Cancer Chemother Pharmacol (2005) 56: 55–62
DOI 10.1007/s00280-004-0957-0

ORIGINAL ARTICLE

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Hyperthermic isolated regional perfusion with CDDP for bone and soft-tissue sarcoma of the lower limb: pharmacokinetics, thermal dose, toxicity, and feasibility

Received: 23 July 2004 / Accepted: 12 November 2004 / Published online: 25 March 2005
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Abstract The objectives of this study were to investigate the pharmacokinetics of cisplatin (CDDP) and the thermal dose, toxicity, and feasibility of hyperthermic isolated regional perfusion (HIRP) with CDDP for bone and soft-tissue sarcomas of the lower limb. A total of 43 patients were treated with HIRP using CDDP. The dose of CDDP administered was 62.9 ± 11.8 mg/limb (20 mg/m^2 +20∼30 mg). The mean highest CDDP concentration was 56.9 μg/ml as total platinum (tPt) and 49.0 μg/ml as free platinum (fPt). The tPt concentration remained higher than 10 μg/ml. The highest temperature within tumor was 42.3 ± 1.4°C on average. The complications of HIRP were grade II toxicity in 30 patients, grade III in 9, and grade IV in 4. The mean necrotic ratio in the resected specimen was 84.5%, and the effect was grade IV (no viable tumor cells) in 13 patients, grade III(>90% necrosis) in 12, grade II (50 to <90%) in 9, and grade I (<50%) in 4. We obtained favorable levels of platinum concentration of the perfusate using a lower CDDP dosage compared with previous studies of HIRP. Considering our results of the pharmacokinetics of CDDP and clinical efficacy, we propose a lower dosage of CDDP for HIRP in the treatment of osteosarcoma. Multimodality treatment of HIRP with preoperative chemotherapy and surgery is a relatively safe and reliable therapeutic option for patients with limb sarcomas, and our method offers excellent local control.

Keywords Bone and soft-tissue sarcoma · Hyperthermia · Perfusion · Cisplatin · Limb-sparing surgery · Chemotherapy

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Background

Osteosarcoma is the most common primary malignant bone tumor in children and adolescents. Significant improvement in prognosis can be attributed to developments in systemic chemotherapy. Recent advances in both preoperative and postoperative treatment, operative techniques, and diagnostic imaging modalities have limb-preserving surgery a realistic option for most patients [1–3]. Preoperative chemotherapy with delayed surgery has become a widely recognized strategy in the treatment of osteosarcoma [2, 4, 5]. Bacci et al. [5] have reported a lower local recurrence rate in good responders, and suggested the importance of a local response to preoperative chemotherapy in limb sparing surgery. Among the major benefits of preoperative chemotherapy are control of the local disease and reduction of the rate of local recurrence after limb preservation in good responders [6]. In addition to systemic chemotherapy, adjuvant local treatment can be a means of improving local tumor control and enhancing the safety of the surgical procedure, particularly limb salvage.

Cisplatin (CDDP) is a useful chemotherapeutic agent for preoperative induction therapy for osteosarcoma because of its excellent local effect [7, 8]. Intraarterial infusion of CDDP has been advocated to deliver a high local platinum concentration and to devitalize the local tumor more effectively. Intraarterial infusion of CDDP has been shown to be more effective against the primary tumor than intravenous infusion and to have a favorable therapeutic effect in osteosarcoma of the extremities [8–9]. Dosage escalation of CDDP is desirable to raise the antiblastic effect against the local tumor, but its use is limited in the treatment of intraarterial and intravenous infusion because of systemic toxicities such as nephrotoxicity and ototoxicity.

Isolated limb perfusion with a chemotherapeutic agent was first described by Creech et al. [10] in 1958.

The advantage of isolated limb perfusion with CDDP is that higher local drug concentrations can be obtained without elevating systemic drug concentrations. Avoiding systemic toxicities, isolated limb perfusion with CDDP can achieve a greater biological effect in limited anatomic sites. CDDP has been used for isolated limb perfusion because it does not need metabolic activation.

