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SHORT COMMUNICATION

Pharmacokinetics of carboplatin in a hemodialysis patient with small-cell lung cancer

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Abstract
Purpose We examined a method to determine the dose of carboplatin and the timing of hemodialysis in carboplatin-based chemotherapy for a hemodialysis patient with cancer.
Methods Carboplatin-based chemotherapy was performed for a patient with small-cell lung cancer who was receiving hemodialysis. The dose of carboplatin was calculated based on body surface area in the first cycle (480 mg/body, Day 1) and based on the Calvert formula with the aim of achieving AUC of 5 mg/ml min in the second cycle (170 mg/body, Day 1). Carboplatin was continuously infused for 1 h on Day 1 of each cycle. Hemodialysis was performed for 4 h beginning 1 h after administration of carboplatin.
Results The AUC of free carboplatin administered in the first and second cycles was 13.45 and 5.74 mg/ml min, respectively, and $t_{1/2}$ was 24.66 and 21.84 h, respectively. Protein binding ratio depended on the time after administration and reached a value ≥50% only at ≥24 h administration.
Conclusion Based on the results of this study, a value close to the targeted AUC can be obtained in a hemodialysis patient with cancer when carboplatin is administered at a dose determined based on the Calvert formula. These results may be useful to achieve a targeted AUC in hemodialysis patients. A certain amount of carboplatin can be eliminated by performing hemodialysis in an early phase when protein binding ratio is low after transition to the elimination phase to enable stable the concentration.

Keywords Carboplatin · Hemodialysis patient · Small-cell lung cancer · Calvert formula

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Introduction

The population of patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) has increased worldwide [1–3]. Patients with these diseases also have a high risk of cancer and require hemodialysis (HD) in many cases [4]. Carboplatin (CBDCA) is a platinum derivative that is widely used to treat many types of malignant tumors, including lung cancer. CBDCA is less nephrotoxic than cisplatin and the dose can be titrated according to renal function. Therefore, CBDCA can be used in patients with impaired renal function, including those who require HD [5, 6]. However, it has been reported that protein binding ratio of CBDCA changes with time and that the elimination efficiency of CBDCA changes based on the timing of HD, which suggests that stable blood concentrations may not be maintained. Thrombocytopenia accompanied by bone-marrow

suppression has also been described as a severe side effect of CBDCA [7, 8], and this may prevent continuous chemotherapy. The dose of CBDCA is generally designed based on body surface area (BSA) or the Calvert formula [9], but these methods were not developed for patients with renal failure who require HD [10]. Therefore, to permit continuous chemotherapy without severe side effects in such patients, determination of the appropriate dose and timing of HD are important. The subject in the current study received CBDCA-based chemotherapy concomitantly with etoposide (ETP) for small-cell lung cancer (SCLC) while undergoing HD for chronic renal failure. To ensure safe HD during chemotherapy, we performed an analysis of the pharmacokinetics of CBDCA and examined the appropriate method for dose design and the timing of HD.

Methods

CBDCA concentrations were determined using measurements in heparinized blood samples that were collected during each cycle of chemotherapy. The sampling points were 0.5, 1 (immediately before the 1st HD session), 3, 5 (at the end of the 1st HD session), 7, 24, and 45.5 h (immediately before the 2nd HD session) after the end of CBDCA infusion. The plasma was immediately separated by centrifugation and the ultrafiltrate was obtained using an Amicon Centrifree Micropartition Unit (Millipore, County Cork, Ireland) and stored at −20°C until analysis. Free platinum (Pt) concentrations were determined using an atomic absorption photometer Z5700 (Hitachi Co., Tokyo) according to the method of LeRoy et al. [11]. The CBDCA level was calculated using the molar ratio of Pt/CBDCA (371.25/195.08). Pharmacokinetic measurements of CBDCA were obtained with non-compartmental methods using MOMENT, as developed by Yamaoka et al. [12, 13].

Ethics

This study was approved by the ethics committee of the National Hospital Organization Kumamoto Medical Center. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonization guidelines for good clinical practice [14, 15].

Results

Patient

The patient was a 74-year-old Japanese man with a diagnosis of SCLC (cT4N3M0; T4 shows direct invasion to large blood vessels, and N3 shows enlarged lymph nodes in the ipsilateral supraclavicular fossa). The patient had been receiving HD for ESRD for 4 years. Arteriovenous fistula located in the left forearm was used for vascular access. The dialysate flow was 500 ml/min, with a blood flow of 200 ml/min. HD was provided 3 times per week for approximately 4 h in each session. The dialysate (Kindaly Solution 2E, Fuso Pharmaceutical Industries, 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 dialyzer had a polymethyl methacrylate (PMMA) membrane with a surface area of 1.8 m^2 (BG-1.8PQ, Toray Industries Inc., Tokyo, Japan). The vital signs of the patient were normal. On physical examination, height was 163.0 cm, body weight was 58.0 kg, FEV1 (forced expiratory volume in 1st second) was 72%, and performance status was 0. Laboratory data were as follows: white blood cell (WBC) count 6,500/mm^3, hemoglobin 10.4 g/dl, platelet count 167,000/mm^3, blood urea nitrogen (BUN) 20 mg/dl, and creatinine 5.62 mg/dl.

