International Journal of Hyperthermia

ISSN: 0265-6736 (Print) 1464-5157 (Online) Journal homepage: informahealthcare.com/journals/ihyt20

# Isolated limb perfusion for malignant melanoma; possibly better results with high dose hyperthermia

*Int. J. Hyperthermia*, November 2008; 24(7): 602–603

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## LETTER TO THE EDITOR

# Isolated limb perfusion for malignant melanoma; possibly better results with high dose hyperthermia

**To the editor**

We have enjoyed reading the excellent review by Beasly et al. on regional treatment by isolated perfusion or infusion (ILP/ILI) for melanoma and sarcoma of the limb, in which strategies to optimize treatment are discussed [1]. Possible future directions they summarize are identification of appropriate patients who will benefit from regional treatment, determination of a technique that produces consistent responses across similar populations, and the development of novel strategies and agents that can improve the response. In their list, however, we miss two strategies that we have proposed earlier, and that are applicable for ILP [2]. Both these strategies imply the use of hyperthermia at a temperature of 42 to 43°C.

In most ILP studies, a high dose of melphalan (10 mg per liter perfused tissue) is applied at a temperature of 39–40°C, as higher temperatures result in excessive toxicity. This may not be the optimal combination. In order to benefit from the ability of high-dose hyperthermia to complement the effect of melphalan, a high temperature ILP – without melphalan – can be followed by an ILP with high dose melphalan at normal temperature. The hyperthermic perfusion will kill cells in the hypoxic parts of the tumour, without causing normal tissue toxicity. The second normothermic perfusion with high dose melphalan will attack the residual well-perfused part of the tumour. We have tried this approach in 17 melanoma patients and long-term results were published in 2003 [3]. All patients had extensive disease: 5 patients MD Anderson stage II, 7 stage IIIA, 2 stage IIIAB, 2 stage IIIB and 1 stage IV. The first ILP was with hyperthermia only (2 hours at 42–43°C), followed 1 week later by a 1 hour ILP at normothermia (37–38°C) with 10 mg melphalan per liter perfused tissue. Impressive tumour regressions and central tumour necrosis were found in most of the patients one week after the hyperthermic ILP. A complete response was achieved in 65% of the patients and the 5-year limb recurrence-free survival for patients with a complete response was 63%. The maximum acute toxicity was Wieberdink grade II in 4 patients (24%) and grade III in 6 (35%) patients. The local control rate was better than what is usually reported from a single mild hyperthermic ILP with melphalan, and the grade III toxicity was less. The sequential treatment was abandoned when ILP with TNF$\alpha$ and melphalan was introduced, with the expectation that similar results could be achieved with one surgical procedure.

Another approach, in which both the disadvantage of two surgical procedures can be avoided and the advantage of optimum use of both treatment modalities can be exploited, would be to administer hyperthermia at the maximum tolerated level, and reduce the simultaneously administered melphalan dose on the basis of the maximum acceptable toxicity at that temperature, to be derived from phase I studies. The assumption made for this approach is that the cytotoxicity of melphalan is equally enhanced by high dose hyperthermia in well-perfused tumour tissue and normal tissues. The anti tumour efficacy of a reduced dose of melphalan would then be similar to that achieved with a high dose in the lower temperature application. The main beneficial effect of this approach concerns the cells in insufficiently perfused parts of the tumour. In these areas high-dose hyperthermia is highly effective, as we have seen with the sequential application.

ISSN 0265–6736 print/ISSN 1464–5157 online 
DOI: 10.1080/02656730802235536

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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