Noninvasive Monitoring of Drug Biodistribution and Metabolism: Studies with Intraarterial Pt-195m-Cisplatin in Humans

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ABSTRACT

We have performed a comparative evaluation of systemic (i.v.) and intraarterial (i.a.) cisplatin by using a trace dose of the radiolabeled form of this drug (195mPt-cisplatin) to monitor the drug's biodistribution by dynamic scintigraphic imaging. We have analyzed the drug's metabolism using a compartmental model both following i.a. and i.v. administration in patients with gliomas. Significantly larger amounts of radioactivity (up to 10 times higher than in the uninvolved brain) were measured in tumors following i.a. administration, whereas the differential localization following i.v. drug administration was, at best, only twofold that of the uninvolved brain. On the other hand, no significant differences could be detected in the pharmacokinetics of either free cisplatin or platinated proteins in blood. The washout slope in tumors following i.a. administration may be an indicator of the higher local concentration of free cisplatin; no such washout could be observed in tumors following i.v. administration. The present noninvasive methods may help document the amount and the rate of (active) drug deposition at the desired target site. They may also assist in monitoring, prospectively and/or, on line, the probable effect of chemotherapy in an individual patient. In turn it may lead to novel methods for optimizing chemotherapeutic effectiveness at specific tumor-bearing sites and in defined treatment protocols.

INTRODUCTION

Cisplatin is an important drug for the treatment of a variety of human malignancies (1-5). Its optimal dose, route, and mode of administration remain incompletely defined, as are interpatient variations in drug response. Nevertheless, cisplatin by the i.v. route has been part of accepted treatment regimens for a wide variety of neoplasms for over 10 years (6). A greater therapeutic efficacy has been claimed for cisplatin by an i.a. route (7). Since classical pharmacokinetics of cisplatin, based on measurements of blood levels of the drug (8), provide only limited and indirect information on either the nature (free drug, platinated proteins, or other metabolites) or the time-course of the drug at either the target organ or at key toxic or metabolic sites, i.e., the kidneys, we have employed noninvasive radionuclidic methods. These may provide a unique tool for observing and measuring what proportion of the drug has been targeted to the tumor when using different routes of drug administration in a given, single patient. Cisplatin can be radiolabeled intrinsically with 195mPt, a radionuclide with a half-life of 4 days (9).

MATERIALS AND METHODS

Preparation of Radiolabeled Cisplatin. [195mPt]Cisplatin was produced according to methods originally developed in our laboratory (12) and by others (13), following irradiation of 10-30 mg 195Pt target at a flux of 1-3 x 1014 n/cm²·s for 1-3 weeks. Processing of the target yielded 6-10 mCi of [195mPt]cisplatin of greater than 98% chemical purity as fine crystals, and of a specific activity of 0.4-0.8 mCi/mg at end of synthesis. The pure, crystalline [195mPt]cisplatin obtained was dissolved in sterile normal saline (0.9% NaCl) to give 1.0-1.5 mg/ml, and sterilized immediately by filtration through a 0.22-μm Millipore filter, following which its sterility and its radiochemical and radionuclidic purity (necessary for certifying its radiopharmaceutical quality) were documented for each batch.

Dosimetry Considerations and Drug Preparation. Relying on our prior dosimetry estimations for 195Pt (14) in control rats (15), we estimated that no more than 1 mCi should be administered to each patient in order to limit the radiation doses below 5 rads to the kidneys. Animal biodistribution data had documented the kidney as the "critical" organ (e.g., the one receiving the highest radiation dose). This organ is also of concern because of its drug's nephrotoxicity. Radiation doses in patients accrued to this study were first estimated by the CAMIRD III program (16, 17) operating on USC's Academic MVS mainframe system, and more recently, by a modified version of the MIRDose program available from the Radiopharmaceutical Internal Dose Information Center, Oak Ridge Associated Universities (18). 1 mCi of [195mPt]cisplatin was mixed with the chemotherapeutic dose to be administered to each patient (100 mg/m² for i.v. administration and 40-60 mg/m² for i.a. administration, all in 0.9% NaCl). The drug was infused over a 1-h period, while through a separate i.v. line, 250 ml of 3% NaCl, were administered concurrently, as suggested by Earhart et al. (19) and designed to minimize both renal radiation exposure and risk of nephrotoxicity without major alterations in antitumor effects.

