Different aspects of hyperthermic isolated limb perfusion
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Hyperthermic isolated limb perfusion with cisplatin in four patients with sarcomas of soft tissue and bone

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Abstract
The value of hyperthermic isolated limb perfusion (HILP) with cisplatin in the management of locally advanced soft tissue sarcomas or metastatic bone sarcoma was studied. Four patients were treated with HILP under mild hyperthermia (39-40 °C) with 20-30 mg cisplatin / L perfused limb volume. Toxicity in the perfused limbs was moderate, and the erythema and edema that occurred resolved spontaneously within 7-14 days as did the slight motor and sensory neuropathy over a longer period of time. Clinically, a reduction of pain was observed in all patients. Two weeks after perfusion, tumor biopsies were taken to evaluate tumor response. Two patients showed a pathological complete response, one patient showed >90% necrosis and one patient showed no response. Currently patients are treated with tumor necrosis factor and melphalan as perfusion agents. The above mentioned results make the combination of tumor necrosis factor with cisplatin in the isolated limb perfusion setting an interesting option.

Introduction
Malignant bone and soft tissue sarcomas are a heterogeneous group of lesions, which all arise from tissue of mesenchymal origin. With an incidence of 3 per 100000, and given that somatic soft tissue and skeleton comprise more than 75 % of the average body weight, these cancers are rare. Most sarcomas of soft tissue and bone originate in the extremities and are often quite large at the time of diagnosis. Limb saving treatment of extremity sarcomas of soft tissue and bone is a multidisciplinary matter and has avoided ablative surgical procedures in the majority of patients.1,2 Apart from locoregional treatments, systemic adjuvant chemotherapy is now well established for the treatment of osteosarcoma3, whereas in soft tissue sarcomas it is still a subject of investigation.4 The main goal of the systemic treatment is the eradication of possible micrometastatic disease with a possible favourable response on the primary tumor. With hyperthermic isolated limb perfusion (HILP) it is possible to obtain a higher local chemotherapy concentration in the perfused extremity than with systemically administered chemotherapy.5 Cisplatin, discovered in 1965 by Rosenberg et al.6 is one of the most active chemotherapeutic agents and it has been postulated that a high dose of cisplatin could create significant necrosis of the primary tumor. Before introducing cisplatin perfusions in the clinical treatment for sarcomas of soft tissue and bone, a dose escalating and feasibility study in spontaneous canine osteogenic sarcoma showed a maximum tolerable dose of 30 mg cisplatin / L extremity volume, with improvements in clinical and X-ray parameters after treatment.7,8 The aim of the present study was to investigate the feasibility and efficacy of HILP with cisplatin in the locoregional tumor control of locally advanced soft tissue sarcomas or metastatic...
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Patients and methods

Patients eligible for the study were suffering from histologically proven locally advanced extremity sarcomas of soft tissue or bone. The primary tumor was locally not resectable locally except when an amputation of the affected limb was performed. Patients were treated with the intent of preserving the affected extremity.

Before perfusion the renal function of all patients was normal. Patients were prehydrated with 2.5 L normal saline 12 hours preoperatively, and hydration was maintained during the first 5 postoperative days, in order to protect against nephrotoxicity. The perfusion technique employed is based on the technique developed by Creech and Krementz and was performed during 60 min under mild hyperthermia (39-40°C) and physiologically optimal conditions. Cisplatin (Platinol 0.5 mg/ml, Bristol Myers SAE, Barcelona, Spain) was added to the perfusate over 10 min. In this study the cisplatin dose, administered as part of a phase I-II dose finding study, varied from 20-30 mg / L perfused limb volume. Leakage of cisplatin from the perfused limb to the systemic circulation was checked by an isotope scanner placed over the heart using 131I-albumin in the perfusate.

All patients were followed up clinically by physical examination, chest X-rays and routine blood chemistry for treatment related morbidity. In patients with a sarcoma of bone, response to perfusion was scored on conventional X-rays in two directions. Preperfusion X-rays were compared with 6 weeks postperfusion X-rays. Regression of the tumor was defined as a decrease in tumor volume, increased ossification of intra-osseous tumor osteoid, periosteal new bone, and soft tissue margins more densely ossified, resulting in a more benign appearance of the tumor. One week after perfusion an electromyogram was performed to investigate nerve toxicity of the cisplatin perfusion. The local perfusion toxicity was graded according to the criteria described by Wieberdink et al.

Two weeks after perfusion, biopsies of the tumor were taken in three directions with a 3.5 mm diameter Coombs bone biopsy system to evaluate the response of the tumor to the perfusion treatment. The biopsies were histologically scored: little or no effect of chemotherapy noted (score I), a partial response to chemotherapy with 50% - 90% tumor necrosis noted and attributable to chemotherapy (score II), > 90% tumor necrosis (score III), no viable tumor cells noted in any of the histological sections (score IV).

