Pharmacokinetic Analysis of Carboplatin and Etoposide in a Small Cell Lung Cancer Patient Undergoing Hemodialysis

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Cancer chemotherapy is not well established for patients on hemodialysis (HD). A 77-year-old man on HD presented with small cell lung cancer. He was treated with the combination of carboplatin and etoposide while the pharmacokinetics of the drugs were monitored. The patient showed a response with manageable toxicity and remained progression free for at least 8 months. The area under the concentration-time curve for each antitumor agent in the patient was within the therapeutic range achieved in individuals with normal renal function. Carboplatin and etoposide chemotherapy combined with HD thus allowed the drugs to achieve an appropriate area under the concentration-time curve and sufficient efficacy in a small cell lung cancer patient with chronic renal failure.

Key Words: Small cell lung cancer, Hemodialysis, Pharmacokinetics, Chemotherapy.

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The prognosis of patients with chronic renal failure has improved as a result of progress in hemodialysis (HD), and opportunities to treat malignant tumors that develop in such HD patients are increasing. However, little is known of the safety or efficacy of chemotherapy for malignant tumors in HD patients. We analyzed the pharmacokinetics of combination chemotherapy with carboplatin (CBDCA) and etoposide in a patient with small cell lung cancer (SCLC) undergoing HD.

CASE REPORT

A 77-year-old man with chronic renal failure due to diabetic nephropathy presented with a mass in the left hilar area in March 2007. The general condition of the patient, who had undergone HD, three times a week, was fair, with symptoms such as cough, weight loss, and fever being absent. His Eastern Cooperative Oncology Group performance status was 1.

Radiotherapy was not appropriate for the patient because of his bilateral interstitial pneumonia. Given his good performance status and after obtaining informed consent, we treated the patient with the combination of CBDCA and etoposide (Figure 1). On day 1 of the treatment cycle, the patient received an intravenous injection of etoposide (50 mg/m\(^2\)) over 60 minutes followed by an intravenous injection of CBDCA (250–275 mg/m\(^2\)) also over 60 minutes. HD was initiated 60 minutes after completion of CBDCA administration and was performed for 4 hours. On day 3, etoposide (50 mg/m\(^2\)) was administered over 60 minutes and HD was performed for 4 hours beginning 2 hours after completion of etoposide injection. The doses of CBDCA and etoposide as well as the timing of HD were based on previous studies.2–4 The treatment was well tolerated. Nonhematologic toxicities such as nausea, vomiting, and fatigue were not observed. The patient also did not experience neutropenia or thrombocytopenia (Nadir neutrophil and platelet counts during 3 cycles of chemotherapy were 2200/\(\mu\)l and 15.5 × 10\(^4\)/\(\mu\)l, respectively). Prophylactic administration of granulocyte colony-stimulating was not carried out. After three cycles of chemotherapy, each separated by an interval of 3 weeks, the tumor had decreased in size and the serum neuron-specific enolase level had decreased to within normal limits (6.3 ng/ml). The patient remained progression free 8 months after the initiation of treatment.

Pharmacokinetic analysis of CBDCA and etoposide was performed for the first and third courses of chemotherapy. Serial blood samples were collected 0, 1, 2, 3, 4, 5, 6, 24, 37, 41, 42, 49, 53, and 54 hours after completion of CBDCA administration as well as 0, 2, 3, 4, 5, 6, 7, 25, 48, 50, 52, 54, 55, and 73 hours after completion of the first etoposide administration. Each blood sample was analyzed for free...
platinum and etoposide (Figure 1) as described previously.\textsuperscript{5} In the first cycle, the area under the concentration-time curve (AUC) was 4.10 minutes mg/ml for free platinum and 4401 and 3612 minutes $\mu$g/ml for etoposide on days 1 and 3, respectively. In the third course of chemotherapy, for which the CBDCA dose was increased from 250 to 275 mg/m$^2$, the AUC of free platinum was 4.16 minutes mg/ml. The maximal concentration and half-life of free platinum were 7.7 $\mu$g/ml and 2.51 hours in the first cycle and 9.4 $\mu$g/ml and 1.93 hours in the third cycle.

**DISCUSSION**

Many lung cancer patients undergoing HD as a result of impaired renal function may be “undertreated” because chemotherapy regimens are not well established for such individuals. The lack of pharmacokinetic data for most cytotoxic agents in HD patients makes it difficult to administer chemotherapy effectively. Given his old age, bilateral interstitial pneumonia, and renal dysfunction, the present patient might have been considered too high a risk for chemotherapy and recommended to receive best supportive care. However, taking into account the sensitivity of SCLC to platinum combination chemotherapy, we treated him with CBDCA and etoposide while monitoring the pharmacokinetics of these antitumor agents.

