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Platinum disposition after intraarterial and intravenous infusion of cisplatin for osteosarcoma*

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Summary. Preoperative chemotherapy according to the COSS 86 protocol, including two courses of cisplatin, was used for high-risk osteosarcoma. Patients were randomised to receive either intraarterial (i.a.) or intravenous (i.v.) cisplatin infusions. As measured by flameless atomic absorption spectroscopy (FAAS), platinum (Pt) levels in serum, ultrafiltrate, and urine did not show a decrease in systemic drug availability with i.a. administration. Tumors were surgically removed 3 weeks after the last cisplatin dose and analysed for Pt content and response to chemotherapy. A correlation could not be demonstrated between Pt levels in tumor tissue samples and the mode of CDDP application or extent of tumor cell destruction.

Introduction

cis-Diamminedichloroplatinum(II) (cisplatin, CDDP) is one of the few cytostatic drugs with proven effectiveness against osteosarcoma [1, 10, 21, 23, 25]. In recent years, it has been among the most widely used medications for both adjuvant and neoadjuvant chemotherapy of this highly malignant bone tumor [9, 17, 24, 29, 32]. Efforts to increase tumor cell destruction in the primary lesion have led to the inclusion of regional CDDP application via intraarterial (i.a.) infusion in several treatment protocols [3, 14, 15, 22, 27]. To define a possible advantage for i.a. administration over the traditional intravenous (i.v.) approach, the Cooperative German/Austrian Osteosarcoma Study Group is currently conducting a controlled study (COSS 86). Patients with high-risk tumors are randomised to receive either two i.a. or two i.v. doses of CDDP at 150 mg/m^2 as part of their preoperative polychemotherapy [31]. Within this multicenter study, the regional and systemic availability of CDDP were assessed by the measurement of platinum (Pt) levels in tumor samples as well as plasma, ultrafiltrate, and urine from patients of both treatment arms.

Material and methods

Patients and treatment protocol. Patients with biopsy-proven osteosarcoma received neoadjuvant polychemotherapy according to the high-risk arm of the COSS 86 treatment protocol [31]. Inclusion criteria required that one or more of three defined prognostic indicators (tumor size, $\geq 1/3$ of the affected bone; $\geq 20\%$ cartilage matrix in biopsy specimens; $\leq 20\%$ scintigraphic response at treatment week 4 [31]) be unfavourable. Preoperative chemotherapy consisted of doxorubicin (90 mg/m^2, week 1) and 2 × 12 g/m^2 methotrexate (weeks 3 and 4), followed by two cycles of 150 mg/m^2 CDDP in conjunction with ifosfamide (2 × 3 g/m^2, weeks 5 and 8). After informed consent was obtained from the patients or their legal guardian, patients were randomised for i.a. or i.v. CDDP infusion. To receive CDDP, test subjects had to be in good general condition, with no mucositis or signs of infection (at least 3 days without fever after a prior infection), their body weight had to be $>85\%$ of that measured before the initiation of neoadjuvant chemotherapy, a WBC of $>3{,}000/\mu l$ and a platelet count of $>100{,}000/\mu l$ were required. Renal function had to be sufficient in all patients [normal blood urea nitrogen (BUN), creatinine clearance of >70 ml/min per 1.73 m^2]; no auditory impairment of >30 dB at frequencies of $\leq 2{,}000$ Hz was permitted.

Ifosfamide/CDDP chemotherapy was applied as follows: ifosfamide (3 g/m^2) and mesna were given with 2 l/m^2 daily i.v. hydration on days 1 and 2. On day 3, 12 h prior to CDDP administration, forced diuresis was initiated at 3 l/m^2 per 12 h with 5% dextrose containing 20 g/l mannitol, 100 mmol/l NaCl, 20 mmol/l KCl, 6 mmol/l Mg^{2+} and 6 mmol/l Ca^{2+}, followed by a 15-min drip of 50 ml/m^2 20% mannitol. Immediately afterwards, a 1-h infusion of CDDP dissolved at 1 mg/ml in 3% NaCl was started via venous access or into an artery directly supplying the tumor, according to randomisation. During the i.a. infusion, blood flow to the part of the infused extremity distal to the tumor was obstructed by means of a tourniquet. On cessation of CDDP application, forced diuresis was continued at 3 l/m^2 per 12 h for 12 h. Posthydration was carried out at 1.8 l/m^2 per 12 h until 24 h and at 2 l/m^2 per 24 h until 72 h after the infusion, using a similar dextrose solution containing less NaCl (40 mmol/l) and no mannitol.