Before and during perfusion, 10 ml perfusate samples were collected at 10 min intervals to determine total platinum (tPt) and ultrafiltrated platinum (fPt) levels as previously published. The study was approved by the local Medical Ethical
Committee of the Groningen University Hospital and all patients gave informed consent.

Results
Four patients entered the study. Three patients presented with metas tasized lower extremity sarcoma of bone, in two patients the primary tumor concerned an osteosarcoma and in one patient a malignant fibrous histiocytoma. Both osteosarcoma patients had multiple lung metastases and the patient with the malignant fibrous histiocytoma of bone had multiple skeletal metastases at time of diagnosis. The fourth patient presented with a localised recurrent malignant fibrous histiocytoma of the soft tissues. She had first been treated with local excision followed by radiotherapy (Table 1). All primary tumors were localised in the lower extremity.

Characteristics of the perfusion and cisplatin dose used in each patient are summarized in Table 2. No technical perfusion related problems were encountered. After perfusion, the total serum proteins and albumin levels decreased in all patients. The mean total serum proteins decreased from 73.7±0.5 to 46.7±4.8 g/L on the first postoperative day, and mean serum albumin from 45.3±1.9 to 29.3±4.6 g/L (p<0.05 paired Student’s t-test). Serum albumin was corrected postoperatively with intravenous albumin administration.

The acute treatment related toxicity consisted of a local edema and erythema (Grade II toxicity) in three patients, and one patient had a considerable edema and erythema of the skin with some blistering (Grade III toxicity). The erythema and edema resolved spontaneously within 7-14 days as did the slight motor and sensory neuropathy over a longer period of time. All patients experienced pain relief after perfusion. The X-rays of the first osteosarcoma patient showed regression of the tumor and more than 90% necrosis was found in the tumor biopsies 2 weeks after perfusion. In the second osteosarcoma patient, a 5% leakage of albumin to the systemical circulation occurred. After the treatment, the leaked cisplatin brought about a measurable reduction of the pulmonary metastases before systemic treatment with cisplatin was started and caused temporarily renal function disturbances. Notably, the primary tumor did not respond to the perfusion in terms of the pathological evaluation. The X-rays could not be properly scored in this patient due to bone formation after a pathological fracture. Both osteosarcoma patients received systemic chemotherapy after cisplatin perfusion because of metastatic disease at time of diagnosis. The patient with a malignant fibrous histiocytoma of bone showed progression of the tumor on X-ray, however, tumor biopsies showed a complete response. In none of these three patients was the affected limb amputated, and all three patients died from distant metastatic disease after 6, 12 and 7 months. After an initial complete response clinically and...
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Pathologically, a recurrence was found in the patient with a malignant fibrous histiocytoma of the soft tissues. Subsequently a lower leg amputation was performed and this patient was alive without evidence of disease 36+ months after amputation.

Discussion

HILP was first used to treat patients with melanoma, and the drug employed was the alkylating agent melphalan.9 Although the overall remission in melanoma patients is 80%, 60% of patients fail to achieve a complete response. Drugs which might be more effective or less toxic than melphalan in the treatment of melanoma by HILP have therefore been sought. The first report by Aigner et al15, indicated that cisplatin might be an useful alternative to melphalan in the treatment of melanoma. Cisplatin is a non-cell-cycle dependent drug, which forms DNA-crosslinks and inhibits DNA synthesis.16 Klein and Ben-Ari17 experienced no serious toxicity after HILP with cisplatin. In the present study toxicity was moderate. In a previous experience of HILP with cisplatin however, we found an unacceptable treatment related neuropathy.18 With cisplatin dosages in the same range as in the present study, the only difference from this study was that six of seven patients with recurrent extremity melanoma were treated with one or more melphalan perfusions with or without dactinomycin prior to the cisplatin perfusion.

The pharmacokinetic data from the patients in this study showed extremely high perfusate levels of Pt, up to 30 times higher than systemic levels which remained acceptably low.14 Given that effective intra-arterial and systemic levels of Pt are in the range of 5.5 mg/L, HILP produced 2 to 10 times higher levels. The pharmacokinetic data further indicated that HILP with cisplatin produced high levels of Pt in the tumor and surrounding muscle and fat14, which may harbour malignant cells that later result in local recurrences.