The combination of heat and antitumoral drugs may produce synergistic antitumor effects [11, 12]. Moreover, during the limb perfusion with extracorporeal circulation, it is safe and easy to control the temperature of the perfusate and the isolated limb. Several studies have shown clinical efficacy of hyperthermic isolated regional perfusion (HIRP) with CDDP and an excellent local effect in the treatment of limb sarcomas [11, 13–16]. We have previously reported [17] clinical results of HIRP with CDDP and its excellent local effects in patients with osteosarcoma of lower limb. Hoekstra et al. [15] have reported severe local neurotoxicity caused by CDDP and high temperature in the treatment of melanoma of the lower limb with HIRP.

In spite of several previous reports, little is known about the pharmacokinetics of CDDP, and the thermal dosage, and local complications of HIRP. In this study, we investigated pharmacokinetics of CDDP and thermal dosage during HIRP in combination with local effects and their complications in human bone and soft-tissue sarcoma of the lower limbs. We present preliminary results of a multimodality treatment consisting of HIRP, surgery, and systemic combination chemotherapy and attempt to elucidate the therapeutic advantages and the rationale of HIRP with CDDP.

Patients and methods

Patients

This study was approved by the Ethics Committee at our institute, and all patients signed a written informed consent statement. From 1986 to 2003, 43 patients with bone and soft-tissue sarcoma around the knee and ankle joints were treated with HIRP using CDDP in our institute. The eligibility criteria were (1) bone and soft-tissue sarcoma around the knee and ankle joints, (2) osteosarcoma or other limb sarcoma anticipated to have a favorable response to CDDP, and (3) those expected to be capable of receiving limb-sparing surgery.

There were 29 males and 14 females (Table 1). Patient ages ranged from 8 to 52 years (mean 20.6 ± 11.1 years). All patients were diagnosed by open biopsy prior to treatment and evaluated for surgical staging by computed tomography of the chest and bone scan. The underlying conditions were osteosarcoma in 35 patients (stage IIB in 24 patients, and stage III in 11 patients, according to Enneking's surgical staging system), stage IIB telangiectatic osteosarcoma in 1 patient, stage IIB malignant fibrous histiocytoma (MFH) of bone in 4 patients, non-metastatic (extra-compartment) MFH of soft tissue in 2 patients, and stage III hemangiopericytoma in 1 patient.

Table 1 Clinical characteristics of the patients

Total patients	43
Gender	
Male	29
Female	14
Age (years)	20.6 ± 11.1
Site (limbs)	
Distal femur	28
Proximal tibia	10
Proximal fibula	4
Distal fibula	1
Enneking's stage	
Stage IIB	31
Stage III	12
Histological type and Enneking's stage	
Osteosarcoma (stage IIB)	24
Osteosarcoma (stage III)	11
Telangiectatic osteosarcoma (stage IIB)	1
MFH of bone (stage IIB)	4
MFH of soft-tissue (M0)	2
Hemangiopericytoma (stage III)	1

The locations of the tumors were distal femur in 28 limbs, proximal tibia in 10 limbs, proximal fibula in 4 limbs, and distal fibula in 1 limb.

Thirteen patients with osteosarcoma affecting the proximal humerus and proximal femur were controls who received preoperative chemotherapy without HIRP. These patients were 15.2 ± 5.9 years old, and ten were stage IIB and three were stage III.

HIRP

HIRP was performed using a heat exchanger, roller pump and pump oxygenator circuit operated with the aid of clinical engineers [17–19]. The external perfusion circuit volume was approximately 400 ml when using a pediatric membrane-type oxygenator and heat exchanger (Iso Company, Tokyo, Japan), and reduced to 300 ml by changing the circuit to an oxygenator system for neonates and infants (Terumo Company, Tokyo, Japan). The femoral artery and vein were exposed and after isolating the affected extremity from the systemic circulation with a pneumatic tourniquet, cannulae were connected to form an extracorporeal circuit.

