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INTRODUCTION

HERE, THE value of isolated limb perfusion for malignant melanoma has been discussed, and the "*Contra*" position seems to succeed.

It is true that (i) the trials suggesting improved survival after ILP use historical controls. Only two randomised trials have been reported. The one in favour of perfusion [1] is compromised by extremely poor results in the control group suggesting a major bias. The other trial did not show a survival benefit [2]; and (ii) in trials evaluating therapeutic perfusion, the rates of complete response range up to 91%, but are biased because entry of the patients was not standardised and excision of lesions was allowed prior to or after perfusion [3].

Alternatively, we have to bear in mind that a registry on the treatment of melanoma primary tumours conducted by dermatologists will logically not include those patients referred for surgical (e.g. perfusional) treatment after onset of regional recurrence, particularly when it is based mainly on regions where no limb perfusions are performed. This does not compromise the rationale of ILP. What criteria do we apply to judge the efficacy of a treatment and what does "regional disease control" really mean? An unlimited number of local excisions? Are some residual melanoma nodules allowed? How satisfactory are the results of long-term "regional disease control" using Nd-YAG or CO_2-lasers, or systemic treatment proposed?

Response is not the "magic formula", as pointed out, but regional control or disease-free survival should be.

RATIONALE OF ISOLATED LIMB PERFUSION TODAY

The claim that surgeons look primarily for immediate effects can be counterbalanced with the dermatologists' routine of performing repetitive surgery for single lesions to avoid a one-step curative approach. Surgeons are not only fascinated by complicated procedures, but also by efforts that lead to a cure. To mock this attitude is not a useful tool in scientific controversies.

Currently, we really do not know whether there is a subgroup of patients with melanoma of the extremities with their metastatic disease confined to the limbs (predominantly in-transit metastases) during their whole course of disease. This group of patients represents a positively selected group, but would require regional treatment only. It is true that the value of ILP in the treatment of melanoma is unproven. However, there is a unique opportunity to evaluate its role now.

- Perfusion has shown complete remissions in single patients after numerous approaches of excision, electrofulguration, laser application, topical cisplatinum, cryotherapy, systemic chemotherapy, and/or immunotherapy with interferons or IL-2.
- The best technique of isolation perfusion has not been fully exploited (bubble- versus membrane-oxygenators, pulsatile versus fixed-rate perfusion, blood or asangineous circuit, type of leakage control, value of hyperthermia, combined use of cytokines and cytostatic drugs to circumvent resistance of tumour cells).
- There is now a clearcut rationale for the use of tumour necrosis factor alpha (TNFα). Its mode of action seems to be via inducing damage to endothelial cells [4]. The molecular effectors of tumour toxicity have been identified and can be evaluated [4, 5], for example, VEGF, p-selectins, or release of endothelin [6].
- The regional toxicity spectrum has been carefully observed and can be controlled [7, 8].
- The mechanism of inducing side-effects (cytokine network) has been analysed [9] and systemic effects can be meticulously assessed and treated [10].
- A multicentre trial including only centres experienced in ILP has been initiated to evaluate the therapeutic benefit of TNF.
- Finally, isolation perfusion seems to be the only way to administer safely TNF in patients. This approach can also stimulate other fields of research (lymphocyte extravasation, heat-shock proteins, apoptosis) [5, 11].

With the use of TNF in ILP, several new problems will arise. Assessing its efficacy will be difficult due to the lack of tumour shrinkage. Therefore, WHO criteria of response cannot be applied and angiography, positron emission tomography, or magnetic resonance spectroscopy will have to be taken into account [12, 13]. Cost-effectiveness will be of major interest. The costs of isolation perfusion using TNF range from £13000–17000, but, the costs for treatment with IFN a2b in the EORTC-18952 study were £22000 (based on German prices). The toxicity of ILP using TNF will have to be carefully weighed against that of IFN alpha 2b. Two years of flu-like symptoms will severely affect the quality of life of patients, possibly more than the short-term risk of a septic-shock syndrome after ILP. From the point of view that cytokines carry great hope for improved treatment options in patients with melanoma or sarcoma, we should not denigrate isolation perfusion. At this time, it provides the only system for administering high-dose cytokine treatment in patients safely. Today, it is available only for limb perfusion, but lung or liver perfusion could follow soon.

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