Tumor Necrosis Factor–based Isolated Limb Perfusion for Soft Tissue Sarcoma and Melanoma: Ten Years of Successful Antivascular Therapy

Alexander M.M. Eggermont, MD, PhD and Timo L.M. ten Hagen, PhD

Address
Department of Surgical Oncology, Erasmus University Medical Center, Daniel den Hoed Cancer Center, 301 Groene Hilledijk, 3075 EA Rotterdam, Netherlands.
E-mail: eggermont@chih.azr.nl

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Clinical Development of a New Treatment Option

The development of the systemic administration of tumor necrosis factor (TNF)-α as a cancer drug with direct cytotoxic effects on tumor cells failed in the late 1980s because it was the wrong paradigm for this cytokine. Direct antitumor effects of TNF are very limited, and severe dose-limiting systemic toxicity such as hypotension is already encountered at doses that are 10 to 50 times lower than needed for antitumor effects in murine tumor models. Such differences can only be overcome in the setting of isolated limb perfusion (ILP). Moreover, TNF-mediated antitumor effects appear to be completely mediated by changing the pathophysiology of tumors and by indirect vasculotoxic effects of TNF rather than by direct antitumor effects. The pioneering work of Lienard *et al.* [1] using TNF in the ILP setting led to multicenter trials in melanoma and soft tissue extremity sarcomas. The results in patients with unresectable extremity soft tissue sarcomas were spectacular, with overall response rates of about 80% and similar limb salvage rates [2]. The registration file consisted of 270 ILPs in 246 patients. After review by an independent committee of surgical oncologists, orthopedic oncologic surgeons, and radiologists, 196 patients (80%) were considered for the study as individuals whose only option would normally have been amputation. In this group of 196 "confirmed amputation candidates," limb salvage was achieved in the large majority (71%), corresponding closely with a 76% objective response rate (complete response [CR] + partial response [PR]) in these patients. These spectacular results led to approval of TNF by the European Medicine Evaluation Agency in 1998 for the ILP setting in combination with melphalan for locally advanced or unresectable grade 2 and 3 soft tissue sarcomas of the extremities. Since that time there has been an active program of training and implementation of TNF-based ILP methodology. TNF-based ILP is now performed in 30 cancer centers in Europe, with the hope that it will become an option to patients in other European countries.

Efficacy Independent of Tumor Type and Prior Treatment

Angiography before and after ILP in the clinical studies has shown that selective destruction of the tumor-associated vasculature is the essential mechanism by which TNF mediates its antitumor effects in combination with melphalan [2]. This leads to massive necrosis and shrinkage of the tumors, allowing resection of the tumor remnant as a second step along with limb salvage. Its effects on the vasculature as the common denominator of tumors explains the efficacy of TNF against a great variety of different treated tumors. Eighty percent to almost 100% percent response rates have been reported in 20 types of soft tissue sarcoma, drug-resistant bony sarcoma, melanoma, squamous cell carcinoma, and various other tumors as well as the rare condition of multifocal Stewart-Treves lymphangiosarcoma. Moreover, we have demonstrated that TNF-based ILP overcomes drug resistance in melphalan-ILP failures in melanoma and soft tissue sarcoma and is active against tumors in spite of prior radiotherapy. The procedure is safe, and excellent results have been reported as well in elderly patients aged 75 years or older. Studies in Italy have shown that TNF can be used in combination with doxorubicin with results comparable to those for the combination of TNF and melphalan, albeit at the cost of more locoregional toxicity. Because of its very mild regional toxicity at perfusion temperatures of 38° to 39° C, melphalan is the preferred drug. Because of the sustained clinical success of TNF-based ILP, limb amputations should no longer be performed without consideration of TNF-based ILP for limb salvage.

Crucial Findings in Preclinical Models

Dual targeting of both the tumor cell component of the tumor (mainly by melphalan), and the stromal–vascular component (by TNF and melphalan) has remarkable synergy. Further study is required to elucidate the mechanisms involved and to explore the possibility of other settings, for example organ perfusion or liposomal formulation as new targeting mechanisms of TNF, or cytostatic agents in combination with TNF. In Rotterdam we recently demonstrated that the addition of high-dose TNF to the perfusate results in four- to sixfold increased uptake by the tumor of the cytostatic drug [3]. For melphalan and doxorubicin this uptake was demonstrated to be tumor specific, and no increased uptake was noted in the normal tissues, illustrating the selective action of TNF on the tumor-associated vasculature. Furthermore, we demonstrated a threshold for the TNF-mediated effects at a reduced dose corresponding to about 1 mg. This is in line with the Italian experience of TNF in combination with doxorubicin. Importantly, we demonstrated that hyperthermia and actinomycin D should be avoided because of their idiosyncratic toxicity to the normal tissues. In spite of many reports of the synergy between interferon (IFN)-γ and TNF both in vitro and in vivo in murine tumor models, the role of IFN-γ was not very strong in our rat models. We demonstrated an approximately 10% increase in CR rate and an increase of about 20% in overall response rate in our animal models, which resembles the situation in the clinic. Moreover, Ruegg *et al.* [4] have very elegantly demonstrated the synergistic effect of TNF plus IFN on the induction of apoptosis of the endothelial cells of tumor-associated vasculature.

Spin-off Developments

We have demonstrated that the same synergy between TNF and melphalan is observed in the isolated hepatic perfusion (IHP) setting, provided that the liver metastases are hypervascular. These findings correspond well with the experience in the Surgery Branch of the National Cancer Institute with TNF-based IHP for which an overall response rate of almost 80% was reported [5].

Because of the profound changes brought by TNF on the vascular bed and the pathophysiology of solid tumors, we have investigated the impact of various doses of TNF on the homing pattern of long-circulating pegylated (polyethylene glycol) liposomes in our tumor models. We have demonstrated clearly that repeated administration of low doses (clinically applicable) of TNF in combination with doxorubicin-containing liposomes enhanced the uptake of the liposomes in the tumor and the intratumoral drug concentration significantly, resulting in a highly significant antitumor effect [6]. Identical observations have been made in melanoma B16 tumor models in B6 mice. These findings should be the basis for phase I and II clinical study to explore the utility of TNF at low doses in combination with liposomes.

Conclusions

TNF-based ILP is very successful as a treatment to achieve limb salvage in the management of advanced, multiple, or drug-resistant extremity tumors. TNF-based ILP is now performed in 30 cancer centers in Europe. TNF-based antivascular therapy for cancer is here to stay, and its potential needs to be studied further [7].

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