Cancer Chemother Pharmacol (2010) 66:813–817
DOI 10.1007/s00280-010-1366-1

SHORT COMMUNICATION

Pharmacokinetic analysis of carboplatin in patients with cancer who are undergoing hemodialysis

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Received: 18 February 2010 / Accepted: 6 May 2010 / Published online: 19 June 2010

Abstract
Purpose To examine the safety of carboplatin-based chemotherapy and the applicability of the Calvert formula in patients with cancer who are undergoing hemodialysis.
Methods We treated two patients who were undergoing hemodialysis and received carboplatin-based chemotherapy to treat non-small-cell lung cancer or ovarian cancer. The dose of carboplatin was calculated by the Calvert formula. Glomerular filtration rate was considered to be 0, and the target area under the plasma concentration versus time curve (AUC) was 4 (carboplatin dose, 100 mg) for patient 1 and 5 (125 mg) for patient 2. Carboplatin was administered as a 1-h intravenous infusion on day 1. Hemodialysis was performed for 3 or 4 h, starting 24 h after the infusion of carboplatin had begun. Heparinized blood samples were collected during the first cycle of chemotherapy.
Results The AUCs in patients 1 and 2 were 4.7 and 6.1 (mg/ml min), which were about 20% higher than the target values (4 and 5 mg/ml min, respectively). In the absence of hemodialysis, the hypothetical AUCs were 6.2 and 7.6 (mg/ml min), respectively. The pre-dialysis body clearances of carboplatin were 16.1 and 16.5 ml/min, with elimination half-lives of 17.5 and 13.8 h, respectively.
Conclusion By performing hemodialysis 24 h after the start of chemotherapy, we obtained reproducible and robust AUC data. Use of the Calvert formula allowed carboplatin-based chemotherapy to be performed safely. Our results suggest that the non-renal clearance of carboplatin is lower in Japanese patients than in non-Asian patients.

Keywords Carboplatin · Pharmacokinetics · Renal failure · Hemodialysis

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Introduction

The numbers of patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) have been increasing throughout the world, including United States and Japan [1–3]. The risk of cancer in patents with these diseases is higher than that in the general population [4]. Carboplatin, a platinum derivative widely used to treat many types of malignant tumors, including lung and gynecologic cancers, is less nephrotoxic than cisplatin. The dose of carboplatin can be titrated according to renal function. Carboplatin can therefore be used in patients with impaired renal function, including those who require hemodialysis [5, 6]. However, the safety and therapeutic benefits of carboplatin as monotherapy or in combination with other agents have not been fully assessed in patients with renal insufficiency [7–9].

Use of the Calvert formula, i.e., dose (mg) = target area under the plasma concentration versus time curve (AUC) × (glomerular filtration rate [GFR] + 25), to calculate the dose of carboplatin according to renal function is well accepted in clinical practice. In this formula, the total clearance of carboplatin is expressed as the sum of renal clearance (GFR) and non-renal clearance (+25). Because the Calvert formula was developed on the basis of data from British patients with GFRs ranging from 33 to 135 mL/min [10], however, its validity in patients with renal insufficiency treated by hemodialysis remains to be confirmed.

We describe two patients with chronic renal failure treated by hemodialysis who received carboplatin-based chemotherapy for the treatment of non-small-cell lung cancer and ovarian cancer, respectively. We also report the results of pharmacokinetic analysis. Our primary objectives were to confirm the safety of carboplatin-based chemotherapy in patients with cancer who are undergoing hemodialysis and to determine whether the Calvert formula could be used to calculate the dose of carboplatin.

Method: Carboplatin pharmacokinetics

Both patients gave written consent before starting the pharmacokinetic studies. These studies were considered an integral part of the treatment protocol for the patents and were performed in accordance with institutional guidelines. Pharmacokinetic studies were thus conducted to confirm that the target AUC was achieved in each patient.

Heparinized blood samples were collected during the first cycle of chemotherapy in both patients. The sampling points in patient 1 were before starting the carboplatin infusion; at the end of the infusion; 0.25, 0.5, 1, 2, 4, 6, and 8 h after the end of the infusion; at 24 h (immediately before hemodialysis); and at 28 h (at the end of hemodialysis). In patient 2, the sampling points were before starting the carboplatin infusion; at the end of the infusion; 0.25, 0.5, 1, 2, 6, and 8 h after the end of infusion; at 24 h; and at 27 h. The plasma was immediately separated by centrifugation, and the ultrafiltrate was obtained using Amicon Centrifree micropartition units (Millipore, County Cork, Ireland) and stored at −20°C until analysis. The ultrafilterable platinum level was measured by flameless atomic absorption spectrometry [11]. The carboplatin level was calculated on the basis of the molar ratio of platinum:carboplatin (371.25/195.08).