The first cycle of chemotherapy was performed with a regimen of CBDCA (300 mg/m^2 on Day 1) + ETP (50 mg/m^2 on Days 1 and 3); that is, 480 mg/body of CBDCA (Day 1) + 80 mg/body of ETP (Day 1 and 3). On Day 1, HD was performed 1 h after completion of chemotherapy. Non-hematotoxicity was not observed, but decreases in neutrophils and platelets were found and thrombocytopenia of G4 (evaluated using the Common Terminology Criteria for Adverse Events: CTCAE Ver. 4.0) was observed on Day 12. Thus, platelet transfusion was performed. Decreases in WBC count and neutrophils (G4) were also observed on Day 16, and G-CSF was administered. Chemotherapy was suspended until bone-marrow suppression was improved.

The second cycle of chemotherapy was performed on Day 34 after the initial administration. Since severe decreases in neutrophils (G4) and platelets (G4) occurred after the initial administration of CBDCA using a dose calculated based on BSA, the dose of CBDCA for the second cycle was determined using the Calvert formula, with the aim of achieving AUC of 5 mg/ml min; that is, 170 mg/body (Day 1) of CBDCA + 80 mg/body (Day 1 and 3) of ETP. Non-hematotoxicity did not occur, but thrombocytopenia of G4 developed on Day 12, and thus, platelet transfusion was performed. A mild decrease in platelets also occurred, but the subject was discharged from hospital on Day 15.

Pharmacokinetic analysis

The results of analysis of the disposition of total CBDCA and free CBDCA are shown in Table 1 and Fig. 1a, b. With administration of CBDCA at a dose determined based on

Table 1 Results of pharmacokinetic analysis of the disposition of CBDCA

Dose		ER (%)	Rebound rate (%)	$AUC_{(\infty)}$ (mg/ml min)	$MRT_{(\infty)}$ (h)	CL_{tot} (ml/min)	$t_{1/2}$ (h)	AIC
Dose determined based on BSA (480 mg/body)	Total CBDCA	75.84	2.55	32.66	59.75	14.70	44.82	−13.46
	Free CBDCA	79.71	3.58	13.45	26.32	35.69	24.66	−8.39
Dose determined based on the Calvert formula (170 mg/body)	Total CBDCA	67.77	4.63	18.12	70.51	9.38	50.65	−13.03
	Free CBDCA	74.91	6.83	5.74	23.31	29.64	18.05	−4.12

Total and free CBDCA concentrations were converted from total and free Pt concentrations using the molecular weight ratio, respectively. Disposition was evaluated using moment analysis, as described by Yamaoka et al.

CBDCA Carboplatin, *ER* elimination rate, *AUC* area under the blood concentration time curve, *MRT* mean residence time, CL_{tot} total clearance, $t_{1/2}$ half-life, *AIC* Akaike's Information Criterion, *BSA* body surface area

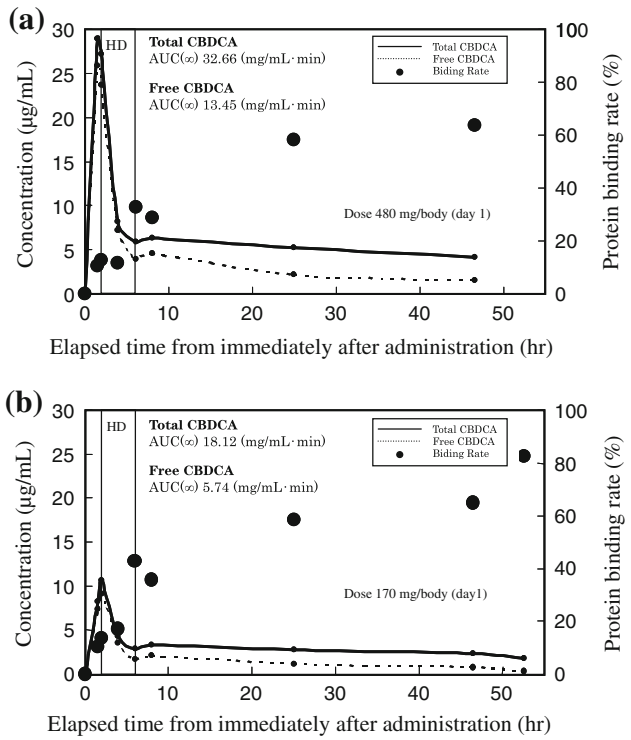

Fig. 1 Changes in concentrations and protein binding of total and free CBDCA in **a** the first cycle and **b** the second cycle. Elapsed time is shown from immediately after administration