Imaging and Pharmacokinetic Studies. For studies monitoring the i.v. administration of cisplatin the patients were properly sedated, hydrated, and placed on an imaging table. A gamma camera (System ZLC 370S, Siemens Medical Systems) was positioned to capture that region of the head where the tumor was located. Data were collected dynamically in 1-min frames during the infusion period (1 h), and for 1 h thereafter. For data analysis, a ROI containing the tumor was selected and the number of counts plotted as a function of time. Other ROIs containing an equal number of pixels were selected from other regions of the brain. At the end of the brain imaging study, 5-min posterior images were obtained from the renal and hepatic regions, respectively. 5-min images of the brain, the liver, and the kidneys were obtained, when possible, at 24 and at 48 h. Blood samples were drawn every 15 min up to 2 h, and at 3, 6, 12, 24 and 48 h following the administration of the drug. The rapid binding of free cisplatin with proteins (20) requires that blood samples be collected from freely circulating blood, and analyzed within a few minutes following its withdrawal from the patient. The composition of the blood was analyzed, using methodology described previously (20, 21). In short, 0.4 ml whole blood was micro-

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The abbreviations and trivial name used are: cisplatin, cis-dichlorodiammineplatinum(II); i.a., intraarterial; ROI, region-of-interest.
fuged, and the plasma treated with 10% trichloroacetic acid, centrifuged again, and all three fractions counted. Urine was collected via a catheter in all patients during the first 24 h, and in some of them up to 48 h postdrug administration.

For monitoring the i.a. administration of cisplatin, the drug was infused through a 2-French catheter placed in the proximal middle cerebral artery, reaching above the ophthalmic artery. This catheter was introduced into the arterial system via a femoral artery puncture, using a 7-French introducer and a 4-French coaxial catheter. The patients received 2000 units of heparin immediately prior to the procedure, and the whole study (catherization, drug infusion, and 1 h of additional postinfusion follow-up) was performed in the angiography suite. Positioning of the catheter was monitored using fluoroscopy. A portable gamma camera was placed on the tumor side of the patient's head, and data again collected dynamically in 1-min frames during the infusion period (1 h), and for 1 h thereafter. Images of the liver and kidneys were obtained as above. Blood and urine collection and analysis were performed as described above.

To qualify for this study, all patients had tumor confirmed by histological examination, had a life expectancy of at least 3 months, and a Karnofsky status of over 40%. No prior chemotherapy within 3 weeks (nitrosourea, 6 weeks) preceding the cisplatin study was allowed. All patients signed an informed consent form for this study, and the California Bill of Rights in Medical Studies. Repeated cycles of the chemotherapy in the same patient required recovery from hematological or other toxic manifestations.

Nine patients have been accrued to this pharmacological study, including three females and six males, 30–57 years of age. The patients' pathological diagnosis included one with recurrent pineal blastoma, one with progressive oligodendroglioma, and seven with recurrent or persistent high-grade astrocytoma (grade III or IV). The initial study which incorporated the first six patients was designed for the patients to receive one cycle of 100 mg/m² of cisplatin i.v. followed at monthly intervals with two cycles of intraarterial cisplatin, 40 mg/m², if technically feasible. Subsequently the study protocol was revised to include an initial randomization between i.v. and i.a. cisplatin for the first cycle with dose escalation steps by 20 mg/m² built in for the i.a. route of every three patients.

RESULTS AND DISCUSSION

The study was terminated as 60 i.a. dose mg/m² was reached. At this dose, all three patients manifested nausea persisting for several days. All patients developed somnolence and asthenia, perhaps related to the procedure and the antiemetics given. Four patients received one cycle each of i.a. and i.v. cisplatin and one patient received two cycles of i.a. cisplatin (40 mg/m²) with no i.v. cisplatin. All but one (noncompliant) patient were monitored for response with a CT scan of the brain every 4 weeks while on study. Because of the heterogeneity of diagnoses, study design and methods of assessment, it is difficult to evaluate therapeutic effects. Overall performance status did not improve following treatment to encourage repeated cycles. However, of those five patients receiving i.a. cisplatin, two patients had a minor response and three patients had stabilization of progressive disease for 2 months. One patient was not retreated after i.v. cisplatin because of technical difficulties in placing the i.a. catheter. The patient remained stable for 7 months. Two patients had progressive disease after the first cycle of i.v. cisplatin and one refused further treatment. We conclude that the 60 mg/m² i.a. is worthy of further therapeutic study (currently being planned), but that further i.a. dose escalations are not warranted in view of toxicities observed by us at our highest dose and by others at higher doses (22).

The time course of the relative activity detected from the region where the tumor is located, as compared to that of an equivalent region-of-interest of the uncompromised area of that patient's brain, is illustrated in Figs. 1 and 2. The patient had received a therapeutic dose of cisplatin radiolabeled with 195mPt cisplatin by either i.v. administration (Fig. 1) or i.a. administration (Fig. 2). These two figures illustrate the general pattern observed. Following systemic drug administration, there was either no detectable or a small differential uptake and retention of activity (1.5- to 2-fold) in the tumor when compared to that of an equivalent unaffected region of the brain. There was also, generally, no discernible change in the activity over the first hour postdrug administration. During i.a. drug administration there was a much larger uptake of the activity in the ROI of the tumor, reaching, at its peak, activities 3–10 times higher than in the control brain, followed by a rapid decrease in the region of the tumor. Such differences are most obvious in patients studied using both modalities of drug administration, as illustrated in Figs. 3 and 4.

