Pharmacokinetic analysis of combination chemotherapy with carboplatin and etoposide in small-cell lung cancer patients undergoing hemodialysis

A. Inoue1*, Y. Saijo1,2, T. Kikuchi1, K. Gomi1, T. Suzuki1, M. Maemondo1, M. Miki3, T. Sato4 & T. Nukiwa1

*Correspondence to: Dr A. Inoue, Department of Respiratory Oncology and Molecular Medicine, Institute of Development, Aging and Cancer, Tohoku University, Sendai; 1Department of Respiratory Oncology and Molecular Medicine and Gene Transfer Research; 2Department of Molecular Medicine, Japanese Red Cross Sendai Hospital, Sendai; 3Department of Blood Purification, Tohoku University Graduate School of Medicine, Sendai, Japan.

Received 25 April 2003; revised 6 August 2003; accepted 13 August 2003

Background: The aim of this study was to use pharmacokinetic analysis to investigate the efficacy and toxicity of combined chemotherapy with carboplatin (CBDCA) and etoposide (ETP) in small-cell lung cancer (SCLC) patients with chronic renal failure undergoing hemodialysis (HD).

Patients and methods: Three SCLC patients with chronic renal failure undergoing HD were treated with CBDCA (300 mg/m²) on day 1 and ETP (50 mg/m²) on days 1 and 3, followed by HD 1 h after completing the administration of anticancer agents on each day. The pharmacokinetic analysis of CBDCA and ETP was planned for at least the first two courses of the chemotherapy in each patient.

Results: Two complete responses and one partial response were achieved in the three patients. Two patients experienced grade 3/4 neutropenia and required blood transfusion due to thrombocytopenia and anemia. Non-hematological toxicities were moderate. The pharmacokinetic analysis revealed that the platinum and the ETP concentrations in the plasma were similar to those in patients with normal renal function during the first 24 h, while the platinum still remained in the plasma for over 90 h.

Conclusions: Chemotherapy with CBDCA (300 mg/m² on day 1) and ETP (50 mg/m² on day 1, 3) as used in the present study may be a suitable regimen for SCLC patients undergoing HD, although careful attention should be given to hematological toxicities.

Key words: carboplatin, chemotherapy, hemodialysis, pharmacokinetics, small-cell lung cancer

Introduction

Lung cancer still remains a leading cause of cancer-related death in the United States, Europe and Japan. Although recent large clinical trials have indicated that platinum-containing chemotherapy should be recommended for patients with small-cell lung cancer (SCLC) and advanced non-small-cell lung cancer, those trials included only selected patients with good performance status (PS) as well as normal organ functions [1, 2]. However, patients in the practical setting sometimes have co-morbidities such as cardiovascular disease, chronic pulmonary disorders, hepatic dysfunctions, diabetes, etc., which may render platinum-containing chemotherapy difficult, even if such patients have a good PS.

Chronic renal failure is also one of the common diseases, for which not a few patients undergo hemodialysis (HD). Unsurprisingly, many patients undergoing HD suffer from various types of cancer [3]. However, the feasibility and effects of chemotherapy for such patients have not been fully studied. Carboplatin (CBDCA), a well-known platinum compound with significant activity against various types of cancer including SCLC, has less nephrotoxicity than cisplatin and is therefore generally used for patients with impaired renal function. Moreover, CBDCA has a favorable profile for treatment with HD in that the platinum in the plasma of patients receiving CBDCA is much more filterable than is the case with cisplatin [4].

Thus, we treated SCLC patients with chronic renal failure undergoing HD with CBDCA-based chemotherapy combined with etoposide (ETP). We also carried out a pharmacokinetic (PK) analysis of CBDCA and ETP during the course of chemotherapy.

Patients and methods

Patients and drug administration

Between January 2002 and October 2002, three SCLC patients with chronic renal failure undergoing HD were treated in our hospital with CBDCA combined with ETP (Table 1). The initial dose of CBDCA was 300 mg/m² on day 1, and that of ETP was 50 mg/m² on days 1 and 3 as recommended in a previous study [5]. Each anticancer agent was diluted in 250 ml 5% glucose solution and
administered intravenously for 1 h. Corticosteroids (8 mg dexamethasone) and serotonin receptor antagonists (e.g. 3 mg granisetron) were used as antiemetic agents on each chemotherapeutic day.

