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Carboplatin Pharmacokinetics in a Patient Receiving Hemodialysis

Mei Ka Fong^{1,*}, Gerald J. Fetterly Jr², Lori J. McDougald², and Renuka V. Iyer²

¹Department of Pharmacy, Roswell Park Cancer Institute, Buffalo, New York

²Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York

Abstract

With refinements and advances in hemodialysis techniques, survival for patients with end-stage renal disease has improved significantly. To our knowledge, however, no prospective trials have been performed in patients receiving hemodialysis who are also diagnosed with cancer and are candidates for chemotherapy. We describe a 73-year-old man who was diagnosed with high-grade neuroendocrine carcinoma, metastatic to the bone and lymph nodes, and was undergoing hemodialysis. Although cisplatin is more commonly used in the treatment of metastatic neuroendocrine cancers, it may not be the best option in patients who suffer from renal insufficiency. Carboplatin is a second-generation, nonnephrotoxic platinum analog that can be hemodialyzed, although no formal guidelines are available regarding the dosing for patients receiving hemodialysis. This case describes a patient who was treated with five cycles of combination carboplatin 115 mg/m² on day 1 and etoposide 50 mg/m² on day 1 and day 3 of a 28-day cycle. Dialysis was performed for 3.5 hours starting 90 minutes after completion of carboplatin on day 1. Pharmacokinetic assessments were performed at 1, 2, 4, and 12 hours after chemotherapy infusion on day 1 of cycle 1. Total carboplatin concentrations in plasma and platinum ultrafiltrate were measured. The plasma concentration of free platinum at the end of the infusion was 31,000 ng/ml, and the area under the plasma concentration–time curve was 2.9 minute·mg/ml. No significant carboplatin-related toxicities were reported. This case report indicates that carboplatin can be safely administered in patients receiving hemodialysis.

Keywords

carboplatin; oncology; dialysis; chemotherapy; pharmacokinetics; neuroendocrine

With refinements and advances in hemodialysis techniques, survival for patients with end-stage renal disease (ESRD) has improved significantly. To our knowledge, however, no prospective trials have been performed in patients receiving hemodialysis who are also diagnosed with cancer and are candidates for chemotherapy. First-line options for the treatment of metastatic neuroendocrine tumors include platinum-based combination therapy, with a high proportion of patients having a significant radiographic response. The most

commonly used platinum compound in metastatic neuroendocrine tumors is cisplatin. Unfortunately, the nephrotoxicity of cisplatin often precludes its use in patients who would otherwise benefit from a platinum-containing regimen. Carboplatin is a second-generation, nonnephrotoxic platinum analog with a chemical structure similar to cisplatin. The difference between cisplatin and carboplatin lies in its leaving group. Cisplatin has two chloride ligands as its leaving group whereas carboplatin has a bidentate dicarboxylate ligand.¹ This change in chemical structure alters carboplatin's pharmacokinetic and toxicity profiles.² Unlike cisplatin, carboplatin can be hemodialyzed, although no formal guidelines are available regarding the dosing used in this setting.

We encountered a patient at our tertiary cancer center who had high-grade neuroendocrine carcinoma, metastatic to the bone and lymph nodes, and was undergoing hemodialysis. Given the excellent performance and expected response to the treatment combination of carboplatin and etoposide, we elected to treat this patient with a rationally-selected dose and schedule of this chemotherapy combination along with prescheduled dialysis; we used pharmacokinetic assessments to confirm adequate platinum exposure. We also describe the pharmacokinetics of carboplatin and discuss the available data on the issue of platinum in patients with ESRD in this case report.

Case Report

A 73-year-old man was diagnosed with high-grade metastatic neuroendocrine carcinoma, with a prominent sarcomatoid and focal glandular involvement extending to the surrounding adipose tissue and skeletal muscles. The patient underwent a parotidectomy neck dissection with a repeat excision for cancerous spread to the surrounding adipose tissue and skeletal muscles. Radiation therapy was delayed due to hydrocephalus, requiring hospital admission and complicated by pneumonia and end-stage renal failure, which led to permanent dialysis dependency. Approximately a year after initial diagnosis, the patient's computed tomography scan revealed a diffuse abdominal lymphadenopathy with a mass in the lateral right peritoneum measuring 3.4 cm by 3.6 cm. Multiple nodes were also seen in the mesentery and between the distal and inferior vena cava. Thus, treatment with chemotherapy was considered.

The patient was treated with five cycles of combination carboplatin 115 mg/m² and etoposide 50 mg/m² on day 1 and etoposide 50 mg/m² on day 3 of a 28-day cycle. Based on the patient's body surface area of 1.78 m², the doses used for carboplatin and etoposide were 200 mg and 90 mg, respectively. Dialysis was performed for 3.5 hours starting 90 minutes after completion of the chemotherapy using a bicarbonate-based dialysate. The patient received bolus heparin as an anticoagulant. A total of 3 liters was removed.