CDDP was injected when the temperature had risen to 39.0°C, and the circuit temperature was raised and maintained at 41.5–43°C. CDDP was injected into this circuit over a period of 60 min. The dose of CDDP was determined and modified according to the body surface area and the volume of the perfusion circuit to achieve 100 μg CDDP/ml of perfusate. The dose of CDDP was 20 mg/m^2 + 40 mg in patients in whom an earlier type of external perfusion circuit system (Iso Company) was used. The dose of CDDP was changed to 20 mg/m^2 + 30 mg as the volume of the external perfusion circuit was reduced from 400 ml to 300 ml using a later type of external perfusion circuit system (Terumo Company).

The actual dose of CDDP injected was 62.9 ± 11.8 mg/limb (50–80 mg).

HIRP was started after injection of CDDP and the total duration of HIRP was 60 min. At the end of HIRP, the circuit blood containing CDDP was washed, the cannulae were removed, and the cannulated vessels were repaired.

Pharmacokinetics of CDDP during HIRP

Samples of perfusates were collected immediately following injection, at 5 min after, and thereafter every 10 min. Samples of body systemic circulation were taken at 30 and 60 min during HIRP, and all samples were transported on ice immediately. Samples were centrifuged for 10 min at 2000 *g*, and the cell fraction was removed. For determination of the concentration of fPt, 1 ml of supernatant was ultrafiltered (2000 *g*, 20 min) using an Amicon Centrifree micropartition system (Millipore, USA). Concentrations of tPt and fPt in the perfusates were determined by simultaneous multielement atomic absorption spectrometry (SIMAA 6000, Perkin-Elmer, USA). Absorption was measured at 265.9 nm with a specific bandwidth of 0.5 nm and deuterium background signal correction. Assay performance (linearity, limits of detection/quantitation, intra- and interday variability and sample preparation) is shown in Table 2.

Systemic CDDP and therapeutic advantage of HIRP

The corresponding systemic CDDP and therapeutic advantage were measured by comparing the platinum concentration of perfusate with that of systemic serum concentration at 30 min and 60 min during HIRP.

Thermal dose of HIRP

The temperatures of the perfused limb were monitored using thermometers (Advance Co., Tokyo, Japan) during HIRP at six points (within the tumor, quadriceps muscle, subcutis, skin, gastrocnemius muscle and inside the cannulae). The highest temperature within the tumor during HIRP was analyzed in combination with local side effects.

Table 2 Assay performance

Linearity	
Standard solution	0.02–1.5 μg/ml
Plasma	0.1–7.5 μg/ml
Filtered plasma (low concentrations)	0.02–1.5 μg/ml
Sample preparation	
Plasma	Dilute with water ×5
Filtered plasma (low concentrations)	No dilution
Detection limit	0.01 μg/ml
Quantitation limit	0.02 μg/ml
Intra- and interday variability	
0.02 μg/ml	CV < 30%
1 μg/ml	CV < 20%
5 μg/ml	CV < 20%

Toxicity and side effects

The patients were followed up with physical examination and blood analysis to check for treatment-related morbidity locally and systemically. Local perfusion toxicity was graded according to the criteria developed by Wieberdink et al. [21]. Local perfusion toxicity was evaluated after HIRP (grade I–V). For grade V toxicity (reaction which may necessitate amputation), the thermal dose was to be reduced so as not to exceed 41.5°C. We investigated the correlations between grade of toxicity and CDDP concentration of the perfusate and thermal dose of HIRP.

Local effect

The pathological effects of the bone sarcomas of 38 patients were evaluated in resected specimens. The histological effects of the preoperative chemotherapy were graded according to the criteria advocated by the Musculoskeletal Tumor Committee of the Japanese Orthopaedic Association (the JOA criteria) [20]. The local effects were compared with those in the 13 control patients with limb osteosarcoma.

Oncological results

Clinical and oncological results of multimodality treatment of HIRP with systemic preoperative chemotherapy and surgery for limb sarcomas were evaluated. The surgical procedure, surgical margin, local control, and prognosis were evaluated.

Statistical evaluation

The data were analyzed using Student's *t*-test to compare means across treatment groups. Mean values ± SD are reported. Univariate analyses were performed using Fisher's exact test. Disease-free survival duration was estimated using the Kaplan-Meier method. All statistical analyses were performed with statistical analysis software (Stat View program; SAS Institute, Cary, N.C.)