CBDCA is a less emetic and less nephrotoxic analog of cisplatin and is preferred over cisplatin for use in patients with renal insufficiency. The desired AUC for CBDCA can be individualized with the use of Calvert’s formula on the basis of individual renal function.\textsuperscript{6} In previous studies of CBDCA-based chemotherapy in patients undergoing HD, a CBDCA dose of 100 to 150 $\mu$g/body was chosen according to this formula, with the glomerular filtration rate set to zero because of the absence of renal function (Table 1).\textsuperscript{7–10} In these studies, HD was performed 16 to 24 hours after completion of CBDCA administration, resulting in an AUC of 4.43 to 6.9 minutes mg/ml. More recently, administration of a relatively high dose (300 mg/m$^2$) of CBDCA with initiation of HD 0.5 to 1.5 hours after completion of drug injection has been shown to be feasible and effective in lung cancer patients undergoing HD.\textsuperscript{2–4} However, the AUC of CBDCA in these latter studies was not determined. In the present study, we found that a CBDCA dose of 250 to 275 mg/m$^2$ administered completely 1 hour before HD gave rise to an AUC for free platinum of 4.10 to 4.16 minutes mg/ml, a therapeutic blood level, consistent with the antitumor efficacy observed.

**TABLE 1.** Previous Studies of Carboplatin-Based Chemotherapy in Cancer Patients on Hemodialysis

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Patients</th>
<th>Carboplatin Dose</th>
<th>Interval Between Carboplatin Infusion and Hemodialysis (h)</th>
<th>AUC (min mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanabe et al.\textsuperscript{7}</td>
<td>Ovarian cancer</td>
<td>1</td>
<td>125 mg</td>
<td>16</td>
</tr>
<tr>
<td>Jeyabalan et al.\textsuperscript{8}</td>
<td>Ovarian cancer</td>
<td>1</td>
<td>125 mg</td>
<td>24</td>
</tr>
<tr>
<td>Chatelut et al.\textsuperscript{9}</td>
<td>Ovarian cancer</td>
<td>1</td>
<td>150 mg</td>
<td>24</td>
</tr>
<tr>
<td>Motzer et al.\textsuperscript{10}</td>
<td>Germ cell tumor</td>
<td>2</td>
<td>100 mg/m$^2$</td>
<td>24</td>
</tr>
<tr>
<td>Inoue et al.\textsuperscript{2}</td>
<td>SCLC</td>
<td>3</td>
<td>300 mg/m$^2$</td>
<td>1</td>
</tr>
<tr>
<td>Yanagawa et al.\textsuperscript{3}</td>
<td>NSCLC/epipharynx ca</td>
<td>2</td>
<td>300 mg/m$^2$</td>
<td>0.5</td>
</tr>
<tr>
<td>Haraguchi et al.\textsuperscript{4}</td>
<td>SCLC</td>
<td>1</td>
<td>300 mg/m$^2$</td>
<td>1.5</td>
</tr>
</tbody>
</table>

N.D, not determined; NSCLC, non-small cell lung cancer.
in the previous studies\textsuperscript{2–4}. Our presented study supports that relatively high dose administration of CBDCA with initiation of HD 1 hour after drug injection would be an alternative strategy for patients with HD-dependent renal insufficiency. 

Etoposide is active against various types of malignant tumors, but its membrane permeability in HD remains unclear. The AUC range for etoposide in 13 patients with normal renal function treated with this drug at a dose of 100 mg/m\textsuperscript{2} was previously shown to be 2291 to 6832 minutes \(\mu\text{g}/\text{ml}\) (Ref. \textsuperscript{11}). The present patient was treated with etoposide at 50 mg/m\textsuperscript{2} on days 1 and 3, with HD being initiated 2 hours after completion of the drug injection. The AUC of etoposide was 3612 to 4401 minutes \(\mu\text{g}/\text{ml}\), values that are within the range achieved in patients with normal renal function. Indeed, the combination chemotherapy in the proband induced a tumor response that persisted for at least 8 months. Administration of etoposide at 100 mg/m\textsuperscript{2} on days 1, 3, and 5 in combination with cisplatin at 80 mg/m\textsuperscript{2} was shown to be acceptable in 4 lung cancer patients with renal dysfunction.\textsuperscript{12} In the previous study, HD was performed soon after drug administration, resulting in an AUC for etoposide of 4800 to 6204 minutes \(\mu\text{g}/\text{ml}\). Data from the previous studies and our present patient thus indicate that etoposide can be administered safely in HD patients.

The present case shows that CBDCA and etoposide chemotherapy combined with HD resulted in AUCs for these drugs within the therapeutic range in a SCLC patient with chronic renal failure. Although further studies are needed, our findings suggest that this regimen of combination chemotherapy can be administered to lung cancer patients with renal insufficiency.

REFERENCES