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REVIEW

Biochemotherapeutic strategies and the (dis) utility of hypoxic perfusion of liver, abdomen and pelvis using balloon catheter techniques

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Abstract *Aims*: To review the development and current status of balloon catheter mediated hypoxic perfusion of abdomen, pelvis and liver for treatment of locally advanced malignancies. Within this context we focus on the addition of tumour necrosis factor-alpha (TNF) to these minimal invasive perfusion procedures.
Methods: A literature search on these topics was carried out in PubMed for indexed articles and in all issues of Regional Cancer Treatment. The findings were related to our own experiences.
Results: Hypoxic abdominal (HAP) and hypoxic pelvic perfusion (HPP) using balloon catheters, are currently applied modalities for treatment of a wide variety of abdominal and pelvic tumours, yet scientific validation of these procedures is poor. Following the results of several Phase I–II trials, both treatments are associated with severe systemic toxicity, significant morbidity and even mortality. The degree of systemic leakage associated with these procedures prohibits addition of TNF. For leakage free liver perfusion surgery is still required, as with current balloon catheter techniques it is not possible to perform leakage free isolated hypoxic hepatic perfusion (IHHP), using either orthograde or retrograde hepatic flow. Experimental and clinical observations suggest that within any perfusion setting, the utilization of TNF is only indicated for treatment of highly vascularised tumours and not for treatment of colorectal tumours.
Conclusion: Balloon catheter technology in its present form does not provide adequate leakage control in any of these settings and is therefore associated with considerable toxicity. It is associated with poor response rates and cannot be considered in any setting as a standard of care.

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Introduction

Regional perfusion with anti-tumour agents is theoretically an attractive option, to achieve in a higher tumour exposure to the agents. This may overcome drug resistance of the tumour,[1] while minimizing systemic exposure to the often highly toxic drugs. Apart from its potential as a palliative treatment modality for various tumours, regional perfusion may also be of use within a neo-adjuvant setting, as it may convert un-resectable malignancies to resectable cases.

In this review we address the developments and current status of balloon catheter mediated hypoxic perfusion of abdomen, pelvis and liver for treatment of locally advanced malignancies. We focus on the addition of tumour necrosis factor-alpha (TNF) and less toxic anticancer drugs to these minimally invasive perfusion procedures. A literature search on these topics was carried out in PubMed for indexed articles and in all issues of Regional Cancer Treatment. The findings were related to our own experiences.

History and background

Regional perfusion with anticancer drugs for the treatment of un-resectable malignancies is well established. Half a century ago, regional perfusion of the liver, pelvis, abdomen and extremities with chemotherapeutic agents was first performed.[2–4] Due to disappointing results, and the invasiveness of the procedures, these methods were generally abandoned, apart from the isolated limb perfusion (ILP). ILP with TNF and melphalan for treatment of sarcoma and melanoma in-transit-metastases, resulted in dramatic tumour responses.[5,6] The high regional TNF concentrations during ILP cannot be achieved with systemic therapy due to its severe systemic toxicity. The question now arises as to whether this success of regional immuno-chemotherapy can be extrapolated to other regional perfusion settings, as in the liver, abdomen and pelvis.

Minimal invasive perfusion procedures

Conventional surgical perfusion procedures of the liver, abdomen or pelvis are major, complex, costly, and time-consuming operations and can only be performed once. Palliation of the malignant disease under control is a more realistic goal than cure. If regional perfusion in these settings is to become a practical treatment option, the extent, complications and costs of the interventions must be acceptable, the procedures should be repeatable, and should yield good response rates.

Developments in balloon catheter technology allow relative and complete vascular isolation of the abdomen, pelvis or liver, by minimally invasive or percutaneous techniques. These procedures can be performed under regional hypoxic conditions, without the high costs of a heart–lung machine operated by perfusionists. Apart from modulation of oxygen pressure, the (relative) vascular isolation also allows perfusing under hyperthermia, to improve the efficacy of anti-tumour agents.

TNF in regional perfusion

TNF in vivo has the ability to induce tumour necrosis with acute softening of the tumour. This is believed to result from selective destruction of the tumour microvasculature, causing acute hemorrhagic necrosis of the tumour.[6–10] TNF has an immediate effect on the uptake of drugs in the tumour. When TNF is combined with cytostatic agents, the uptake of the perfusion drugs is selectively enhanced in the tumour tissue. This results in synergistic anti-tumour responses.[11–13]

Because of its systemic toxicity, TNF cannot be given in effective doses intravenously.[14,15] However, when adequate concentrations are achieved in combination with melphalan, such as in ILP for treatment of sarcoma and melanoma in-transit-metastases, it is highly effective in clinical cases.[5,6,16] The impressive response rates achieved with ILP, have led to the approval and registration of TNF in Europe in 1998. A challenge now lies in identifying other situations, where TNF can be utilized.[17]

Indications for use of TNF

The feasibility of adding TNF to a regional or isolated perfusion procedure is first of all determined by the 'sensitivity' of the tumour to this cytokine. Isolated hepatic perfusion (IHP) studies performed in our institution in hepatic sarcoma bearing rats with TNF and melphalan demonstrated that IHP with TNF and melphalan resulted in a dramatic increase in regional concentrations of perfused agents, with virtually no systemic leakage.[18] IHP with melphalan alone resulted in minimal anti-tumour effects. Perfusion with only TNF had a slight growth stimulatory effect on the liver tumours, in any case no negative effect on tumour growth was observed. When TNF was used in combination with melphalan, a synergistic