Both malignant fibrous histiocytomas responded with total necrosis in the biopsy material. Recently we showed that malignant fibrous histiocytoma of bone is a very

Table 1 Patients characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Primary tumor</th>
<th>Metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>M</td>
<td>Osteosarcoma</td>
<td>Lungs</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>F</td>
<td>Osteosarcoma</td>
<td>Lungs</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>M</td>
<td>Malignant fibrous histiocytoma of bone</td>
<td>Bone</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>F</td>
<td>Recurrent malignant fibrous histiocytoma of soft tissues</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 2  Perfusion characteristics, cisplatin dosage, toxicity and follow-up

<table>
<thead>
<tr>
<th>No</th>
<th>Perfusion type</th>
<th>Limb Volume</th>
<th>Cisplatin dose (mg/L vol.)</th>
<th>Total cisplatin dose (mg)</th>
<th>Flow (ml/min)</th>
<th>Leakage (%)</th>
<th>Local Toxicity grade</th>
<th>EMG</th>
<th>Pathological score 2 weeks after HILP</th>
<th>X-ray of tumor 6 weeks after HILP</th>
<th>Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Iliacal</td>
<td>13.0</td>
<td>20</td>
<td>260</td>
<td>750</td>
<td>4.2</td>
<td>II</td>
<td>Slight motor neuropathy</td>
<td>III</td>
<td>Regression</td>
<td>DOD 6</td>
</tr>
<tr>
<td>2</td>
<td>Iliacal</td>
<td>5.0</td>
<td>25</td>
<td>125</td>
<td>520</td>
<td>5.0</td>
<td>II</td>
<td>Normal</td>
<td>I</td>
<td>Not evaluable due to fracture</td>
<td>DOD 12</td>
</tr>
<tr>
<td>3</td>
<td>Iliacal</td>
<td>11.0</td>
<td>25</td>
<td>275</td>
<td>450</td>
<td>1.4</td>
<td>III</td>
<td>Normal</td>
<td>IV</td>
<td>Progression</td>
<td>DOD 7</td>
</tr>
<tr>
<td>4</td>
<td>Popliteal</td>
<td>3.3</td>
<td>30</td>
<td>100</td>
<td>800</td>
<td>1.5</td>
<td>II</td>
<td>Slight sensory neuropathy</td>
<td>IV</td>
<td>Not performed</td>
<td>NED 36</td>
</tr>
</tbody>
</table>

DOD = dead of disease; NED = no evidence of disease; EMG = electromyogram

Local perfusion toxicity according to Wieberdink\textsuperscript{11}: Grade I, no reaction, objectively and subjectively; Grade II, slight erythema, oedema or loss of sensation; Grade III, considerable erythema or oedema with some blistering, slight functional disturbances; Grade IV, extreme epidermolysis and/or obvious damage to the deep tissues causing definite functional disturbances; Grade V, reaction that might necessitate amputation
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chemosensitive tumor.\textsuperscript{19} The malignant fibrous histiocytoma of soft tissue in the present study however, recurred after 1 month. Fletcher et al. also reported a high local recurrence rate of 66\% (2 of 3 patients) in cisplatin perfusions for recurrent malignant fibrous histiocytoma, indicating the difficulty of controlling local recurrences of malignant fibrous histiocytoma with cisplatin perfusion.\textsuperscript{20}

One osteosarcoma patient in the present study reacted with >90\% necrosis of the tumor, and in one patient the tumor showed no response after perfusion. These moderate histological results in osteosarcomas are in accordance with our histological data in canine experiments.\textsuperscript{8} The reason for this wide variation in response may be exists in the sensitivity of the osteosarcoma cells, or that the pH changes in the tumor occur during HILP, resulting in a less active form of cisplatin.\textsuperscript{16,21} Vaglini et al.\textsuperscript{22} found more favourable results with 95-100\% necrosis of the tumor in eight of 11 evaluable osteosarcoma patients, 60-70\% necrosis in two patients and 40\% necrosis in one patient after HILP with cisplatin combined with intra-arterial infusion of cisplatin and systemic high-dose methotrexate.\textsuperscript{22}. HILP with cisplatin was well tolerated. The only significant complication was an extensive edema of the extremity that spontaneously resolved in 2-3 weeks. Clinically, they observed a significant reduction of pain, macroscopic reduction of tumor diameter, functional improvement and rearrangement of the bone on the X-ray.

In the present study, no limb-salvage procedures were performed because of rapid progression of systemic disease. In one osteosarcoma patient with a 5 \% albumin leakage, the accordingly leaked Pt brought about a measurable reduction of the pulmonary metastasis, although the primary tumor did not respond. Di Filippo demonstrated a systemical peak of Pt 3 hours after HILP due to the release of bound Pt. Although this was encouraging, since a prolonged presence of Pt in the perfused limb may contribute to lower recurrence rates, this indicated the need for adequate and prolonged hyperhydration therapy after HILP with cisplatin, in order to prevent nephro- and ototoxicity.

Following the treatment of the four patients described in this study, the Groningen University Hospital now participates in a trial with a new perfusion modality, which combines melphalan with biological response modifiers such as tumor necrosis factor and interferon.\textsuperscript{23,24} As the endothelial cells are the main target cells of tumor necrosis factor in these new perfusion schedules, treatment with this modality of sarcomas of soft tissue and bone with a high extent of tumor vessels are of particular interest. A trial which combines tumor necrosis factor with cisplatin as perfusion agents in the treatment of sarcomas of soft tissue and bone could be clinically important.
Chapter 4

References


