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Short communication

Pharmacokinetics and tumor concentration of intraarterial and intravenous cisplatin in patients with head and neck squamous cancer*

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Summary. Tumor-tissue platinum levels and major pharmacokinetic parameters were determined in 11 patients with head and neck squamous cancer (HNSC) who were given cisplatin (50 mg/m^2 daily $\times 2$ days) and 5-fluorouracil (5-FU; 1000 mg/m^2, continuous infusion $\times 5$ days) either i.a. or i.v. The plasma peak platinum concentrations (c_{max}) and the areas under the curve for total platinum concentration versus time (AUC) during i.a. infusions were lower than the i.v. c_{max} (mean, 1.92 ± 0.28 and 4.08 ± 2.80 mg/l, for i.a. and i.v. infusions, respectively) and AUC values (mean, 22.55 ± 4.96 and 40.66 ± 10.71 mg h^{-1} l^{-1} for i.a. and i.v. treatment, respectively), suggesting a first-passage extraction of the drug by the tumor mass during i.a. infusion. However, no statistically significant difference was found in platinum tumor concentrations after i.a. administration versus i.v. infusion. The lack of a difference in tumor platinum concentrations between the i.a. and the i.v. administration routes might be explained either by a relatively high blood supply to the tumor area, enabling efflux of the surplus free platinum from the tissue, or by the delay between drug infusion and biopsy. After three cycles of i.a. treatment good tumor remission was obtained with minimal local toxicity. Larger clinical studies testing the advantages of the i.a. administration route over i.v. infusion appear to be necessary.

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Abbreviations: HNSC, head and neck squamous cancer; AUC, area under the total platinum concentration versus time curve; OS, overall survival; 5-FU, 5-fluorouracil; DFS, disease-free survival; CR, complete response; PR, partial response; SD, stable disease; PRO, progression

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Introduction

Patients with head and neck squamous cancers (HNSC) of stages III and IV have a poor outcome, the cure rate being less than 30% [5], despite combined surgery and radiotherapy. Two-thirds of patients die of local recurrence and disseminate metastases in spite of salvage therapy, including new chemotherapy regimens [14]. Adjuvant chemotherapy is often difficult for HNSC patients, since many of them suffer from associated chronic oral, respiratory and gastrointestinal diseases due to their tobacco and alcohol addiction and to their poor nutritional and oral hygienic conditions [1].

Preoperative or induction chemotherapy with cisplatin and 5-fluorouracil (5-FU) produces response rates of 90% in HNSC patients, with 50%–60% complete clinical response rates being achieved after three cycles of treatment, although this regimen has not yet been proven in randomized studies to prolong disease-free survival (DFS) or the overall survival (OS) as compared with standard radiosurgical treatment [2, 5, 18]. In induction therapy, cisplatin together with 5-FU is considered to be the standard combination due to the higher response rates it achieves in comparison with single-drug treatment and to the evidence for the synergistic action of 5-FU with cisplatin in animal models [10]. Forastiere et al. [6] have shown that a high dose of cisplatin given systemically is extremely useful in induction therapy, but peripheral neuropathy, ototoxicity, and nephrotoxicity become important and dose-limiting toxicities. A response advantage for induction therapy could derive from a combination of the delivery of a high drug dose to the tumor mass and less systemic toxicity.

The i.a. administration of cisplatin might offer the advantage of a lower plasmatic concentration and less systemic toxicity, assuming that part of the drug is trapped by the tumor mass [7, 9, 16]. Many investigators have explored i.a. chemotherapy in HNSC patients because, theoretically, i.a. drug delivery should result in increased concentrations of cytotoxic drug in the blood perfusing the tumor and in lower systemic toxicity.

The present study comparing the i. a. and the i. v. administration routes, although limited by the small number of patients involved, yielded some pharmacokinetic parameters, tumor platinum concentrations, and feasibility and toxicity data. Clinical response data were also obtained in patients bearing HNSC who were treated with i. a. and i. v. infusions of cisplatin in combination with 5-FU. The study was undertaken in December 1987, and the patients were followed until March 1990.