Blood samples were collected at 1, 2, 4, and 12 hours after chemotherapy infusion on day 1 of cycle 1. Total carboplatin concentrations in plasma and platinum ultrafiltrate were measured (Table 1, Figure 1). The plasma concentration of free platinum at the end of the infusion was 31,000 ng/ml, and the area under the plasma concentration–time curve (AUC) was 2.9 min·mg/ml.

Discussion

In the era of good supportive care and prolonged survival with combinations of chemotherapy, along with the longevity of patients with ESRD who receive dialysis, not having published guidelines on dosing of platinum agents may become an increasing problem for patients with lung, colon, ovarian, esophageal, gastric, and other cancers where platinum agents are the backbone of treatment. The safety of carboplatin in patients with chronic renal insufficiency has been reported as case studies; the results of which have been used to guide clinical practice.² The safety findings of four published reports of patients who received carboplatin and etoposide in the setting of hemodialysis are summarized, and the results of a pharmacokinetic analysis provide treating physicians with data on carboplatin exposure achieved and timing of dialysis after infusion. Patients with good performance who are candidates for platinum chemotherapy may benefit from these authors' experiences.

The mechanism of action of platinum agents includes intrastrand cross linking by acting as a DNA adduct.³ Although cisplatin is more commonly used in the treatment of neuroendocrine cancers, it may not be the best option in patients who suffer from renal insufficiency, as the nonlinear nature of free platinum clearance depends on the urine flow rate, dose administered, and degree of renal function.⁴ Cisplatin is a highly nephrotoxic platinum analog as it causes necrosis in the proximal tubules by oxidative stress, hypoxic injury, and reactive nitrogen species.⁵ The use of cisplatin in patients with poor creatinine clearance is controversial. In certain references, cisplatin may be decreased by 50% in the setting of hemodialysis.⁶ However, the package insert does not recommend the use of cisplatin in the setting of hemodialysis.⁴ Cisplatin itself may cause renal dysfunction through damage to the renal tubules and, therefore, it is recommended that cisplatin therapy be withheld until renal function returns to baseline.⁴

The second-generation platinum agent carboplatin is a good alternative in many treatment scenarios in which a patient may benefit from the use of a platinum compound but cannot receive cisplatin due to renal dysfunction. The incidence of carboplatin-induced nephrotoxicity is lower compared with cisplatin due to lower interaction with the organic cation transporter, the main transporter of cisplatin into the renal tubules, which causes direct tubular damage.⁵ However, carboplatin may cause renal dysfunction at doses greater than 800 mg/m², and subclinical renal damage can be seen at doses of 400 mg/m².⁵

The pharmacokinetic profile of carboplatin is different from that of cisplatin, with less protein binding and 55–70% of the drug being excreted renally within the first 24 hours.^{2, 7} In the setting of renal insufficiency, carboplatin elimination does not activate compensatory mechanisms of excretion and is correlated with the ultrafilterable carboplatin concentration versus time curve.² The recommendation for a creatinine clearance of 41–59 ml/minute and 16–40 ml/minute includes an initial carboplatin dose of 250 mg/m² and 200 mg/m², respectively.⁸ There are currently no recommendations for the use of carboplatin in patients with a creatinine clearance less than 16 ml/minute.⁸ Fortunately, carboplatin is not as avidly protein bound,² lending the opportunity for dialysis.

At the time of treatment of our patient, we found no case reports that addressed the use of carboplatin in patients with both renal insufficiency and neuroendocrine carcinoma. The National Comprehensive Cancer Network guidelines currently recommend the use of cisplatin or carboplatin in combination with etoposide for metastatic neuroendocrine carcinoma.⁹ The risk of nephrotoxicity associated with carboplatin is significantly lower than that of cisplatin due to its clearance as an unchanged drug.¹⁰ However, the risk of carboplatin nephrotoxicity increases in patients with baseline renal dysfunction. Although carboplatin nephrotoxicity does not directly affect the renal tubules, the concentration of carboplatin would increase greatly in patients with insufficient renal function and result in increased toxicity and adverse drug reactions. The calculation of the carboplatin dose incorporates the glomerular filtration rate (GFR) along with the target carboplatin AUC as part of the Calvert formula. For convenience of measurement, the Cockcroft-Gault equation was used instead for GFR for the calculation of creatinine clearance in the case of our patient. In the population with no renal dysfunction; the target AUC of 4 correlated with a dose range of 125–412 mg/m².¹¹ The β half-life ranges between 2.6 and 5.9 hours in the general population with a total body clearance and apparent body of distribution of 4.4 L/hour and 16 L, respectively.⁸ Our patient received carboplatin 115 mg/m² with scheduled dialysis sessions, resulting in an AUC of 3. Although this is lower than our anticipated target, the patient tolerated the chemotherapy well, with no acute issues or toxicities. The total body clearance of carboplatin for our patient case was 2.28 L/hour, which is lower than the referenced value. However, the β half-life of 4.86 hours falls within the reference range.