Sample preparation and analytical method. Plasma samples (5 ml) were obtained before, at the midpoint and at the end of each 1-h infusion, as well as 30 and 180 min thereafter. One-half of each plasma sample was immediately processed to ultrafiltrate by centrifugation in a Centrisart I

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tube (SM 13249, Sartorius GmbH, Göttingen) at 2,000 *g* for 15 min. Plasma samples from 38 and ultrafiltrates from 29 i.a. drug cycles were obtained accordingly, as was plasma from 18 and ultrafiltrate from 9 i.v. drug doses. In addition to plasma and ultrafiltrate, samples were obtained from urine voided immediately before each CDDP infusion and from three further collection periods (during the infusion and 0–3 h and 3–24 h thereafter). Urine from 24 i.a. and 18 i.v. infusions was collected in such a fashion. All samples were then sent to one laboratory by regular mail and stored at −18° C until analysis.

All tumors were scheduled for resection 3 weeks after the second CDDP dose. One-half of the undecalcified osteosarcoma was embedded in acrylate [8] and sent to the reference pathologist (Prof. Delling, Universität Hamburg) for determination of the response to preoperative chemotherapy according to the criteria of Salzer-Kuntschik et al. [26].

Pt levels were measured by flameless atomic absorption spectroscopy (FAAS) at 265.9 nm using a graphite tube atomizer (GTA-95, Varian) and a Varian AA-1275 spectrophotometer. The heating program included drying at 85°–120° C for 75 s, charring at 1,000° C for 42 s and atomisation at 2,700° C for 2.9 (fluids) or 3.9 (solids) s. Argon was the inert carrier gas at a flow rate of 3 l/min. Background compensation was achieved by use of a deuterium lamp. Standard absorption curves were obtained by injecting 20 µl standardized Pt solutions (Sigma Corp.) over a range of 0–500 ng Pt/ml and measuring peak heights. Calibration was repeated at least once daily with the same standard solution at 100, 200, and 500 ng Pt/ml. After every 10–15 measurements, absorption was checked at 100 ng/ml.

Biological samples were prepared as follows. Fluids (plasma, ultrafiltrate, and urine) were diluted with demineralized water at 1:10 and immediately injected into the graphite tube of the GTA-95 atomizer. If necessary, further dilution was done to reach the linear part of the calibration curve. Duplicate measurements were made for all fluid samples.

For determination of Pt in osteosarcoma tissue, the undecalcified, acrylate-embedded tumor samples were cut into 20-µm slices. If present, excess acrylate around the edges of the tumor material itself was meticulously removed. The samples were then weighed and 5–10 mg was introduced into the graphite tube without further preparatory steps. Triplicate measurements were carried out for all solid samples. Multiple slices from 29 tumors (14 i.a. and 15 i.v. CDDP infusions) were analysed in this fashion. Samples from osteosarcomas with no CDDP pretreatment were analysed accordingly to exclude an interference of acrylate or tumor with absorption at the point of the curve dedicated to Pt quantification.

Data analysis. Student's *t*-test was used for all statistical analyses. In addition, Wilcoxon's test for matched pairs was used to detect possible differences between the first and second CDDP cycles.

Results

FAAS method

Using standard solutions as described above, a linear absorption/concentration curve was found for Pt concentrations from 0 to 300 ng/ml. Detection limits (signal-to-background-noise ratio, 3:1) were 25 ng Pt/ml in fluid samples and 50 pg Pt/mg tumor in tissue samples. No interfering peaks were observed when CDDP-naive osteosarcomas were analysed. Background effects were well compensated by the deuterium lamp.