Preoperative chemotherapy

Prior to HIRP, neoadjuvant chemotherapy was performed according to our protocols, including CDDP intraarterial infusion (CDDP IA) with or without high-dose methotrexate (HD-MTX), doxorubicin (ADM) in the treatment of osteosarcoma and MFH. After clinical and imaging evaluation of the effects of chemotherapy, HIRP was performed in combination with open biopsy for histological evaluation. Neoadjuvant chemotherapy

Table 3 Type of treatment and clinical results (*M* HD-MTX, *C/A* CDDP/ADM, *A* ADM, *IFO* ifosfamide, *CYT* cyclophosphamide)

Preoperative chemotherapy (*n*)	
B-2 (CDDP IA×3 + HIRP + M×2)	10
B-3 (CDDP IA×2 + M×2 + HIRP + M×2)	9
B-4 (CDDP IA×2 + M×3 + HIRP + C/A×2 + M×4)	9
B-5 (M×3 + CDDP IA×2 + M×2 + HIRP + C/A×2 + A + M×6)	13
Other (CDDP IA×2 + HIRP + A, IFO, CYT)	2
Surgery (*n*)	
Excision	35
Amputation	5
None	3
Surgical margin (*n*)	
Inadequate (intralesional margin)	10
Adequate (wide margin)	30
Local recurrence (*n*)	
Osteosarcoma	2
MFH	2
Necrosis (%)	
Overall	84.5 ± 21.9
Osteosarcoma	86.4 ± 21.2
MFH	74.2 ± 24.6
Survival (%)	
Overall	41.5
Stage IIB (*n* = 31)	58.6
Stage III (*n* = 12)	0.0
Osteosarcoma (IIB) (*n* = 24)	60.9
Osteosarcoma (III) (*n* = 11)	0.0
MFH (IIB) (*n* = 6)	50.0
Patient status (*n*)	
Died of disease	23
Died of intercurrent disease	1
No evidence of disease	2
Continuously disease free	17

was performed based on our protocols (B-2, B-3, B-4, B-5) using CDDP IA, HD-MTX, and ADM.

We developed our preoperative chemotherapy protocols, albeit for small populations, to be more intensive in order to achieve more local effects for safer limb salvage surgery. The differences in preoperative chemotherapy between the B-2/3 and B-4/5 protocols were determined based on previous local responses in order to perform more intensive preoperative chemotherapy in the B-4/5 protocols [18] (Table 3).

B-2 protocol Ten patients received B-2 protocol which consisted of three cycles of CDDP IA prior to HIRP, followed by two cycles of HD-MTX as preoperative chemotherapy.

B-3 protocol Nine patients received B-3 protocol which consisted of two cycles of CDDP IA and two cycles of HD-MTX prior to HIRP, followed by an additional two cycles of HD-MTX as preoperative chemotherapy.

B-4 protocol Nine patients received B-4 protocol which consisted of two cycles of CDDP IA and three cycles of HD-MTX prior to HIRP, followed by two cycles of CDDP/ADM and four additional cycles of HD-MTX as preoperative chemotherapy.

B-5 protocol Thirteen patients received B-5 protocol which consisted of three cycles of HD-MTX, two cycles of CDDP IA and two cycles of HD-MTX prior to HIRP, followed by ADM, two cycles of CDDP/ADM and six cycles of HD-MTX as preoperative chemotherapy.

The good responders to initial preoperative chemotherapy in B-4/5 protocols continued preoperative chemotherapy to achieve a complete local response [18, 19]. Two patients with MFH of soft tissue and hemangiopericytoma of bone received two cycles of CDDP IA before HIRP followed by other chemotherapeutic agents including ADM, cyclophosphamide and ifosfamide.

Results

CDDP concentration in perfusate during HIRP

The total and free platinum concentrations in the perfusate were assessed at 5- and 10-min intervals over 60 min during HIRP. The mean highest total platinum and free platinum concentrations were 56.9 and 49.0 μg/ml, respectively, just after starting perfusion with CDDP. The total and free platinum concentration curves of the perfusate during perfusion are shown in Fig. 1. The platinum concentrations decreased gradually and total platinum concentration remained higher than 10 μg/ml throughout the perfusion.

