Long-term Survival in a Patient with Small-cell Lung Cancer Undergoing Hemodialysis Who Received Multiple Courses of Chemotherapy

Yosuke Togashi, Young Hak Kim*, Katsuhiro Masago, Yuichi Sakamori, Chiyuki Okuda, Tadashi Mio and Michiaki Mishima

Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

*For reprints and all correspondence: Young Hak Kim, Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaracho, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail: ekim@kuhp.kyoto-u.ac.jp

Received September 30, 2010; accepted December 22, 2010

The prognosis of small-cell lung cancer remains poor and it is speculated that small-cell lung cancer patients with end-stage renal failure undergoing hemodialysis have a poorer prognosis. In this article, we present a Japanese woman with extensive small-cell lung cancer with end-stage renal failure undergoing hemodialysis who received multiple courses of chemotherapy. Although she achieved long-term survival of more than 2 years, the last-line chemotherapy, consisting of irinotecan, induced grade 4 febrile neutropenia and her performance status deteriorated even with a reduced dose according to the analysis of UDP-glucuronosyltransferase 1A1. We also conducted a pharmacokinetic analysis of irinotecan, the resulting values of which were much higher than in previous reports. Although further studies are needed, chemotherapy for small-cell lung cancer patients should not be withheld just because they are undergoing hemodialysis; however, chemotherapy should be performed more carefully because more severe toxicities can occur than expected.

Key words: small-cell lung cancer — hemodialysis — multiple courses chemotherapy — irinotecan — pharmacokinetics

INTRODUCTION

Although the incidence of small-cell lung cancer (SCLC) has decreased, its prognosis remains poor: the median ranges of survival for limited disease and extensive disease (ED) are reportedly 15–20 and 8–13 months, respectively (1).

Patients with end-stage renal failure (ESRF) undergoing hemodialysis (HD) are potentially at increased risk of cancer for several reasons, including the presence of chronic infection, a weakened immune system, nutritional deficiencies and altered DNA repair (2). It is speculated that more patients who undergo HD will be diagnosed with SCLC with the recent advances in HD.

Some previous reports have indicated the safety and efficacy of chemotherapy in such patients; however, evidence is still lacking. In this article, we present a patient with ED-SCLC undergoing HD who received multiple courses of chemotherapy and survived for more than 2 years. We also performed pharmacokinetic analysis of irinotecan in this patient.

CASE REPORT

A 78-year-old Japanese woman was diagnosed with ED-SCLC with liver, bone and adrenal metastases, and her performance status (PS) in the Eastern Cooperative Oncology Group was 1. She had been undergoing HD three times a week for 2 years because of renal sclerosis. HD was performed for 4 h using a polysulfone membrane (APSTM;
Asahi Kasei, Tokyo, Japan). She received a monthly cycle of chemotherapy consisting of carboplatin (300 mg/m²) on day 1 and etoposide (50 mg/m²) on days 1 and 3 followed by HD 1 h after administration each day (3). She had grade 3 neutropenia and grade 4 thrombocytopenia, and so the dose was reduced to 80% from the second cycle. Although she had grade 1 fatigue and grade 1 anorexia, she completed three additional cycles of chemotherapy without serious toxicity. After receiving four cycles of chemotherapy, she achieved partial response (PR).

Fourteen months after treatment, her tumor recurred with multiple brain metastases, and her PS was two. She received monthly cycles of a different chemotherapy consisting of amrubicin (35 mg/m²) on days 1–3. The timing of HD was not considered for this regimen because it is exclusively metabolized in the liver. The toxicity was generally mild (grade 2 neutropenia and grade 1 thrombocytopenia). She received four cycles of chemotherapy, she achieved partial response (PR).

Two months later, her brain metastases worsened and her PS deteriorated to three. After receiving whole-brain irradiation, she received irinotecan on days 1, 8 and 15 as her third-line chemotherapy. Because she had UDP-glucuronosyltransferase (UGT) 1A1*28/*28 analyzed by invader assay (SEKISUI MEDICAL CO. LTD, Tokyo, Japan) and considering that she was undergoing HD, the dose was reduced from the standard 100–50 mg/m². Even with a reduced dose on day 1, she experienced grade 4 febrile neutropenia although diarrhea was mild (grade 1); therefore, she could not receive irinotecan on days 8 and 15.