Patients and methods

Patients. A total of 11 previously untreated patients with histologically confirmed squamous epithelioma of the oral cavity (2 patients in stage III and 9 in stage IV) were entered in the study. All subjects had bidimensionally measurable disease, a life expectancy of at least 12 weeks, adequate bone marrow, normal renal function, no evidence of obstructive liver disease and tumor lesions easily accessible for biopsy. All subjects underwent a complete historical and physical examination, including measurements of height, weight, performance status (WHO), and tumor size, along with chest radiography, ECG, urinalysis, a blood chemistry profile, and complete blood cell and platelet differential counts.

All patients were admitted to Vicenza Regional Hospital for therapy and received identical chemotherapy consisting of 50 mg/m^2 cisplatin given daily for 2 days (4-h infusion) and 1000 mg/m^2 5-FU given daily for 5 days as a continuous infusion. The cisplatin infusion rate was 12.5 mg m^{-2} h^{-1}. Prior to treatment, patients were hydrated with 1000 ml saline/2 h along with 40 mg furosemide; postinfusion hydration involved 1000 ml saline with 40 mEq KCl. Intraarterial infusions were given via a catheter that had been surgically placed through the temporal artery into the vessel suppling the tumor; the appropriate position and the perfused area were checked by methylene blue dye injection. A Deltec CADD 1 infusion pump (Pharmacia Sweden) was used for cisplatin and 5-FU infusions.

Treatment was repeated every 3 weeks for three cycles in responding and stable patients; local treatment (surgery and/or radiotherapy) was performed at the end of the chemotherapy. Between the cycles, the i. a. catheter was kept open with a continuous infusion of 1000 IU heparin/day.

Responses were defined as follows:

1. Complete response (CR): the disappearance of all clinical evidence of active tumor for at least 4 weeks. Bone (lytic) lesions should have been replaced by new ossification during this period.
2. Partial response (PR): a measurable decrease of 50% or more in the sum of the products of the greatest perpendicular diameters of all lesions for a minimum of 4 weeks without the appearance of new lesions.
3. Stable disease (SD): a steady state or a response amounting to less than a PR for at least 4 weeks in the absence of symptom aggravation.
4. Progression (PRO): an increase of at least 25% in the size of any measurable lesion and/or the appearance of new lesions.

Standard WHO definitions of toxicity were used.

For the analysis of plasma platinum levels, blood samples were drawn into heparinized tubes at 0, 15, and 30 min and at 1, 2, 4.5, 8, 20, 24, 28, 30. 37, 44, 68, 72, 92, and 120 h after the beginning of the cisplatin infusion. Tumor biopsies were performed on the same lesion in each patient at 48 and 120 h after the cisplatin infusion during the first cycle.

Platinum analysis. Assays of the levels of platinum in biological fluids and tissue samples were carried out using a Perkin Elmer 1030 atomic absorption spectrophotometer (equipped with a graphite furnace) according to the technique described by Leroy et al. [12]. Biopsies of the tumor (no more than 150 mg wet tissue) were weighed and digested in concentrated (approx. 14 *N*) nitric acid at 100° C in a sand bath until they had completely dissolved to a volume of no more than 1 ml. The mixture was then taken up in concentrated HCl and adjusted to a known volume with 0.1 *N* HCl. The solutions were then analyzed for platinum concentration. Blood samples were centrifuged twice, the pellet was discarded, and the supernatant was treated exactly as described for the tissue samples.