Contrary to the major differences in the images and the time-course of the activity in brain, no such differences emerge in the pharmacokinetic profiles. Fig. 5 illustrates the time course of the concentration of the various blood fractions containing 195mPt, including the free drug, platinated protein, and the fraction of the activity retained by the erythrocytes. No differences are seen between concentrations when the drug is administered systemically (Fig. 5, top) or intraarterially (Fig. 5, bottom). While Gouyette et al. (23) reported small differences...
between the levels of the free cisplatin in the jugular and the peripheral blood, they did not document what proportion of the drug administered had been incorporated into the tumor tissue itself. Conclusions drawn from such inferential data (what is remaining in the blood, rather than what has been targeted) are quite limited.

Inasmuch as during noninvasive imaging all that one monitors is the activity of \(^{153}\text{Pt}\), simple imaging measurements provide no direct information on the chemical nature of the activities one is observing. Various assumptions may begin to unravel the chemical nature of the product(s) measured. Compartmental model approaches, as used in the radiopharmaceutical method, allow to relate activity measured to specific product(s) present and have been used, successfully, for estimating the time course of the concentration of cisplatin and its biotransformation products in living systems. Originally, a 7-compartment model had been proposed (24, 25) and subsequently expanded to 8 compartments (26), to account for the biodistribution of cisplatin in control rats. The input required simultaneous time-course data of the drug’s activity in kidney, blood, urinary bladder + urine and whole body, as well as serial measurements of the composition of blood fractions.

Contrary to animal models, in patients dynamic data can only be acquired from limited regions of the body using a gamma camera. A reduced model based on a subsystem (27) approach is presented in Fig. 6: the drug enters the blood as the free drug (compartment 1), it can then be transferred to the target site (compartment 3), and then to other organs and tissues, including the detoxification sites, while it can also be platinated by reaction with blood proteins (compartment 2). The latter compartment (a material no longer active) eventually becomes the major component of the circulating platinum in the blood. The free drug or the platinated proteins that have...
diffused into the tumor space (first into the tumor's extracellular fluid, a domain with low protein concentration), may then reach the tumor cell. Because such a transfer is solely diffusion controlled, it would allow the free drug (MW 300) to diffuse in and out readily, whereas diffusion of platinated proteins (macromolecules) should be significantly slower. Presumably, the free drug can, following penetration into the tumor cell, react with that cell's DNA and proteins, thereby convening the antitumoral effect. Platinated proteins have no known antitumor activity.

Thus, the presence of a significant washout slope in the tumor, following i.a. administration, may be indicative of the high local concentration of free cisplatin, a readily diffusible substance, as seen in Fig. 5, top. On the other hand, the absence of detectable washout, and poor or absence of uptake of $^{195m}$Pt following i.a. administration, may be indicative of mostly poorly diffusible (and inactive) macromolecules, such as platinated proteins.

The importance of first-passage phenomena is reinforced by a study of a patient with a soft-tissue sarcoma in her right ankle, who received 120 mg of cisplatin, labeled with 1 mCi of $^{195m}$Pt cisplatin into the femoral artery over 6 h, as stipulated in this protocol (28). Significant retention of platinum at the tumor site as well as major differences in the activity deposited in other soft tissues (muscle, skin) were noted relative to the opposite (left) leg. The difference between the two legs must be accounted by the high regional concentration of the free cisplatin during first passage.

The radiation burden in patients receiving radiolabeled materials must be kept as low as possible (below the limits defined by 21CFR 361.1). From our prior studies in rats we had estimated the radiation dose in humans, assuming a similar biodistribution of $^{195m}$Pt cisplatin. Table 1 summarizes the human radiation dose estimates generated from the actual biodistribution data obtained. The adult male and/or female model (MIRD Committee, 1988) were used. These radiation exposure values differ slightly from those obtained in control rats (15), which were 4.4 R/mCi for the kidneys and 1.0 R/mCi for the liver. Such differences could be due to differing metabolism of cisplatin in rats and humans, or to the 3% NaCl used clinically in conjunction with cisplatin administration.

What is the potential significance of the type of data generated in this work? While localization data have not been correlable with therapeutic outcome, a study by Stewart et al. in autopsy specimens (29) reported that mean tumor platinum concentrations were higher in those patients who had responded to cisplatin-containing regiments than in the tumor of those that had not responded. Thus, estimates of the amount of the active drug targeted a tumor (e.g., a Quantitative Localization Activity Relationship) (30), might relate to the clinical (pharmacological) response of the patient.

In conclusion, the current study has documented that we can monitor, noninvasively, the relative degree of targeting of cisplatin to human tumors. While we cannot reach any conclusions on the relative therapeutic efficacy of i.a. cisplatin in patients with malignant gliomas, our experience (28) and those of others (31) with i.a. cisplatin in extremity bone sarcomas has been very favorable. Superiority of i.a. over conventional i.v. administration of cisplatin cannot be firmly claimed in the absence of randomized trials, but current observations provide a basis for future clinical and radiopharmacokinetic studies.

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