Pharmacokinetic measurements of carboplatin were obtained with non-compartmental methods using WinNonlin version 5.2 software (Pharsight, Mountain View, CA, USA). The actual AUC of carboplatin in the ultrafiltrate was calculated by the trapezoidal method according to the pre-dialysis, during dialysis, and post-dialysis intervals, with extrapolation to infinity. The elimination half-life ($T_{1/2\beta}$) of carboplatin was estimated by the equation $T_{1/2\beta} = \ln 2/\beta$, where β was the elimination rate as estimated by linear regression, with the log concentration as the outcome variable. The pre-dialysis body clearance of carboplatin was estimated by dividing the administered dose of carboplatin by the theoretical AUC extrapolated to infinity using the data up to the start of dialysis, assuming that hemodialysis had not been performed.

Results

Patient 1

A 51-year-old Japanese man was given a diagnosis of adenocarcinoma of the right lung with massive pleural effusion and multiple metastases to the pleura and to the parenchyma of both lungs (T4N2M1, stage IV). The patient had been receiving hemodialysis because of diabetic nephropathy for 7 years. Arteriovenous fistulas located in the left forearm were used for vascular access. The dialysate flow was 500 ml/min, with a blood flow of 200–220 ml/min. Hemodialysis was provided for approximately 4 h 3 times per week. The dialysate (Kindaly Solution AF-2, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan) contained 2 mEq/L of potassium and 3.0 mEq/L of calcium. The bicarbonate content of the dialysate was 30 mEq/L, and the acetic acid content was 8 mEq/L. The membrane of the dialyzer was polysulfone, with a surface area of 1.6 m^2 (PS-1.6uw, Kawasumi Laboratories Inc., Tokyo, Japan).

The vital signs were normal. On physical examination, the height was 162.0 cm, the body weight was 60.2 kg, the breath sounds over the right lung were diminished, and the performance status was 1. The laboratory data were as follows: white cell count (WBC) 10,800/mm^3, hemoglobin level 12.2 g/dl, platelet count 198,000/mm^3, blood urea nitrogen level (BUN) 20 mg/dl, creatinine level 6.08 mg/dl (normal 0.4–0.7), and serum CEA level 1.1 ng/ml. The patient was scheduled to receive combination chemotherapy with carboplatin and gemcitabin. The dose of carboplatin (100 mg) was calculated with the Calvert formula. The GFR was assumed to be 0, and the target AUC was 4: [4 × (0 + 25) = 100 (mg)].

Carboplatin was administered as a 1-h intravenous infusion on day 1, followed by a 30-min infusion of gemcitabin in a dose of 1,000 mg (650 mg/m^2) on days 1 and 8, both of which were non-dialysis days. The dose of gemcitabin was reduced to 650 mg/m^2 because of renal insufficiency [12].

During the first cycle of chemotherapy, fever (37.5°C) developed on day 4, and the patient received antibiotics, despite no convincing evidence of infectious disease. The

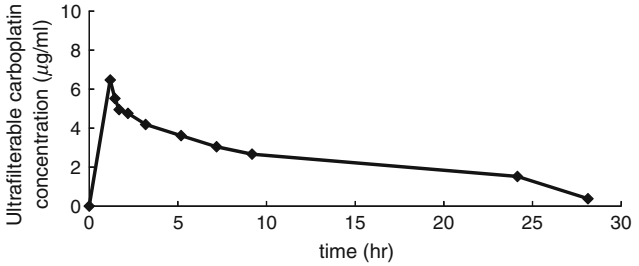

Fig. 1 Ultrafilterable carboplatin concentration in plasma after administration of carboplatin in patient 1

patient also had grade 3 anemia requiring red blood cell transfusion on day 7, grade 3 neutropenia requiring granulocyte colony stimulating factor (G-CSF) support on day 7, and grade 2 thrombocytopenia on day 9. Gemcitabine was not administered on day 8 because of the hematologic toxicity. A computed tomography scan of the chest after the first cycle of chemotherapy showed progression of the pleural metastases, and the treatment was terminated (Fig. 1).