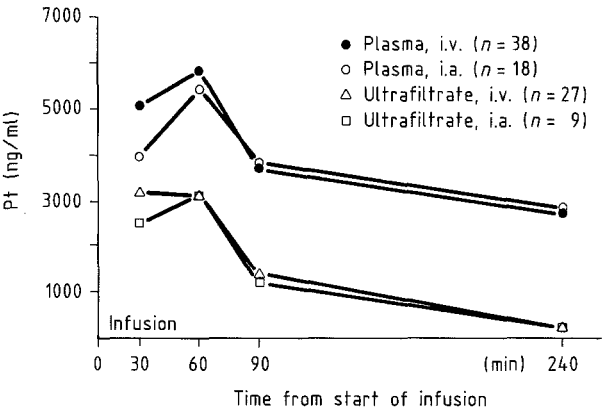

Fig. 1. Mean values (in ng/ml) of total Pt (plasma) and free Pt (ultrafiltrate) after i.a. vs i.v. infusion of 150 mg/m^2 cisplatin over 1 h. No significant differences between i.a. and i.v. administration were observed

Pt in plasma and ultrafiltrate

The i.a. and i.v. infusion of 150 mg/m^2 CDDP led to practically identical Pt concentrations during the whole observation period for both total Pt (plasma) and the free pt moiety (ultrafiltrate) (Fig. 1). Maximal levels of total Pt were reached at the end of the 1-h infusion at 5,464 ± 1,186 ng/ml (i. a.) and 5,820 ± 2,559 ng/ml plasma (i. v.) (not significant). Maximal values for Pt in ultrafiltrate were 3,115 ± 1,160 mg/ml (i. a.) 3,107 ± 812 ng/ml (i.v.), respectively (not significant). Pt was still detectable in plasma before the second CDDP infusion (3 weeks after the first dosage) at concentrations close to 10% of the peak level due to the very long elimination half-life of protein-bound Pt. As expected, the disappearance of ultrafiltrable Pt was much more rapid, such that free Pt was no longer measurable before the second CDDP dose.

Urinary Pt elimination

Cumulative urinary Pt excretion is shown in Fig. 2. Due to difficulties in urine collection, the intervals for the first two collection periods often could not be correctly observed. As a result, the cumulative amount of Pt in urine during the first 4 h after the CDDP infusion began had to be calculated by adding the Pt values found during both periods. Once more, practically identical results were achieved with i.a. and i.v. infusions (Fig. 2).

First and second CDDP infusions

As two preoperative CDDP infusions were given to each patient, the values found after the first and second treatments were analysed for possible differences. No significant variations in the amount of ultrafiltrable Pt or urinary Pt excretion were observed. Due to the slow elimination of the protein-bound fraction, levels of almost 500 ng/ml Pt could still be detected in plasma at the start of the second CDDP infusion, leading to increased concentrations of

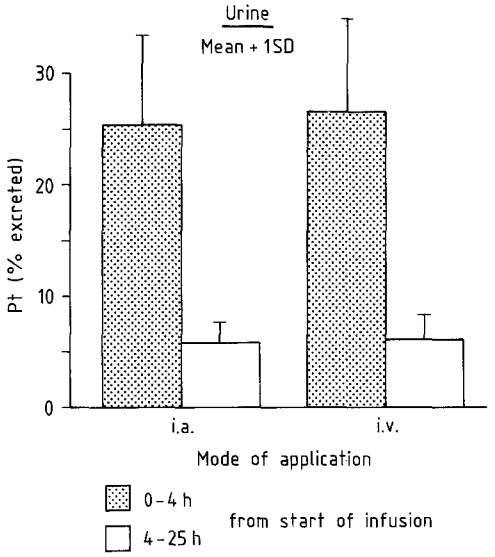

Fig. 2. Cumulative urinary Pt excretion at 0–4 and 4–25 h after the beginning of i.a. ($n = 22/24$) or i.v. ($n = 17/18$) infusions. Values are reported as the percentage of excretion of the given dose (mean ± 1 SD)

total Pt during the second drug cycle. Statistical analysis yielded the same results when the first i.a. and i.v. or the second i.a. and i.v. infusions were compared; the same held true after comparison of the combined cycles, indicating no differences between the treatment arms.

Pt in tumor tissue

Pt concentrations found in slices of tumor tissue are shown in Fig. 3. Levels ranged from unquantifiable (< 50 pg/mg) to a maximum of 950 pg/mg. Although the highest concentrations were found in two tumors from the i.a. treatment arm and all four tumors with no quantifiable Pt had been treated i.v., as a whole no significant differences in Pt levels could be observed between the two groups when