Table 1. Patients' characteristics

Characteristic	Group A (i. a.)	Group B (i. v.)
Sex (M/F)	5/1	5/0
Median age (range)	51 (39–73)	47 (40–60)
PS 0–1/2–3 (WHO)	6/0	4/1
Stage III/IV (TNM)	2/4	0/5
Tumor localization:		
Floor of the mouth	3	2
Oropharynx	1	1
Pelvilingual	1	2
Hard palate	1	0
Clinical response:		
CR/PR	4/2	1/1
Total series	6	5
Subsequent treatment:		
Surgery	4	3
Radiotherapy	4	5
Outcome[a]:		
Alive/dead	6/0	2/3

[a] Median follow-up, 26 months

Pharmacokinetic analysis. Pharmacokinetic parameters were calculated using a simplified $t_{1/2\alpha}$ and $t_{1/2\beta}$ two-compartment model for both i. a. and i. v. serum platinum-concentration curves) and a model-independent estimation of pharmacokinetic parameters based on statistical moment theory derived from the medical engineering data-analysis method [3]. AUC values were calculated according to the trapezoidal method [3].

Statistical analysis. Comparison of the pharmacokinetic parameters found for patients receiving i. a. versus i. v. chemotherapy were made using Student's unpaired *t*-test for two arithmetical means.

Results

Clinical findings

The 11 patients received 3 cycles of cisplatin and 5-FU, with group A ($n = 6$) being treated i. a. and group B ($n = 5$), i. v. The patients' characteristics are detailed in Table 1. Two patients in group A were switched to the i. v. administration route after the first cycle because of the development of severe arthritis and facial nerve paralysis in one case and due to catheter displacement in the other.

In group A, we obtained four CRs and two PRs (the two patients who had been switched to i. v. treatment after the first cycle; two of the four CRs were confirmed histologically after surgery. In group B, we obtained 1 CR, which was confirmed histologically after surgery, 1 PR, and 3 SDs. No patient experienced progression of disease after chemotherapy.

Radical surgical resection was performed in seven subjects (four in group A and three in group B). One patient in group A refused further treatment; he was alive, albeit with local recurrence, at 28 months after the end of the chemotherapy cycles. Radiotherapy was given to nine subjects (four in group A and five in group B). All six patients in group A are presently alive after a median follow-up of more than 30 months (range, 7–36 months), and five of

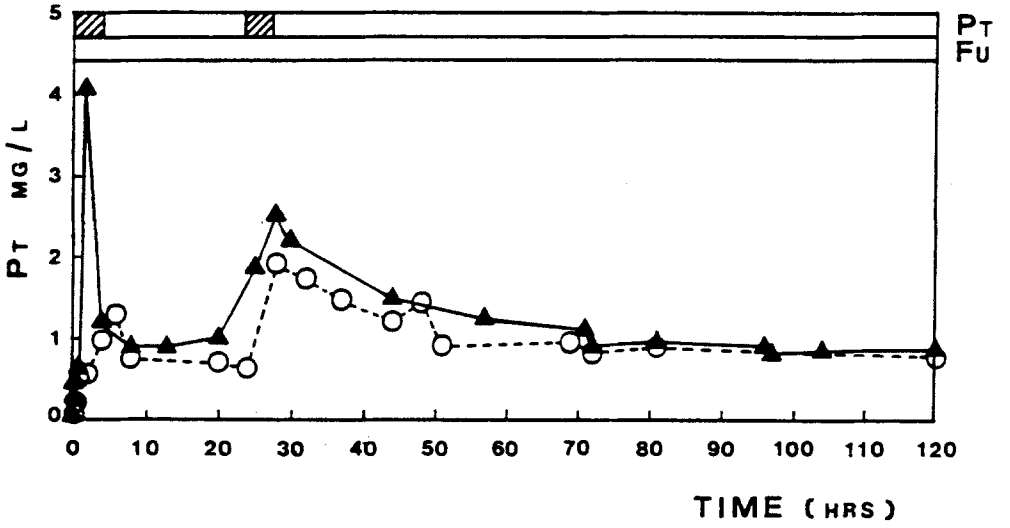

Fig. 1. Mean plasma platinum concentrations measured over a 120-h sampling period during i.a. (○, *dotted line*) and i.v. (▲, *solid line*) infusions of cisplain. In all, 6 HNSC patients were treated by i.a. infusion and 5 received i.v. infusions

them show no evidence of disease recurrence. Three patients in group B died at the 3rd, 10th, and 11th month after the chemotherapy cycles respectively; two died of progressive disease and one of a heart attack. One patient is alive at the 17th month of follow-up and shows no evidence of recurrence, and the other subject is alive despite the development of lung metastasis.