Patient 2

A 53-year-old Japanese woman was admitted to the chemotherapeutic unit because of a recurrence of ovarian cancer. The patient had undergone curative surgery for the disease 1 year previously. The very high serum CA-125 level of 657.3 U/ml (normal 0–35) indicated that disease had recurred in the abdominal lymph nodes. The patient had been undergoing hemodialysis because of polycystic kidney for 1 year. Arteriovenous fistulas in the right forearm were used for vascular access. The dialysate flow was 500 ml/min, with a blood flow of 200 ml/min. Hemodialysis was performed for approximately 3 h 2 times per week. The dialysate (AK-SOLITA FL, Ajinomoto Pharma Co., Inc. Tokyo, Japan) contained 2 mEq/L of potassium and 2.5 mEq/L of calcium. The bicarbonate content of the dialysate was 27.5 mEq/L, and the acetic acid content was 9 mEq/L. The membrane of the dialyzer was cellulose triacetate, with a surface area of 1.5 m^2 (FB-150, Nipro Corp, Osaka, Japan) (Table 1).

The vital signs were normal. On physical examination, the body height was 160.2 cm, and the body weight was 63.1 kg, palpitation revealed bilateral enlargement of the inguinal lymph nodes, and the performance status was 0. The laboratory data were as follows: WBC 5,410/mm^3, hemoglobin level 11.1 g/dl, platelet count 263,000/mm^3, BUN 43 mg/dl, and creatinine level 8.72 mg/dl. The patient received combination chemotherapy with carboplatin and paclitaxel.

Similar to the patient 1, the dose of carboplatin was calculated with the Calvert formula, given a target AUC of 5: [5 × (0 + 25) = 125 mg]. The calculated dose of 125 mg was given as a 1-h intravenous infusion on day 1 (a non-hemodialysis day), followed by a 3-h infusion of a full dose of paclitaxel (285 mg) [13]. Hemodialysis was performed over the course of 3 h, starting 24 h after treatment with carboplatin.

The patient had grade 4 neutropenia requiring G-CSF support on day 10, accompanied by grade 2 peripheral neuropathy. After the completion of two cycles of combination chemotherapy, a partial response (PR) was achieved (Fig. 2).

Table 1 Pharmacokinetic parameters of ultrafilterable carboplatin

Parameter	Patient 1	Patient 2
C_{max} (μg/ml)	6.47	9.27
AUC (mg/ml min)		
Target	4	5
Pre-dialysis	3.90	5.52
Post-dialysis	0.58	0.36
Total (actual AUC)	4.7	6.1
$T_{1/2\beta}$ (h)		
Pre-dialysis	17.5	13.8
Pre-dialysis CL (ml/min)	16.1	16.5

C_{max} maximum plasma concentration, *AUC* area under the curve *versus* time curve, $T_{1/2\beta}$ elimination half-life, *CL* plasma body clearance

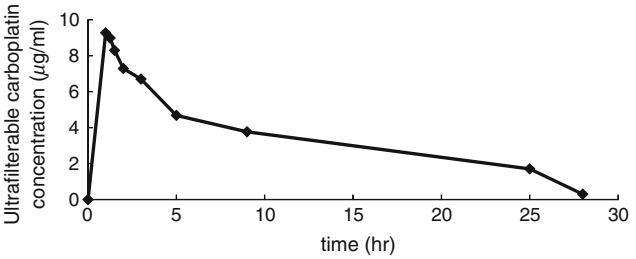

Fig. 2 Ultrafilterable carboplatin concentration in plasma after administration of carboplatin in patient 2

Pharmacokinetic data

The actual AUC in patient 1 was 4.7 (mg/ml min), which exceeded the target AUC of 4 (mg/ml min). If hemodialysis had not been performed, the hypothetical AUC would have been 6.2 (mg/ml min). The pre-dialysis body clearance was 16.1 ml/min, and the $T_{1/2\beta}$ was 17.5 h.

The actual AUC in patient 2 was 6.1 (mg/ml min), which exceeded the target AUC of 5 (mg/ml min). If hemodialysis had not been performed, the hypothetical AUC

would have been 7.6 (mg/ml min). The pre-dialysis body clearance was 16.5 (ml/min), with a $T_{1/2\beta}$ of 13.8 h.