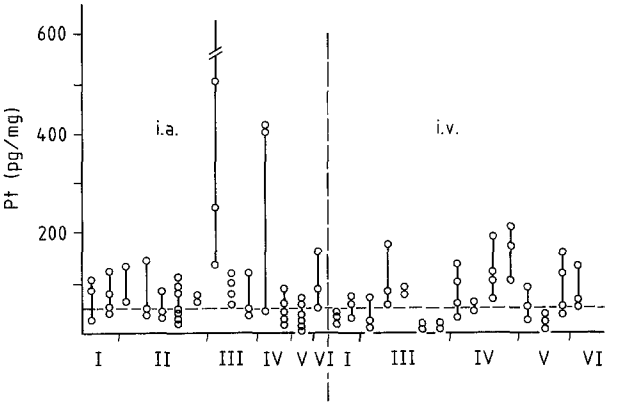

Fig. 3. Pt content (in pg/mg tumor) in acrylate-embedded slices of osteosarcoma tissue. Each point represents the concentration found in one tissue sample; different samples from the same tumor are connected by a *solid vertical line.* Tumors are grouped by mode of cisplatin administration and, within these two groups, by tumor response according to the criteria of Salzer-Kuntschik et al. [26] (*I,* no viable tumor; *II,* occasional viable tumor cells; *III,* <10% viable tumor; *IV,* <50% viable tumor; *V,* >50% viable tumor; *VI,* no effect of chemotherapy)

maximal, minimal or mean Pt levels were compared. Also, we could not demonstrate any correlation between the response of an individual tumor to chemotherapy and its Pt content. Notable intratumor variability was common; Pt levels from undetectable to 1 or several hundred pg/mg could repeatedly be demonstrated within the same osteosarcoma.

Discussion

Intraarterial cisplatin is currently being used by several institutions to enhance the effect of preoperative chemotherapy for osteogenic sarcoma [3, 14, 15, 22, 27, 31]. However, to our knowledge, results of trials comparing the efficacy of i.a. vs i.v. CDDP administration for osteosarcoma have not been published, leaving the suggested superiority of the regional approach to be proven.

At least two distinct pharmacokinetic aspects that may independently determine the success or failure of i.a. treatment with any drug should be kept in mind. First, the *regional advantage* must be great enough to justify the invasive, complicated, time-consuming and potentially hazardous procedure. The extent of this advantage will vary substantially with the total body clearance of the drug used and the plasma flow to the tumor, the ideal situation being a medication with a very high clearance and a tumor with only limited blood supply. For cisplatin, the theoretical advantage of regional application has been calculated to be 5 for arteries with low blood flow (100 ml/min) and only 1.4 for arteries with high flow (1,000 ml/min) [6]. It has been suggested that the pharmacological advantage for i.a. CDDP is limited to situations where the regional plasma flow does not exceed 350 ml/min [5].

Even more important than regional concerns is the *systemic efficacy* of the chemotherapeutic regimen; in osteosarcoma, the effect against micrometastatic disease of the lungs must not be compromised by regional drug administration. Therefore, one important aim of the present study was to exclude negative effects of regional CDDP administration on systemic drug availability by comparing the Pt levels in plasma, ultrafiltrate, and urine after i.a. vs i.v. administration. Our second intention was to search for a possible correlation between tumor Pt, on the one hand, and the mode of CDDP application or tumor response to chemotherapy, on the other.

Systemic drug availability

The concentration of total Pt in plasma alone will not provide sufficient information about the amount of active drug present, as a considerable amount of CDDP is presumably irreversibly bound to plasma proteins within a very short time [7, 16]. Therefore, the level of the concomitantly determined free Pt in ultrafiltrate is much more likely to correlate with the amount of antitumor activity [13].

The concentrations of the two Pt species measured in the present study after i.v. infusions of CDDP are in good agreement with those previously reported by several other investigators [2, 13, 28]. More importantly, our results indicate essentially identical systemic availability of cisplatin, regardless of whether i.a. or i.v. infusion is used. Therefore, the amount of drug capable of acting against micrometastatic lung disease does not seem to be compromised by regional therapy. We could in no way demonstrate a

decrease in systemic drug exposure by i.a. infusion, as was previously suggested by Hecquet et al. [12], who studied i.v. and bilateral hypogastric arterial infusion for advanced uterine cervical tumors. Our conclusion that systemic availability of CDDP is not lessened by i.a. infusion, even when stop-flow mechanisms are used, is further strengthened by observations made by Wile et al. [30]: decreased systemic drug availability in rabbits was observed only after isolated limb perfusion or with outflow occlusion. Mere i.a. infusion or even additional use of stop-flow techniques did not alter systemic availability [30].