Systemic CDDP and therapeutic advantage

The average level of systemic serum total platinum was 0.40 μg/ml at 30 min and 0.38 μg/ml at 60 min after the start of perfusion, suggesting minimum leakage from the perfused limb. The total platinum concentration in the perfusate was 21.5 μg/ml at 30 min and 14.7 μg/ml at 60 min. The therapeutic advantage was calculated by

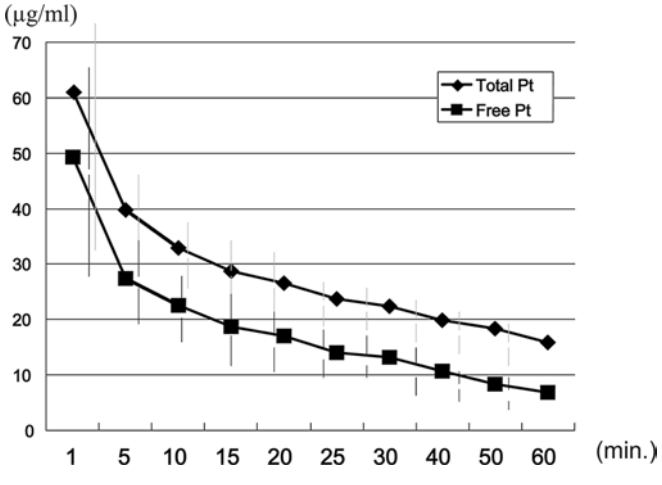

Fig. 1 CDDP concentration in perfusate during HIRP

comparing the corresponding total platinum concentrations of systemic serum and the perfusate. The therapeutic advantage was 54:1 at 30 min and 38:1 at 60 min.

Thermal dose

The temperature within the tumor was monitored during perfusion. The highest temperature was 42.3 ± 1.4°C on average.

Complications of HIRP

There were no systemic complications, but local toxicity (edema, erythema, numbness, and hyperesthesia of the affected limb) was observed in all patients after HIRP.

Grade II toxicity (slight erythema, edema, or loss of sensation) which resolved spontaneously within 2 to 3 weeks postoperatively was seen in 30 patients. Grade III toxicity (considerable erythema or edema with some blistering, slight functional disturbances), including transient peroneal or tibial nerve palsy and thrombosis of the femoral artery, was seen in 9 patients. Thrombosis of the femoral artery was found in 2 patients after HIRP; they required arterial reconstruction at the time of definitive surgery. Transient peroneal nerve palsy was observed in 7 patients, but this motor and sensory neuropathy did not continue permanently.

Grade IV toxicity (extreme epidermolysis or obvious damage to the deep tissues causing definite functional disturbances) was seen in 4 patients. They suffered moderate myolysis, and motor and sensory neuropathy improved gradually, but remained slightly. Although four patients showed grade IV toxicity with functional disturbance (pain and limping), we continued the study because only the peak reaction was determined to be grade IV, and the damage was tolerable, not limb-threatening and decreased to an acceptable range shortly thereafter.

A correlation between grade of local toxicity and maximum temperature in the tumor was not demonstrated in this study (Table 4). We compared the grade of limb reaction and the maximum temperature in the tumor using the method of Di Filippo et al. [29]. No significant grade differences were found at temperatures above or below 41.5°C.

Clinical and oncological results

The mean necrotic ratio was 84.5 ± 21.9%, ranging from 20.3% to 100% in 38 bone sarcomas examined. The effects of preoperative chemotherapy were grade IV (no viable tumor cells) in 13 patients, grade III (> 90% necrosis) in 12 patients, grade II (50 to < 90%) in 9 patients, and grade I (< 50%) in 4 patients. As for the histological evaluation, we excluded areas of degenerated tumor cells from necrosis (Table 3).

In patients with MFH of bone, the mean necrotic ratio was 74.2 ± 24.6%, ranging from 40% to 100%. In patients with osteosarcoma, the mean necrotic ratio was 86.4 ± 21.2%, ranging from 20.3% to 100%. The effects of preoperative chemotherapy were grade IV in 11 patients, grade III in 12 patients, grade II in 7 patients, and grade I in 3 patients.