Discussion

The dose of carboplatin was estimated on the basis of target AUCs of 4.0 and 5.0 (mg min/ml) in patient 1 and patient 2, respectively. GFR in the Calvert formula was considered to be 0, assuming that these patients had no renal function (GFR = 0). Pharmacokinetic analysis revealed that the actual AUCs in these patients were 4.7 and 6.1 (mg/ml min), respectively. These values were about 20% higher than the target AUCs [14], but were within the clinically acceptably range.

We recently evaluated the Calvert formula in Japanese patients with cancer in whom accurate GFR values were calculated on the basis of inulin clearance, the gold standard for the estimation of GFR. By analyzing the pharmacokinetics of carboplatin in 21 patients with GFR of 17.2–91.4 ml/min, it was found that the Calvert formula using GFR calculated on the basis of inulin clearance overestimated actual carboplatin clearance with a mean prediction error of 14.3% (unpublished data). Although the Calvert formula does not provide a precise estimate of non-renal clearance, the findings suggested that apparent non-renal clearance (+25) in the formula might be lower in Japanese patients than in those in the United Kingdom. In any case, this overestimation of apparent non-renal clearance would, at least in part, lead to overdosing of carboplatin in Japanese patients. We therefore proposed the following formula for Japanese patients: dose (mg) = target AUC (mg min/ml) × (GFR + 15), in which non-renal clearance is decreased to 15 instead of 25, used in the original formula (in submission). In fact, the pre-dialysis body clearances of ultrafllterable carboplatin in the present study were 16.1 and 16.5 ml/min, which are similar to the mean non-renal clearance in our revised formula, consistent with the results of our previous study.

We achieved reproducible and robust AUC data by performing hemodialysis 24 h after starting chemotherapy in both patients. If hemodialysis had begun immediately after the end of chemotherapy, the actual AUC values would have been less reliable and more unstable because they strongly depend on the hemodialysis schedule, especially during the first few hours after chemotherapy, i.e., pharmacokinetic data indicate that drug concentrations in blood would rapidly decrease during the distribution phase. In addition, this AUC-based strategy for calculating the dose of carboplatin allowed us to base our assumptions on the extensive clinical evidence obtained in patients with normal renal function.

In patient 1, the dose of gemcitabin was reduced from the standard dose of 1,000–650 mg/m^2 (1,000 mg) because of renal insufficiency [12]. Gemcitabine exerts its cytotoxic effects after intracellular phosphorylation to its active metabolites, gemcitabine diphosphate and triphosphate. Therefore, renal dysfunction appears not to contribute to the accumulation of cytotoxic metabolites in the body. This is supported by a case report in which a patient who was undergoing hemodialysis received a standard dose of gemcitabine (1,000 mg/m^2). The pharmacokinetics of gemcitabine itself were not altered, whereas the AUC and the half-life of the inactive metabolite dFdU were significantly larger and longer than usual, respectively. Plasma dFdU was effectively eliminated by hemodialysis [15, 16].

Renal impairment altered the clearance of gemcitabine and caused increased drug toxicity in another trial [12]. In that study, a reduced dose of gemcitabine (650 or 800 mg/m^2) was given to patients with renal dysfunction (serum creatinine level 1.6–5.0 mg/dl). Although the pharmacokinetics of gemcitabine and its metabolite dFdU were similar to those previously reported in patients with normal renal function, clinically significant toxicity developed, despite the reduced dose of gemcitabine.

In our study, a full dose of paclitaxel was administered in the patient 2. A combination of carboplatin and paclitaxel is currently the standard treatment of choice for first-line chemotherapy in patients with ovarian cancer [13]. Paclitaxel is extensively metabolized by hepatic cytochrome P450 enzymes and excreted mainly into bile; less than 10% is excreted by the kidneys. Therefore, standard doses of paclitaxel can be administered to patients with renal impairment who are receiving hemodialysis, with no changes in pharmacokinetics [17, 18].

Although our experience is limited to 2 patients, our pharmacokinetic analysis indicates that the Calvert formula can be used to calculate the dose of carboplatin in patients with cancer who are undergoing hemodialysis. By performing hemodialysis 24 h after the start of chemotherapy, we obtained reproducible and robust AUC data on carboplatin. When the original Calvert formula was used to calculate the dose of carboplatin, actual AUC values were higher than the target AUC by about 20%, suggesting that non-renal clearance is lower in Japanese patients than in non-Asian patients.

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