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Short communication

Platinum concentration in human tumors of head and neck, uterine cervix, and breast following treatment with cisplatin

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Summary. Intratumoral platinum concentrations were measured in three tumor sites (head and neck, uterine cervix, and breast) 48 h after cisplatin administration according to the same protocol.

The platinum levels were in the same order of magnitude in all tumors, but the concentration in breast tumors was found to be higher than that in tumors of the head and neck and of the uterine cervix.

Introduction

The rationale for measurement of antineoplastic agent levels in tumors is that poor permeability of the tissue can decrease the tumor cell kill.

The tissue distribution of platinum after the administration of cisplatin has been studied in animals [3, 6, 8–10] and man [1, 5, 12–14]. The highest concentrations of platinum were found in kidney, liver, and skin for animals, and in kidney, liver, and prostate for man. In human studies the platinum level measurements were performed in autopsy tissue samples of patients who had received cisplatin at widely varying times before death. Platinum levels were higher in the surrounding organ than in the tumor, except in the case of intracerebral tumors. But the comparison of concentrations in tumors at several different sites in the previously published studies was difficult, since there was no standard schedule of administration and the time of biopsying was also not standard.

Therefore, the current study was designed to measure the average platinum concentration in tumors at three sites (head and neck, uterine, cervix, breast) following cisplatin injection according to a standard schedule.

Patients and methods

Patients. In all, 22 patients with tumors easily accessible for biopsy procedures were entered in the study: 9 patients with advanced cancer of the uterine cervix (7 squamous epithelioma, 1 adenocarcinoma, 1 undifferentiated epithelioma); 10 patients with exophytic and non-necrotic head and neck cancer (squamous epithelioma of the oral cavity) (these 19 patients were previously untreated); and 3 patients with breast cancer (recurrent bulky thoracic tumors); the patients with breast cancer had received previous treatment (surgery, radiotherapy, and chemotherapy) but had not been treated with cisplatin.

Protocol of cisplatin administration. Cisplatin (100 mg/m^2) was given IV as a 30-min to 2-h-infusion in normal saline solution. All patients were hydrated IV with normal saline solution 6 h before cisplatin infusion (2 l) and 6 h after cisplatin infusion (2 l). Mannitol was added (250 ml 10% mannitol solution) 30 min before and 30 min after cisplatin injection.

Total platinum serum levels. Serum samples were taken at 5 min, 20 min, and 1 h, 2 h, 4 h, 8 h, 20 h, and 44 h after the end of the cisplatin infusion. Plasma was digested in nitric acid (1 h at 100 °C). After evaporation of the nitric acid, platinum was measured by flameless atomic absorption spectrophotometry (FAAS) according to the methods previously published [4, 7].

Unbound platinum serum levels. Serum samples were ultrafiltered by centrifugal ultrafiltration with centriflo CF50 filters (Amicon SARL, Paris, France) to separate ultrafilterable and protein-bound platinum. Platinum in ultrafiltrates was measured as described above.

Platinum tissue levels. Samples of tumor tissue were removed by a biopsy performed between 44 and 48 h after the cisplatin infusion. The sampled tissues were weighed, air-dried to constant weight, and digested in nitric acid (1 h at 100 °C). After evaporation the platinum was measured as before.

Kinetic analysis. Individual serum concentration time curves were fitted to the appropriate compartment model using the iterative CFT 4A computer program [11]. The desired parameters $t_{1/2}\alpha$, $t_{1/2}\beta$, and AUC were calculated from the estimated parameters by standard pharmacokinetic equations [2].

Statistical analysis. Relationships among the pharmacokinetic parameters were explored using a nonparametric statistical analysis. The Mann-Whitney U-test was used to examine differences between parameters of patients with tumors at different sites. The Spearman rank correlation coefficient was computed to examine any correlation between pharmacokinetic parameters and platinum tumor levels.

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Table 1. Plasma pharmacokinetic parameters and platinum concentrations in tumor biopsies taken 48 h after cisplatin administration (100 mg/m²)

Tumor localisation	Total platinum in plasma			Unbound platinum in plasma		Platinum in tumors
	t1/2 α (min)	t1/2 β (h)	AUC (mg·h·l⁻¹)	t1/2 (min)	AUC (mg·h·l⁻¹)	(μg/g tissue)
Uterine cervix $n = 9$	25±10	120±70	591±430	34±5.3	2.71±1.6	1.8±1
Head and neck $n = 10$	27±16	129±80	656±323			1.6±0.8
Breast $n = 3$	21±14	79±75	672±553			4.2±1.4

Results

Calculated pharmacokinetic parameters and platinum tumor levels 48 h after cisplatin administration are listed in Table 1.

The Mann-Whitney analysis of t½α, t½β, and AUC for total platinum revealed no statistical significant differences in patients with tumors at different sites. Although there is intersubject variability, the plasma pharmacokinetic parameters can be considered as homogeneous in the different populations. The same analysis procedure applied to platinum concentrations in tumors indicated no difference between uterine cervix and head and neck, but did show differences between breast and uterine cervix ($P < 0.04$) and between breast and head and neck ($P < 0.02$).

According to the Spearman coefficient, there was no correlation between the pharmacokinetic parameters (total platinum in plasma) and the platinum levels in tumors when the three populations were considered together. Analysis of the tumors at each site separately indicated a correlation between t½ β and platinum levels in tumor of the uterine cervix only ($P < 0.01$).

Analysis of the pharmacokinetics of free platinum in plasma revealed no significant additional correlation with platinum levels in tumors of the uterine cervix.

Discussion

Human tumor platinum concentration was measured in 22 patients after cisplatin administration. There was good homogeneity of drug dose (100 mg/m²) and of schedule and time of tumor sample (48 h), which allows comparison of tissue levels at different tumor sites. The consistency of administration was verified by statistical analysis of the plasma pharmacokinetic parameters.

No significant correlation was found between plasma pharmacokinetics and platinum tumor levels 48 h after cisplatin administration, except in the case of tumors of the uterine cervix (t½ β).

The tumor levels of platinum found were consistent with the tissue results previously published by others [1–14]. Our data indicate that platinum concentrations are of the same magnitude in the tumors at all three sites studied. While no difference can be noted between platinum levels in tumors of the uterine cervix and head and neck tumors, we observed significantly higher levels in breast cancer.

No response (according to the UICC criteria) was observed for the three heavily pretreated patients with breast cancer. These patients died variously at 3,3, and 12 months after cisplatin treatment. But it should be noted that the number of patients and the eligibility criteria do not allow any conclusion on clinical efficacy of cisplatin on breast cancer tumors.

The platinum levels in breast cancer must be confirmed by a more extensive study but indicate a good permeability of breast tumors to platinum, though these are not currently treated with cisplatin.

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