Of the 11 patients, 6 developed grade II toxicity, namely at oral mucosa and at the skin level in group A ($n = 4$) and in the form of leukopenia in group B ($n = 2$). Skin toxicity involved edema, erythema, and desquamation. No nausea or vomiting was observed in group A, but grade II nausea and vomiting occurred in two group B patients. However, no delay or reduction in the dose was necessary in these subjects.

Table 2. Mean pharmacokinetic parameters determined for cisplatin after the first course of treatment

Parameter	Group A (i.a.)	Group B (i.v.)
c_{max} (mg/l)[a, *]	1.92 (± 0.28)	4.08 (± 2.80)
$t_{1/2}$ (min)	45.19 (±25.25)	67.60 (±40.20)
$t_{1/2}$ (h)	23.10 (± 1.84)	25.60 (± 5.89)
AUC (mg h^{-1} l^{-1})[b, **]	22.55 (± 4.96)	40.66 (±10.71)
AUC (mg h^{-1} l^{-1})	109.29 (±27.8)	143.51 (±44.8)
Pt dry tissue (ng/mg)[d]	17.18 (± 8.56)	65.40 (±61.69)

* $P = 0.05$, ** $P = 0.005$

[a] Peak plasma concentration

[b] Calculated using the trapezoidal method at 30 h

[c] Calculated using the trapezoidal method at 120 h

[d] Mean of tumor concentrations found in the two biopsies at 48 and 120 h

Pharmacokinetics

The pharmacokinetic parameters determined during i.a. infusions differed from those found during i.v. infusions as shown in Fig. 1. The distribution half-time values ($t_{1/2\alpha}$) were longer for i.v. treatment (mean, 67.60±40.20 min) than for i.a. infusions (mean, 45.19±25.25 min), but the values found for the half-time of terminal elimination ($t_{1/2\beta}$) were the same for both routes (mean, 23.10±1.84 h for i.a. treatment and 25.60±5.89 h for i.v. infusion) as shown in Table 2. Plasma peak platinum concentrations and AUC values determined after i.a. treatment (at 30 h) were significantly lower ($P < 0.005$) than those measured after i.v. infusion; the mean values are depicted in Table 2. Intratumoral platinum concentrations expressed in nanograms per milligram of dry tissue were higher during i.v. infusions (mean, 65.40±61.69) than during i.a. infusions (mean, 17.18±8.56) as shown in Table 2.

However, it is difficult to have any confidence in the intratumoral platinum – concentration data obtained, since the interindividual variation, the heterogeneous distribution of platinum in tumor tissues, the lack of knowledge about the relative proportions of free and bound platinum, the uncertainty about long-term/low-dose versus short-term/high-dose platinum infusion, and the question of the real pharmacokinetic distribution of the drug, render the data on tissue drug concentration extremely variable. Further studies providing much more information about these problems are needed for the resolution of this uncertainty.

Discussion

Standard management of patients with HNCS consists of surgery, when possible, and postoperative radiation therapy. Despite objective tumor regressions in the locally advanced or recurrent disease with single-agent or combination chemotherapy, these treatment modalites have not resulted in durable remissions or improved survival [18]. The role of induction or neoadjuvant chemotherapy has not yet been established. Several uncontrolled studies have shown impressive results (response rates ranging from 38% to 93%), but randomized studies have failed to prove a prolongation of survival over that achieved using radiotherapy and/or surgical therapy [5]. The present approaches, namely, neoadjuvant chemotherapy given i.v. or i.a., might produce a better response rate and, consequently, might enable "less radical" local treatment and result in longer survival.

