Successful Chemotherapy for Small-Cell Lung Cancer in an Elderly Patient Undergoing Continuous Ambulatory Peritoneal Dialysis

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Abstract

A standard treatment has not yet been established for elderly small-cell lung cancer patients, especially when they have end-stage renal disease. We report the first case of successful chemoradiotherapy in an elderly small-cell lung cancer patient undergoing continuous ambulatory peritoneal dialysis. A 77-year-old Japanese man on continuous ambulatory peritoneal dialysis was diagnosed as having limited disease small-cell lung cancer. He received four monthly cycles of chemotherapy consisting of carboplatin at 240 mg/m² on day 1 and etoposide at 40 mg/m² on days 1 and 3. He underwent additional hemodialysis on days 1 and 3, while continuous ambulatory peritoneal dialysis continued as usual on the other days. Following chemotherapy, he underwent hyperfractionated radiotherapy to a total dose of 45 Grey, resulting in complete remission of the disease. A pharmacokinetic study showed an area under the concentration-time curve of carboplatin of 3.41 to 4.88 mg·min/mL, increasing gradually over the first three cycles, while etoposide did not show this gradual increase. The increased area under the concentration-time curve of carboplatin may have reflected a worsened renal function during chemotherapy. Despite dose reductions and favorable areas under the concentration-time curve of carboplatin, the patient suffered grade 3-4 hematological toxicities, necessitating transfusions and a further dose reduction. The patient died of recurrent small-cell lung cancer 19 months after diagnosis.

Key words: small-cell lung cancer, continuous ambulatory peritoneal dialysis, chemotherapy, pharmacokinetic study, carboplatin, etoposide

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Introduction

Small-cell lung cancer (SCLC) constitutes 10-15% of total lung cancers (1, 2). It progresses aggressively but usually responds well to the initial chemotherapy, compared with non-small-cell lung cancer (NSCLC). In clinical practice, however, many SCLC patients have various comorbidities, which renders the standard platinum-based chemotherapy difficult to complete. Most elderly lung cancer patients have some comorbidities, including chronic obstructive pulmonary disease, ischemic heart disease and cerebrovascular disease (3). Even fit elderly patients experience a higher incidence of adverse effects and treatment-related deaths in clinical trials of SCLC (4-6). Thus, a standard treatment has not yet been established for elderly SCLC patients, especially when they have other diseases as well.

End-stage renal disease (ESRD) is also common in Japan.

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At the end of 2006, a total of 264,493 patients were receiving chronic dialysis, representing a prevalence of 2069.9 per million population (7). Advances in renal replacement therapy have resulted in longer survival of ESRD patients, so that they sometimes develop life-threatening neoplastic diseases. Platinum-based chemotherapy can prolong survival of SCLC patients with normal renal function, but a standard treatment has not been established for ESRD patients (4-6).

We report an elderly SCLC patient undergoing continuous ambulatory peritoneal dialysis (CAPD). With additional hemodialysis (HD), a course of platinum-based chemotherapy was completed, resulting in complete remission (CR). In recurrent ovarian cancer, successful paclitaxel and carboplatin treatment has been reported in a patient with ESRD on CAPD (8). There are also several reports of chemotherapy in SCLC or NSCLC patients on HD (9-11). However, the present report is the first to describe successful chemotherapy in an SCLC patient on CAPD, partly because among the current renal replacement therapies in Japan and the United States, limited numbers of patients have elected to receive CAPD (7, 12).

### Case Report

#### Clinical course

A 77-year-old Japanese man was diagnosed with limited disease small-cell lung cancer (LD-SCLC). The TMN classification was cT2N2 (bulky No. 3), M0=Stage 3A and performance status (PS) one (hemoptysis). He had been undergoing CAPD for one year because of renal sclerosis. At presentation, he dialedyzed three times a day, and retained small amounts of urine output. Blood urea nitrogen (BUN) was 36.9 mg/dL and serum creatinine was 5.9 mg/dL.

He received four monthly cycles of chemotherapy consisting of carboplatin (CBDCA) at 240 mg/m² on day 1 and etoposide (ETP) at 40 mg/m² on days 1 and 3. The dose of CBDCA and ETP was determined based on the previous report by Inoue et al (9). Considering the patient’s age, however, it was reduced by 20% from the original regimen in order to avoid severe hematological toxicities. Furthermore, because of severe pancytopenia after the first three courses, the dose was reduced again at the fourth course to 200 mg/m² CBDCA on day 1 and 30 mg/m² ETP on days 1 and 3. The patient underwent additional HD on days 1 and 3, while CAPD was continued as usual on the other days. During most courses he had grade three anemia, grade four neutropenia and grade three or four thrombocytopenia, and received transfusions several times (Table 1). Renal function worsened during the chemotherapy but recovered almost to baseline after its completion: BUN was 32.1 mg/dL and serum creatinine 5.8 to 6.5 mg/dL (Fig. 1).

Following four cycles of chemotherapy, the patient underwent hyperfractionated radiotherapy (HFRT) to the mediastinum and right lung to a total dose of 45 Gy. This sequential chemoradiotherapy resulted in CR of the disease. He was unwilling to receive prophylactic cranial irradiation (PCI) because he was worried about cognitive impairment after PCI.