To assist in carboplatin dosing, a Pubmed literature search was performed using the search terms carboplatin, etoposide, hemodialysis, and pharmacokinetic, which resulted in eight matches. Four studies were eliminated from the literature review; one was due to the use of both hemodialysis and peritoneal dialysis, two other studies looked at peritoneal dialysis only, and one article was in Japanese with no English translation.^{12–15} The remaining articles were four case reports that administered carboplatin doses ranging from 100–300 mg/m² on day 1 and etoposide 50 mg/m² on day 1 and day 3.^{16–19} Our patient's dosing was based on several published case reports (Table 2). As there was a wide range of doses with different corresponding dialysis schedules, we administered carboplatin at 115 mg/m² as detailed in one report.¹⁶ Our patient received carboplatin 115 mg/m² and etoposide 50 mg/m² for a total of 200 mg and 85 mg, respectively. Dialysis was performed 60 minutes after the first course of chemotherapy, resulting in a free platinum level of 11,700 ng/mL, correlating with an AUC of 4.6 min-mg/mL. For the second cycle of chemotherapy, hemodialysis was administered 2 hours after chemotherapy completion, which resulted in a free platinum level of 11,500 ng/mL and an AUC of 4.8 min-mg/mL. Another report used a similar dose of 100 mg/m² for the treatment of a patient with a germ cell tumor, with an AUC ranging from 4.93–6.17 when dialysis was performed 24 hours after carboplatin administration.¹⁷ A third report¹⁸ described a patient who received carboplatin and etoposide for the treatment of small cell lung cancer. Hemodialysis was initiated 60 minutes after the administration of carboplatin on day 1, and no significant toxicities were reported. Free platinum levels were obtained, which supported the use of carboplatin dose of 250–275 mg/m² to achieve an AUC of 4 min-mg/mL. Similarly, another report¹⁹ used carboplatin and

etoposide in three patients in the setting of small cell lung cancer. Carboplatin 300 mg/m² was administered on day 1 followed by etoposide 50 mg/m² on day 1 and day 3. Hemodialysis was performed 60 minutes after administration of carboplatin. Due to grade 2 toxicities, the doses of carboplatin and etoposide were reduced to 240 mg/m² and 40 mg/m², respectively. The reported total platinum concentration ranged between 14.3 and 15 µg/ml, which decreased to between 0.79 and 1.53 µg/ml by 24 hours after completion of carboplatin administration. The authors did not report the AUC. However due to the toxicities reported in this case, the decision was made to start with the lower dose of carboplatin.

We did not investigate the pharmacokinetics of etoposide. However, in previous reports, the etoposide level could not be controlled by hemodialysis, as it did not show membrane permeability.¹¹⁻¹³ The dosage for etoposide in patients with normal renal function is 100 mg/m² on day 1 for 3 consecutive days.²⁰ However, as etoposide has been reported to be poorly dialyzed, and previous studies involving renal dosing of etoposide employed 50 mg/m² on days 1 and 3,^{18, 19} the dose of etoposide in our patient remained consistent with this recommendation.

Our patient did not report any significant carboplatin-related toxicity and was able to proceed with activities of daily living with an Eastern Cooperative Oncology Group score of 1. He had a radiographic response and good quality of life after completing six cycles of therapy. The patient died 6 months after completion of chemotherapy, surviving 29 months from initial diagnosis, which was significantly greater than that expected if he received no treatment.

Conclusion

Our patient, who had poor renal function and was receiving hemodialysis, was successfully treated for neuroendocrine carcinoma with carboplatin 115 mg/m² for a target AUC of 3.

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Figure 1.

Total carboplatin concentrations in plasma and PUF at 1, 2, 4, and 12 hours after chemotherapy infusion on day 1 of cycle 1. PUF = platinum ultrafiltrate.

Table 1

Carboplatin Concentrations at Various Time Points after Chemotherapy Infusion on Day 1 of Cycle 1

Time Point (hrs)	Total Carboplatin Concentration (ng/ml)	
	Plasma	Platinum Ultrafiltrate
1	37,490	31,000
2	4649	3840
2.5	4211	3440
4	2811	2120
12	926.2	570

Table 2

Summary of Published Cases of Carboplatin and Etoposide Dosing in Patients Receiving Hemodialysis

Author	Disease	No. of Patients	Carboplatin Dose	Etoposide Dose	Time Interval Between Carboplatin and Hemodialysis	AUC (mg·min/ml)
Takezawa et al. ¹⁸	Small cell lung cancer	1	250–275 mg/m ²	50 mg/m ² on days 1 and 3	1 hr	4.10–4.16
Inoue et al. ¹⁹	Small cell lung cancer	3	300 mg/m ² on day 1	50 mg/m ² on days 1 and 3	1 hr	Not reported
Motzer et al. ¹⁷	Germ cell tumor	2	100 mg/m ²	100 mg/m ² on days 1–4 (patient 1) 100mg/m ² on days 1–3 (patient 3)	24 hrs	4.93–6.17
Suzuki et al. ¹⁶	Merkel cell carcinoma	1	150 mg	50 mg on day 1	Cycle 1: 1 hr after administration Cycle 2: 2 hr after administration	Cycle 1: 4.6 Cycle 2: 4.8

AUC = area under the plasma concentration–time curve