BSA (480 mg/body on Day 1), the areas under the blood concentration time curves (AUCs) of total CBDCA and free CBDCA were 32.66 and 13.45 mg/ml min, respectively; the $t_{1/2}$ values were 44.82 and 24.66 h, respectively; and the mean residence times (MRTs) were 59.75 and 26.32 h, respectively. In contrast, with administration of CBDCA at a dose calculated based on the Calvert formula (170 mg/body on Day 1), the AUCs of total CBDCA and free CBDCA were 18.12 and 5.74, respectively; $t_{1/2}$ values were 50.65 and 18.05 h, respectively; and MRTs were 70.51 and 23.31 h, respectively. Rebound phenomena were observed after completion of each HD session, with rebound rates of free CBDCA in the first and second cycles of 3.58 and 6.83%, respectively.

Discussion

In this study, a patient with SCLC who was receiving HD showed a favorable response to chemotherapy with CBDCA + ETP, with an adverse effect of treatable hematotoxicity. Administration of CBDCA at a dose determined BSA gave values of AUC, $t_{1/2}$, MRT and CL_{tot} for free CBDCA of 13.45 mg/ml min, 24.66, 26.32 and 35.69 ml/min, respectively, whereas after administration of a dose determined using the Calvert formula, these values were 5.74 mg/ml min, 18.05, 23.31, and 29.64 ml/min, respectively (Table 1). These data show that the rate of CBDCA excretion in this case was lower than that in patients with normal renal function [16].

There are various opinions on the timing of HD in patients who are receiving CBDCA. Generally, it is thought that protein-bound drugs are difficult to eliminate in HD. Sooriyaarachchi et al. [17] reported a protein binding rate of CBDCA of approx. 40% at 24 h after administration, and in the current study we found that protein binding of CBDCA was time-dependent, with 24 h required to achieve 50% binding (Fig. 1a, b). The slope in the plot of blood concentrations showed that distribution ended approx. 3 h after the end of CBDCA infusion. Based on these findings, we suggest that HD should be performed in a period when protein binding ratio is low immediately after administration of CBDCA after completion of the transition to the elimination phase to ensure maintenance of a stable CBDCA concentration.

The Calvert formula is widely used to determine the dose of CBDCA. In this formula, the dose (mg) = target area under the plasma concentration vs. time curve (AUC) × (glomerular filtration rate [GFR] + 25) [9]. The total clearance of CBDCA is expressed as the sum of renal clearance (GFR) and non-renal clearance (+25). However,

the Calvert formula was developed using data from British patients with GFRs ranging from 33 to 135 ml/min and its validity in patients with renal insufficiency treated by HD remains to be confirmed [9]. Inoue et al. [10] suggested that chemotherapy with CBDCA (300 mg/m^2/day) + ETP (50 mg/m^2/day) may be appropriate as a regimen for SCLC patients who were receiving HD. However, the pharmacokinetic analysis in this study suggested that a concentration close to the targeted AUC was achieved when HD was performed immediately after the administration of a dose determined with the Calvert formula using the GFR of HD patients. Therefore, we suggest that a dose of CBDCA determined using the Calvert formula is appropriate in carboplatin-based chemotherapy for patients receiving HD.

The plasma Pt concentration in HD patients measured 24 h after administration of CBDCA has been reported to be equivalent to that in patients with normal renal function. However, a small amount of plasma Pt may not be filtered after HD and may be retained for a longer period in patients with renal dysfunction [16]. This may be a contributory factor in bone-marrow suppression. Consistent with this suggestion, we found an increase in AUC in our patient after administration of CBDCA at a dose determined based on body surface area, and this may have caused subsequent hematotoxicity. Only a small number of HD patients are treated with chemotherapy with a CBDCA + ETP regimen for SCLC and measurement of blood concentrations of CBDCA requires a specific methodology that cannot be performed in routine examinations. Therefore, we were only able to describe a single case in this study. In addition, we did not examine ETP pharmacokinetics because this drug is metabolized in the liver. Thus, the effect of decreased renal function on ETP is likely to be small.

Within these limitations, we were able to examine the timing of HD and compare AUC values after CBDCA administration at doses determined based on BSA and the Calvert formula. We conclude that HD should be performed approx. 3 h after the end of CBDCA infusion of a CBDCA-based chemotherapy regimen for HD patients with SCLC, in order to maintain a stable CBDCA concentration. We found that the CBDCA dose determined based on the Calvert formula was more appropriate, but this requires validation in further studies. Chemotherapy in HD patients should be performed carefully with particular attention to the development of hematological toxicities.

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