When patients experienced hematological or non-hematological toxicities higher than grade 2 (National Cancer Institute Common Toxicity Criteria) except for nausea/vomiting in their first course of chemotherapy, the doses of CBDCA and ETP in the subsequent chemotherapy courses were reduced to 240 and 40 mg/m$^2$, respectively. Prophylactic administration of granulocyte colony-stimulating factor (G-CSF) or antibiotics was not carried out. G-CSF was administered when the neutrophil count decreased to <1000/µl and continued until it recovered to over 5000/µl. Blood transfusion was considered when the hemoglobin level or platelet count decreased to <8.0 g/dl or <40 000/µl, respectively. Although the platelet transfusion trigger is usually 20 000 or 10 000/µl during chemotherapy, we considered it should be elevated for patients undergoing HD because they are frequently catheterized to an arterio–venous shunt for HD. The administration of erythropoietin (6000–9000 IU/week) for nephrogenic anemia, which had already begun before the chemotherapy, was continued throughout the chemotherapy.

Patients 1 and 3, both with multiple brain metastases, were treated with whole-brain irradiation (2 Gy/day, total 40 Gy) concurrently during the chemotherapy. Patient 2 with limited-disease SCLC was treated with thoracic irradiation (2 Gy/day, total 50 Gy) concurrently during the chemotherapy.

Hemodialysis

The dialyzer (BG-1.8U; Toray Medical, Tokyo, Japan; AM-BC13F and 11F; Asahi Medical, Tokyo, Japan) and HD schedule including the frequency and duration were determined individually. Model DDB72 (Nikkiso, Shizuoka, Japan) and Kindary solution AF-2 were used as the HD apparatus and dialysis solution, respectively. The details of the HD procedure for each patient are summarized in Table 2. Fluid removal was programmed individually to obtain the desired dry weight. Low molecular weight heparin was used as an anticoagulant. HD was started 1 h after completing the administration of CBDCA and ETP on days 1 and 3.

Pharmacokinetic analysis

PK analysis of CBDCA and ETP was planned for at least the first two courses of chemotherapy in each patient. Blood samples were collected at 1, 4, 6 and 24 h after the administration of anticancer agents on day 1 of each course. In the third course of patient 3, blood samples were additionally collected at 49 and 97 h after the administration of anticancer agents on day 1. Each blood sample was centrifuged at 1000 r.p.m. for 10 min and the obtained plasma samples were stored at $-20^\circ$C until analysis. The platinum and ETP in the plasma were analyzed according to the method of LeRoy et al. [6] and Allen [7], respectively.

Results

Averse effects of chemotherapy

Two of the three patients (patients 2 and 3) received four complete courses of chemotherapy with dose modifications. Patient 1 received only two courses because he refused to continue chemotherapy. Since two patients (patients 2 and 3) experienced grade 3 and 4 neutropenia and were supported with G-CSF (Table 3) during the first course of chemotherapy, the doses of CBDCA and ETP were decreased in the subsequent courses according to the protocol. Febrile neutropenia was not observed during the courses of chemotherapy in any of the three patients. Patients 2 and 3 underwent blood transfusion for thrombocytopenia and anemia without any adverse events. Non-hematological toxicities such as nausea, vomiting, appetite loss, and fatigue were moderate and non-hematological toxicities grade >1 were not observed.

Effects of chemotherapy

Tumor regression was observed in all three patients. A complete response (CR) was achieved in patients 2 and 3, and a partial

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Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Case/gender</th>
<th>Age</th>
<th>PS</th>
<th>Stage</th>
<th>Distant metastasis</th>
<th>Laboratory data before chemotherapy</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WBC (µl)</td>
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<td>53</td>
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<td>IV</td>
<td>Brain, adrenal</td>
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<tr>
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<td>77</td>
<td>0</td>
<td>IV</td>
<td>Brain</td>
<td>7200</td>
</tr>
</tbody>
</table>

Hb, hemoglobin; PS, performance status; WBC, white blood cell count.

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Table 2. Details of hemodialysis procedure in each patient

<table>
<thead>
<tr>
<th>Case</th>
<th>Dry weight (kg)</th>
<th>Blood flow (ml/min)</th>
<th>Dialysis solution flow (ml/min)</th>
<th>Dialyzer</th>
<th>Dialyzer surface area (m$^2$)</th>
<th>Dialysis time (min)</th>
<th>Dialysis frequency (per week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70.0</td>
<td>200</td>
<td>500</td>
<td>BG-1.8U</td>
<td>1.8</td>
<td>240</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>44.0</td>
<td>180</td>
<td>500</td>
<td>AM-BC13F</td>
<td>1.3</td>
<td>180</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>63.5</td>
<td>180</td>
<td>500</td>
<td>AM-BC11F</td>
<td>1.1</td>
<td>180</td>
<td>3</td>
</tr>
</tbody>
</table>
response (PR) was obtained in patient 1. Recurrence of SCLC was observed only in patient 3 at 5 months after the initiation of chemotherapy. Although patients 1 and 2 continued as CRs, patient 1 died at 8 months after the initiation of chemotherapy because of an exacerbation of renal failure.