The similarity of urinary Pt excretion, which was observed after i.a. and i.v. infusions of CDDP, has previously been noted by Gouyette et al. [11] in 24 head and neck cancers and provides additional proof that any alteration of systemic distribution that might be induced by regional treatment with this drug is, at the most, negligible.

Pt in tumor tissue

Is there a regional advantage for i.a. CDDP application in terms of increased local Pt content? An augmentation of regional venous Pt concentration with i.a. CDDP has previously been described for sarcomas of the extremities [14, 20]. However, we could not demonstrate such an effect in tissue samples of the resected osteosarcoma itself.

Other authors who have compared i.a. and i.v. CDDP infusions in animal models or human tumors came to seemingly conflicting results. When comparing muscle tissue concentrations in an infused extremity of a dog with those on the contralateral side, Mangues et al. [20] found a relative advantage of 500% 3 h after the infusion. Also using a dog model, Madajewicz et al. [19] could demonstrate Pt in brain tissue only after intracarotid, but not i.v., CDDP application. Wile et al. [30] could not demonstrate higher Pt levels after i.a. vs i.v. infusion in tumor samples of experimental VX-2 carcinoma obtained 45 min after the infusion of rabbits. However, the additional use of stop-flow mechanisms during the i.a. infusion led to a significant rise in tumor Pt compared with either i.v. or simple i.a. infusion, as did outflow occlusion or isolated limb perfusion [30]. Gouyette et al. [11], who biopsied head and neck tumors on day 3 after CDDP, observed a tendency towards higher Pt levels after i.a. infusion but could not substantiate an advantage over i.v. application by statistical analysis. Hecquet et al. [12], who treated nine advanced uterine cervical tumors with one i.a. and one i.v. dose each, found higher Pt levels in seven of these after i.a. infusion, in biopsies obtained on the following day.

Could the delay from the last CDDP infusion to surgical resection of the primary osteosarcoma have influenced our findings? Changes in tumor Pt content probably did occur during this time. In fact, Hecquet et al. [12] have demonstrated a substantial decrease in Pt in uterine cervical cancers over a similar perirod of time. However, there is no reason to assume that the disappearance of Pt from sarcoma tissue should be influenced in any way by how the drug got there. Therefore, this time factor does not seem to provide a sufficient explanation for the lack of significant enhancement of tumor Pt with regional treatment.

From a pharmacokinetic viewpoint, the lack of increased Pt deposition in osteosarcoma tissue after i.a. vs i.v. application, as found in our series, is best explained by a relatively high blood supply to these generally well-vascularised tumors. With the given clearance of active, intact CDDP, a high regional plasma flow would reduce the regional benefit of i.a. CDDP for osteosarcoma, or any other cancer, to very small values [6].

In the present study, the amount of tumor destruction achieved by preoperative chemotherapy did not correlate with Pt levels in the primary osteosarcomas. On the other hand, such a correlation has previously been described by Jaffe et al. [14]. This apparent contradiction may be explained by differences in the design of both studies: whereas the preoperative treatment in the latter study consisted of no other drugs than repeated i.a. CDDP infusions, additional antitumor medication in the form of doxorubicin, high-dose methotrexate and ifosfamide was part of the COSS 86 treatment protocol [31]. The effect of these three drugs on the primary tumor may well have obscured any possible relationship between the CDDP effect and the Pt level. Moreover, Jaffe et al. gave up to eight preoperative CDDP doses to each patient, whereas COSS patients were limited to two infusions before removal of the tumor.

A very striking finding in the present study is the pronounced nonuniformity of Pt disposition within the same tumor. Intratumor variations of several hundred picograms Pt/milligram tumor tissue were no rarity (Fig. 3). A similar observation has been made by Gouyette et al. [11] in one case of head and neck cancer. In our study, all tumors were embedded in acrylate in an identical manner; therefore, this procedure would certainly not suffice to explain the variations seen in our cases. In vitro and in vivo models have identified infusate streaming with different drug concentrations in different branches of the blood vessel used for infusion as one possible explanation of intratumor variations [4, 18]. Tumor heterogeneity is another probable reason for this phenomenon.

Conclusion

Intraarterial infusion of CDDP for osteosarcoma in an extremity did not alter systemic drug availability. Therefore, the activity of CDDP against micrometastatic disease should not be compromised by regional administration. No correlation of Pt in tumor tissue with the mode of application or response of the sarcoma to preoperative chemotherapy could be demonstrated. An advantage of regional over systemic CDDP application in this clinical setting remains unproven.

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