After seven months the tumor recurred with a single brain metastasis. The patient underwent stereostatic radiotherapy and remained well until the tumor recurred in the bladder and peritoneum two months later. He opted for best supportive care without any additional chemotherapy and died at
Figure 1. Renal function and the area under the concentration-time curve (AUC) of carboplatin (CBDCA) and etoposide (ETP) during chemotherapy.

Figure 2. Pharmacokinetics (PK) of carboplatin (CBDCA) and etoposide (ETP) over the first course. a. PK of CBDCA (total platinum). b. PK of ETP.

Hemodialysis

The dialyzer was FB-150 UB and its surface area was 1.5 m$. Dry weight was 65.0 kg with fluid removal of 150-250 mL, blood flow of 120 or 150 mL/min and dialysis solution flow 500 mL/min. Low molecular weight heparin was used as an anticoagulant. HD was started one hour after completing the administration of CBDCA and ETP on days 1 and 3, and dialysis time was 240 minutes. The dialysis was scheduled according to the previous report (9).

Pharmacokinetic analysis

Pharmacokinetic (PK) analysis of CBDC (total platinum) and ETP was carried out for each course. Blood samples were collected at one hour (before HD), 5 (after HD), 24, 49 (just before HD on day 3), 53 (just after HD on day 3) and 72 hours after the administration of anticancer agents on day 1. The platinum and ETP in the plasma were analyzed according to the methods of LeRey et al and Allen, respectively (13, 14).

The PK of CBDCA (total platinum) and ETP over the first course is shown in Fig. 2. The area under the concentration-time curve (AUC) of CBDCA was 3.41 mg min/mL for the first course. It gradually increased through the second and third courses to 4.67 and 4.88 mg min/mL, respectively, although the doses administered were unchanged. Dose reduction for the fourth course resulted in a decreased AUC of CBDCA. The AUC of ETP did not show this gradual increase through the first three courses but also decreased during the last course because of the dose reduction (Fig. 1).

Discussion

In the present case, initial platinum-based chemotherapy and sequential radiotherapy led to the induction of CR of SCLC in an elderly ESRD patient on CAPD. PK studies revealed that the additional HD on days 1 and 3 and continued CAPD resulted in CBDCA and ETP PK patterns comparable with those in patients with normal renal function (15-17). There is no doubt that the initial chemotherapy was associated with increased survival time in this case, without any fatal complications due to the therapy, although a long-term CR was not achieved. However, some modifications of the previously reported regimen were required to complete the chemotherapy safely. First, the initial dosage of CBDCA and ETP was reduced by 20% from the original regimen (9). Despite this dose reduction, the AUC of CBDCA remained close to the target of 4 to 5 mg min/mL (18). Moreover, hematological toxicities became more severe and more prolonged over the first three courses, even though the doses administered were unchanged. This may be reflected in the gradual increase in the AUC of CBDCA. Second, over the fourth course, a further dose reduction was necessary to avoid potentially fatal complications. At the same time, of course, these dose reductions also resulted in a reduced dose intensity. Ardizzoni et al reported that reduction in the dose intensity worsened survival in elderly SCLC patients (19). It is challenging to balance dose intensity against risk of treatment-related death, in particular when radiological CR has been achieved.

In addition, the patient did not receive PCI for fear of post-PCI cognitive impairment. While PCI decreases the incidence of brain metastases and provides an overall survival...
benefit to patients with SCLC in CR, central nervous system toxicity, including cognitive impairment, has been postulated to be a complication of this treatment (20-22). Some studies showing that PCI caused no significant neurological toxicity did not include patients older than 70 years (23, 24). A recent prospective study which did include elderly SCLC patients, however, also showed no deterioration of cognitive function (25). Nonetheless, the impact of PCI in elderly LD-SCLC patients remains to be definitively determined.

The present report has some limitations. First, PK analysis in urine, HD solutions or CAPD solutions was not performed. Thus, the exact clearance pathway was not determined. In particular, renal excretion may have contributed to clearance, because the production of small amounts of urine was maintained throughout the treatment. A gradual increase in the AUC of CBDCA may have reflected worsened renal function during chemotherapy (Fig. 1). Carboplatin or CBDCA-derived platinum is mainly cleared (70%) by renal excretion (16). CAPD eliminates none or only 14-20% of the administered CBDCA during the first 24 hours (8, 9, 26). Although PK analysis in the present case certainly did reveal a rapid clearance of platinum via HD, the residual renal excretion may have played a larger role than anticipated. Etoposide is eliminated by renal (60%) and hepatic (40%) mechanisms in patients with normal renal function (26). Previous studies indicated that the hepatobiliary route completely compensates for the renal route in ESRD patients (11, 26). In our patient, ETP concentrations were decreased as expected on the next day, although the exact clearance pathway was also undetermined. Second, the frequency of blood sampling was lower than in previous reports (8, 9, 16, 26). More frequent blood sampling could have enabled more precise PK analysis.

In conclusion, successful chemoradiotherapy was completed in an elderly ESRD patient on CAPD. Some modifications of the regimen may be necessary according to the patient’s condition and clinical course, and further investigations of the generality of these findings is required.

References