In control patients with osteosarcoma not treated with HIRP, the mean necrotic ratio was 66.5 ± 35.8%, ranging from 5% to 100%. There was a statistically significant difference ($P = 0.0253$, t-test) in the necrosis ratio in patients with osteosarcoma between those receiving and those not receiving HIRP (Table 5). The effects of preoperative chemotherapy were grade IV in 2 patients, grade III in 4 patients, grade II in 2 patients, and grade I in 5 patients.

Surgical treatment was amputation in 5 patients and tumor excision in 35 patients. The surgical margin was wide resection in 30 and intralesional resection sparing the joint surface in 10 patients. As for local control, local

Table 5 Comparison of clinical results in patients with osteosarcoma

	HIRP	Control (without HIRP)	P value
Total patients (n)	35	13	
Preoperative chemotherapy			
B-2	9	4	
B-3	8	0	
B-4	9	4	
B-5	9	5	
Necrosis ratio	86.4 ± 21.2%	66.5 ± 35.8%	0.0253
Grade of effects (JOA criteria)			
I (< 50% necrosis)	3	5	
II (50 to < 90% necrosis)	7	2	
III (> 90% necrosis)	12	4	
IV (100% necrosis)	11	2	
Local reurrence	2	2	0.2936

Table 4 Limb reaction grade according to the criteria developed by Wieberdink et al. [21]

Limb reaction (grade)	No of patients	Mean maximum tumor temperature (°C)	Maximum tumor temperature < 41.5°C (no. of patients)	Maximum tumor temperature > 41.5°C (no. of patients)
II	30	42.25 ± 1.17	5	25
III	9	42.33 ± 2.21	2	7
IV	4	42.3 ± 0.67	0	4

II/III: $P = 0.8767$, chi-square $P = 0.6022$. II/IV: $P = 0.9302$. III/IV: $P = 0.9774$

tumor recurrences occurred in two patients with osteosarcoma and two patients with MFH of bone. A grade I or II chemotherapeutic response was obtained in three patients, and grade III response in one patient. Surgical margins in these patents were wide in two and intralesional in two.

Prognosis

Mean follow-up of living patients was 108 months ranging from 38 to 189 months. With regard to patient status, 17 patients were continuously disease free, 2 showed no evidence of disease, 23 died of disease, and 1 died of intercurrent disease (secondary leukemia) (Table 3). The overall survival rate was 41.5% in this study and 58.6% in the patients with stage IIB disease. In the patients with stage IIB osteosarcoma, the overall survival rate was 60.9%.

Discussion

Increasing the systemic CDDP dosage with the aim of achieving a higher response is limited due to systemic toxicity such as nephrotoxicity. Nagai et al. [22] have advocated maintaining the systemic plasma level of unchanged CDDP under 2 μg/ml to minimize nephrotoxicity following pharmacodynamic studies. To avoid systemic toxicity, but to raise the effect on local tumor, we have employed regional perfusion.

In previous studies of the pharmacokinetics of CDDP administered by intravenous infusion, the free platinum fraction ranged from 0.05 to 0.10 μg/ml, and total platinum from 0.5 to 5 μg/ml [23–28]. In our study, we were able to achieve significantly greater peak levels of CDDP in the perfusate, representing far higher local concentrations than plasma concentrations following systemic intravenous infusion of CDDP.

Compared with systemic chemotherapy, the therapeutic advantage of HIRP has been shown in previous studies of CDDP concentration [11, 15, 16, 29]. Fletcher et al. [16] showed the primary advantage of isolated limb perfusion comparing the doses of CDDP in the perfusate and systemic CDDP concentration. In our study, we obtained the same level of therapeutic advantage in terms of CDDP concentration as reported in the literature, which suggested minimal leakage from the perfused limb and adequate systemic plasma CDDP levels below those associated with systemic toxicity such as nephrotoxicity and ototoxicity.

Hajarizadeh et al. [30] defined maximum tolerable dose for HIRP with CDDP as 6 mg/kg body weight (200 mg/m^2) for leg CDDP perfusion in the treatment of melanoma of the lower limb. The dose of CDDP in their study was far higher than our CDDP dose (20 mg/m^2 +30–40 mg). The dosages of CDDP for HIRP in other studies were also higher than those in our study [13–16, 29, 30].

