was the most effective agent to inhibit the growth of malignant melanoma in mice. Since then, it has become the agent of choice in perfusions. In 1967, Cavaliere and colleagues [5] laid the foundations for perfusion under hyperthermia when they described the selective susceptibility of cancer cells to high temperatures.

Numerous investigators have reported favourable results with isolated limb perfusion. It is not possible to perform isolated perfusion of melanoma on another part of the body because there would be extensive leakage into the systemic circulation, and the advantages of regional perfusion—high local dosage of the cytostatic agents without any systemic toxic reactions—would be lost. Historically, the first indication for perfusion was in-transit metastases from a melanoma not amenable to surgery. The response rate was so high that ILP has become well-recognised as a limb salvage procedure over the past 30 years. As good results have been obtained for stage II, IIIA and IIIAB malignant melanoma, attempts have been made to use isolated perfusion to reduce the rate of recurrence and to improve survival in high-risk primary cases.

The only way to resolve this controversy and the theoretical shortcomings of retrospective evaluation, is to perform a prospective study on the influence of ILP on disease recurrence and survival in stage I patients, in which the patients are randomised over the two treatment methods.

Since 1984, the European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organisation (WHO) have been conducting a multicentre prospective randomised trial to evaluate ILP. Seventeen centres in Europe, the U.S.A. and Australia are taking part; patient data are recorded at the EORTC Data Centre in Brussels.

Entry to the trial was closed in 1994; 832 patients were randomised. The process of randomisation was based on patient and tumour parameters, such as sex, age, the anatomical location of the melanoma, Clark level, Breslow thickness and ulceration. Moreover, patients were randomised per institute in order to avoid bias from an excessive number of ILPs being entered into the trial by one or several institutes.

The Surgery Quality Control Programme, initiated by the EORTC, has been monitoring the results obtained over the past few years. In the appraisal of adjuvant ILP treatment, additional risks and burdens to the patient have proved to be important factors that must also be weighed against the expected survival gains.

ILP in itself is a complicated procedure. Temporary cytotoxic tissue reactions are sometimes seen in the postoperative period, such as pain, redness, oedema and occasionally some degree of blistering. Late morbidity in the form of joint stiffness or fibrotic tissue reactions has also been reported [6, 7]. All these risks of ILP are being evaluated in the EORTC/WHO trial.

THERAPEUTIC PERFUSION IN STAGE II, IIIA AND IIIAB PATIENTS

To assess the value of a new chemotherapy modality, the method should first be tested in situations where measurable

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disease can be used to make objective response evaluations. However, because most surgeons excise all the tumour present in a limb prior to perfusion, with the aim of achieving favourable end-point survival, such data are relatively scarce. In the literature on perfusion with melphalan for the treatment of melanoma, an average remission rate (complete and partial) of approximately 80% has been observed [8, 9]. Five-year survival rates after perfusion for local recurrence, satellites or in-transit metastases, with or without lymph node involvement, have ranged from 27 to 80%, while 10-year survival rates have ranged from 23 to 63% (Table 1), with a tendency towards better survival in stage II patients and poorer survival in stage IIIAB patients [9–17].

Survival after conventional therapy in patients with tumour recurrence from melanoma of the extremities is extremely low (8–15% at 5 years) and resembles that of patients with distant skin metastases [18]. This low survival rate may be due to the fact that, in approximately half the patients with distant metastases from melanoma of the extremities, the metastases are detected at the time of diagnosis of the primary tumour or within 6 months [19].

No definite conclusions can be drawn from these results because recurrence rates after surgery alone are very scarce and the seemingly improved survival after perfusion may purely be the result of patient selection. Patient selection may arise because, generally, only patients without distant metastases at the time of local recurrence are selected for perfusion; their tumours may be characterised by a low potential for distant metastases. However, the majority of melanoma experts hold the view that perfusion probably prevents uncontrollable locoregional disease that would otherwise necessitate amputation of the limb, as this is seldom seen nowadays.

A drawback of the perfusion method is that fractionation and protraction are difficult to realise. These well-known mechanisms in systemic chemotherapy increase the difference in tolerance between normal and malignant cells. Other technical limitations include the duration of perfusion (maximum of a few hours) and the number of repeat perfusions (maximum of three).

Perfusion under mild hyperthermia (tissue temperature of between 39 and 40°C) is widely used, but it is questionable whether it is effective, because the specific killing effect of heat is obtained at temperatures of above 41.5°C [8]. Although encouraging antitumour effects have been observed with true hyperthermia, it is not often applied in cytostatic perfusion treatment because of unacceptably high toxicity. However, it should be mentioned that this high toxicity has been encountered under the following circumstances: very high tissue temperatures (of up to 43.5°C), perfusion times of up to 4 h and in many cases, probably non-optimal physiological conditions in the perfused limb [5, 20]. It is interesting that recent studies have reported a similar encouraging response after cytostatic perfusion at tissue temperatures of between 40.5 and 42°C [21].

Some studies have described objective responses to perfusion with drugs other than melphalan. However, none of the cytostatic agents (DTIC, cisplatin, nitrogen mustard) have been as effective as melphalan, either as a single agent or in combination. Similarly, the combination of melphalan with other drugs, such as thiotepa, actinomycin-D and nitrogen mustard, has not improved the remission rate. It is not recommended to use cisplatin at tissue temperatures of above 40°C, because of the risk of severe nerve damage.

Recently, Lejeune and colleagues [22] found that perfusion with a combination of high-dose recombinant tumour necrosis factor alpha (TNF), interferon gamma (IFN) and melphalan, produced an impressive response in patients with in-transit metastases. It is well-known, from experimental studies, that TNF has potent antitumour activity and that the combination of TNF and IFN is highly synergistic. However, in humans, the administration of TNF is hampered by severe systemic side-effects. The maximum tolerated dose ranges from 350 to 500 mg/m^2, which is at least ten times lower than the effective dose in animals.

ILP enables the administration of a high dose of TNF in a closed system with acceptable side-effects [22]. The very promising results of a multicentre pilot study have been published recently. In 53 patients (33 stage IIIA, 15 stage IIIAB and 5 systemic disease in association with in-transit metastases) complete remission was achieved in 91% and good partial remission in the remainder. Therefore, the treatment can be considered to have been successful in all the patients, with a limb-sparing rate of 87%. ILP with a combination of TNF, IFN and melphalan was compared to ILP

Table 1. Results of regional perfusion in patients with local recurrence (II), in-transit metastases (IIIA) and local recurrence and/or in-transit metastases + positive lymph nodes (IIIAB)

[Ref.]	Cytostatics	Number of patients	Local recurrence rate (% in perfused limb)	5-year survival rate (%)			10-year survival rate (%)		
				II	IIIA	IIIAB	II	IIIA	IIIAB
[9]	Melphalan	182	—	64	35	31	58	28	28
[10]	Nitrogen mustard	18	—	—	50	38	—	—	—
[11]	Melphalan	39	—		58*	29		44*	29
[12]	Melphalan	117	—	75	70	36	—	50	23
[13]	Melphalan ± actinomycin-D	110	38	74	67	40	63	45	34
[14]	Melphalan	116	—	80	55	35	—	—	—
[15]	Melphalan (dacarbazine, cisplatin)	106	—	—	51	35	—	—	—
[16]	Melphalan	65	—	61	58	33	—	—	—
[11]	Melphalan	184	41	57	45	27	—	—	—

*Hartley and Fletcher did not discriminate between stage II and IIIA.

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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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.