We initiated the present study on the effects of a multimodal therapy (cisplatin and 5-FU) on advanced nonpretreated HNSC patients for several reasons:

1. When given i.v., this combination, produces the best response rate.

2. Both cisplatin and 5-FU are active against HNSC and have been extensively used in locoregional therapy, with moderate mucositis and skin erythema occurring in the infused area due to 5-FU and with no local toxicities being attributable to cisplatin [19].

3. Studies by Forastiere et al. [6] and Havlin et al. [8] have indicated a dose-response effect for cisplatin, but the severe myelosuppression, ototoxicity, and neuropathy encountered were dose-limiting. These results led us to check whether high doses of cisplatin given via the carotid artery would produce platinum plasmatic c_{max} and AUC values different from these resulting from i.v. administration of the drug [13, 15].

4. The therapeutic advantage (Rt) of i.a. administration over i.v. infusion can be described as Rt = 1 + apparent plasma clearance/tumor flow [4]; as seen from this point of view, the data obtained in our patients favor i.a. over i.v. infusion. The superselective catheterization of the temporal artery should actually decrease the rate of blood flow to the tumor.

All of the pharmacokinetic parameters presented in this report were calculated on the basis of total platinum, since the ultrafiltration and other techniques used by our group for the separation of total from free platinum would have introduced even more uncontrolled variables into our considerably scattered data. On the other hand, free platinum levels can easily be calculated from the plasma platinum-concentration curves depicted in Fig. 1, using the graphic calculation suggested by Gouyette et al. [7].

In conclusion, the information provided by the present data includes the following:

1. Presumably, cisplatin delivered by i.a. infusion is rapidly trapped by the tumor mass during the first infusion. In Fig. 1, the plasma peak concentration (c_{max}) and AUC values for total platinum in the i.v. curve are higher than those in the i.a. curve. On the other hand, the intratumoral concentration of platinum found after i.a. infusion was no higher than that measured following i.v. infusion. Our failure to find an obvious reason for this discrepancy in the theoretical equation lower plasma peak = higher intratumoral platinum concentration may be explained in several ways: (a) platinum might bind normal and tumoral tissue proteins in different ways [20]; (b) the optimal duration of the infusion/drug dose has not yet been determined, although recent data [11] obtained in experimental animal models have confirmed that only prolonged arterial infusions (lasting 24 or 48 h as compared with our infusion period of only 4 h) enable a real increase of 4–10 times in the concentration of cisplatin in tumor tissues (29 μg/mg tissue for a 48-h i.a. infusion and 2.02 μg/mg tissue for a rapid i.a. infusion); and (c) the optimal time between the infusion and the biopsy has not been determined; the interval that we used might be inappropriate, since there is a lack of information about the way in which platinum is transported from the capillary bed to the body tissues and about the firmness of its retention by normal and tumoral tissues at different times during and after the infusions. For the first cycle, an analysis of the two (i.a. and i.v.) curves (Fig. 1) also reveals that if the cisplatin is trapped by the tumor mass, this occurs only during the first infusion, since the i.a. and i.v. peaks of the second infusion do not significantly differ and the two curves are superimposable after the first infusion.

2. Our pharmacokinetic results indicate that i.a. infusion should favor local drug exposure during the first passage along with minimal alteration of systemic pharmacokinetic parameters; hence, i.a. administration of the drug has the potential of augmenting the antitumor concentration in the locally infused area without altering the systemic antitumor effect. Hecquet et al. [9] obtained similar results in nine patients with advanced uterine cervical cancer, as did Gouyette et al. [7] in HNSC patients.

3. The reduction in c_{max} and AUC values during i.a. administration could enable an increase in the drug dose for the first i.a. infusion that would not enhance systemic toxicities.

4. Our clinical results, which are in line with those presented by Thiss et al. [17], who obtained a total response rate of 95% (including a 60% CR rate) using cisplatin and 5-FU given for three cycles by i.a. infusion as first-line therapy to HNSC patients, lead us to conclude that in advanced HNSC, i.a. infusion of cisplatin and 5-FU should be reconsidered in larger, randomized clinical trials.

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