We obtained favorable levels of platinum concentration of the perfusate using a lower CDDP dosage in our study. Complications of HIRP such as vascular occlusion and severe muscle damage should be avoided for safer limb sparing surgery and better limb function in the treatment of osteosarcoma. It seems appropriate to use lower and effective dosages of antiblastics for such chemosensitive tumors. We propose a lower dosage of CDDP (20 mg/m^2 +40–30 mg) for HIRP following the favorable platinum concentration of the perfusate and its clinical efficacy in the treatment of osteosarcoma.

Heat may increase antitumor effects by increasing tumor blood flow and membrane permeability. Combining hyperthermia with antitumoral drugs may produce an additive effect. These combinations may have the synergistic effects by increasing the levels of the agents in the tumor cells, by enhancing the DNA crosslinking effect of CDDP, and by inhibiting DNA repair [31]. The temperature of hyperthermia in the treatment of limb sarcoma is limited due to an increased risk of local toxicity including edema, neurotoxicity, and muscle damage.

Hoekstra et al. [15] discussed the possibility that local toxicity of HIRP may be caused by a combination of neurotoxicity of CDDP and increased compartment pressure. Di Filippo et al. [29] considered that a temperature of 41.5°C is a safe set point, because they found a correlation between this cutoff level of hyperthermia and the grade of limb reaction. Our results demonstrated different findings as to the maximum temperature during perfusion. We could not find any significant differences in the maximum temperature between the patients with grade II limb reaction and grade III/IV reaction. Moreover, patients were treated with a higher thermal dose (mean 42.3°C), but the complications of HIRP were usually mild and endurable, and regressed spontaneously. The design of this study and the relatively small number of patients do not enable us to reach any firm conclusions with regard to maximum temperature. Nevertheless, the possibility exists that the optimal thermal dosage could be more than 41.5°C with lower CDDP dose in HIRP.

Further studies including a controlled trial are needed to determine optimal CDDP and thermal dose in HIRP. Advances in extracorporeal circuit technology including the heat exchanger and pump oxygenator and reducing the volume of the circuit would improve the safety and control of the CDDP and thermal dose.

This investigation was conducted with a combination of preoperative systemic chemotherapy consisting of ADR and HD-MTX. We could not evaluate the effectiveness of HIRP in terms histopathological necrosis ratio because our results did not exactly reflect the local antiblastic effect of a single HIRP with CDDP. Our data about the cure rate in stage IIB osteosarcoma was 60.9%, which does not exceed the results of the several recent trials without intraarterial chemotherapy [32–36]. HIRP did not seem to have improved patient survival in spite of its favorable local tumor necrosis rate. Some

studies have shown this discrepancy between local response and general outcome [7, 32].

This local intensification of the dose of CDDP by HIRP cannot solve the general problem of exhibiting systemic micrometastases. Considering the treatment of limb sarcomas, HIRP improved local tumor control and helped achieve safer limb salvage surgery which led to better quality of life of the patients. We compared the postchemotherapeutic histological changes in patients with osteosarcoma treated with conventional preoperative chemotherapy between those receiving and not receiving HIRP. We obtained higher local effects in patients with HIRP than in those without HIRP. Furthermore, a complete local response with 100% necrosis of the local tumors was seen in 11 patients receiving HIRP. And in these good responders, we achieved safer limb salvage surgery with minimization of the surgical margins of the osteosarcoma [19]. Following the favorable local effects found in this study, HIRP using CDDP is considered to be best indicated for patients with osteosarcoma around the knee who are expected to be able to receive limb-sparing surgery. Improvement in local tumor control by local intensive preoperative chemotherapy including HIRP with CDDP could enable us to achieve a safer surgical margin and safer limb salvage surgery.

If we can control local tumor completely, more conservative surgery with minimization of surgical margins of osteosarcoma would be possible. Multimodality treatment of HIRP with preoperative chemotherapy and surgery is a relatively safe and reliable therapeutic option for patients with limb sarcomas, and our method offers excellent local control.

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