Pharmacokinetic analysis

Figure 1 shows the PK of CBDCA (total platinum) on day 1 of the chemotherapy for each patient. The total platinum concentrations in the plasma at the initiation of HD were 14.3–15.0 µg/ml and decreased to 0.79–1.53 µg/ml at 24 h after the administration of CBDCA. This pattern of PK was similar to those in patients with normal renal function [8]. In accord with the dose reduction of CBDCA in the second and third courses in patient 3, the platinum concentrations decreased comparably at each point. However, the platinum concentration did not decrease dose-dependently in patient 2, although the dose of CBDCA in the second course was reduced. In the third course for patient 3, the PK analysis carried out from day 1 to day 5 showed that the platinum remained in the plasma more than 90 h, with gradual dissipation after the administration.

The PK of ETP for each patient revealed that the ETP concentration in the plasma decreased rapidly with no ETP remaining in the plasma on day 2, and this was also comparable with the PK data of ETP in patients with normal renal function as reported previously (Figure 2) [9].

Discussion

In the present study, the chemotherapy with CBDCA and ETP demonstrated good tumor responses (two cases with CR and one case with PR) with manageable toxicity in all three SCLC patients. Many cancer patients with impaired renal function undergoing HD might have been ‘under-treated’ because chemotherapy regimens had not been well-established for such patients. In fact, although several small studies have been reported previously about CBDCA-based chemotherapy for cancer patients undergoing HD [5, 10–13], most of the doses of CBDCA used in those reports were relatively lower (100 mg/m² or 100–150 mg/body) than those widely used in patients with normal renal function. In contrast, the dose of CBDCA in our study, 300 mg/m², was comparable with those generally used for patients with normal renal function and seemed to be appropriate for achieving sufficient efficacy in SCLC patients with moderate myelosuppression. Although our small study cannot support a definitive conclusion, the CBDCA-based regimen of the present study may improve the prognosis of SCLC patients undergoing HD. Therefore, we con-
sider that at least patients with a chemosensitive cancer such as SCLC should be treated with chemotherapy of sufficient potency. A recent report by Watanabe et al. [14] demonstrated that full-dose chemotherapy consisting of 80 mg/m² cisplatin on day 1 and 100 mg/m² ETP on days 1, 3 and 5 was feasible and effective for lung cancer patients with HD. In our study, a lower dose of ETP (50 mg/m² days 1 and 3) was initially selected in terms of the safety, which resulted in grade 3 and 4 neutropenia in two of three patients. Thus, we considered the dose of ETP might be appropriate when used in combination with CBDCA (300 mg/m² day 1).

The PK analysis revealed that the platinum concentrations in the plasma of patients undergoing HD were comparable with those in patients with normal renal function during the first 24 h after the administration of CBDCA [8]. However, it is easily conceivable that the remnant platinum in the plasma after HD remains longer in patients with impaired renal function than in patients with normal renal function, and could cause severe and prolonged myelosuppression. In this context, physicians should pay careful attention to the peripheral blood cell count during chemotherapy and consider a dose reduction in subsequent courses according to the severity of the hematological toxicity. In fact, the PK data of patient 3 showed that dose reduction in the second and third courses resulted in a decreased platinum concentration in the plasma and a reduction in the hematological toxicity.

Of interest, the platinum concentration of patient 2 did not change dose-dependently in spite of the dose reduction. Although the reason why the PK data of patient 2 were less dose-dependent is difficult to interpret, we hypothesized that it might be attributed to the remnant renal function of patient 2. Because her own urinalysis was relatively better than those of the other patients (e.g. the creatinine clearance of patients 2 and 3 were 10 and 6 ml/min, respectively), the clearance of the platinum of patient 2 might also have been influenced by the renal condition more than those of others.

The HD setting after the administration of anticancer agents is also a very important factor that influences the concentration of anticancer agents in the plasma and therefore influences the efficacy and the safety of the chemotherapy. Although our treatment regimen appeared to be safe and appropriate, further study is needed.

In conclusion, the CBDCA (300 mg/m² on day 1) and ETP (50 mg/m² on days 1 and 3) chemotherapy of the present study may be a suitable regimen for SCLC patients undergoing HD, although careful attention should be paid to hematological toxicity.

Acknowledgements

The authors thank Bristol Pharmaceutical KK, Hokkaido, Japan, for help in performing the pharmacokinetic analysis.

References