We obtained written informed consent from the patient, and plasma concentrations of irinotecan, its active metabolite SN-38 and its inactive metabolite SN-38 glucuronide (SN-38G) were investigated by the high-performance liquid chromatography. The pharmacokinetics is summarized in Tables 1 and 2. The area under the plasma SN-38 concentration-time curve from 0 to 72 h (AUC₀–₇₂) was much higher than in a Japanese phase-I study (4). Although she recovered from febrile neutropenia, her PS was much worsened and chemotherapy was stopped. She died of SCLC 28 months after diagnosis.

Table 1. Plasma concentration of irinotecan, SN-38 and SN-38G

<table>
<thead>
<tr>
<th>Time after administration (h)</th>
<th>Irinotecan (µg/ml)</th>
<th>SN-38 (ng/ml)</th>
<th>SN-38G (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Just after administration)</td>
<td>0.73</td>
<td>15.11</td>
<td>45.08</td>
</tr>
<tr>
<td>1</td>
<td>0.52</td>
<td>15.51</td>
<td>59.29</td>
</tr>
<tr>
<td>4</td>
<td>0.28</td>
<td>9.68</td>
<td>44.31</td>
</tr>
<tr>
<td>8</td>
<td>0.19</td>
<td>7.00</td>
<td>34.79</td>
</tr>
<tr>
<td>20 (Just before HD)</td>
<td>0.072</td>
<td>4.01</td>
<td>21.47</td>
</tr>
<tr>
<td>24 (Just after HD)</td>
<td>0.055</td>
<td>12.84</td>
<td>14.05</td>
</tr>
<tr>
<td>72</td>
<td>&lt;0.025</td>
<td>2.81</td>
<td>7.13</td>
</tr>
<tr>
<td>168</td>
<td>&lt;0.025</td>
<td>&lt;1.00</td>
<td>&lt;2.00</td>
</tr>
</tbody>
</table>

SN-38G, SN-38 glucuronide; HD, hemodialysis.

DISCUSSION

Although it is uncertain that patients with ESRF undergoing HD are at risk for lung cancer, more patients undergoing HD will be diagnosed with lung cancer because recent advances in HD have resulted in longer survival than ever. In addition, more patients undergoing HD will be diagnosed by regular chest X-ray. Therefore, the treatment for such patients, who are often elderly and have poor PS, becomes a more important subject. In patients undergoing HD with early stage non-SCLC (NSCLC), surgery can be performed safely with appropriate HD and general management in the perioperative period (5,6). In patients undergoing HD with advanced NSCLC, however, there has been no prospective study about chemotherapy. Although we previously reported the

Table 2. Pharmacokinetics parameters of irinotecan, SN-38 and SN-38G

<table>
<thead>
<tr>
<th></th>
<th>Cₓmax</th>
<th>AUC₀–₇₂</th>
<th>T½</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Irinotecan (µg/ml)</td>
<td>SN-38 (ng/ml)</td>
<td>SN-38G (ng/ml)</td>
</tr>
<tr>
<td>This case</td>
<td>0.73</td>
<td>15.51</td>
<td>59.29</td>
</tr>
<tr>
<td>Previous (n = 3)</td>
<td>0.72 ± 0.15</td>
<td>21 ± 5</td>
<td>NR</td>
</tr>
</tbody>
</table>

Cₓmax, maximal plasma concentration; AUC₀–₇₂, area under the plasma concentration-time curve from 0 to 72 h; T½, half period; Previous, Japanese phase-I study (4); NR, not reported.
safety of erlotinib (molecular-targeted agent) for three cases of advanced NSCLC undergoing HD (7), administration of cytotoxic agent for such patients is controversial because NSCLC is not a chemosensitive cancer and more severe toxicities can occur than expected. In contrast to NSCLC, chemotherapy for patients undergoing HD with SCLC is often recommended because SCLC is a chemosensitive cancer (3) and many cases of successful chemotherapy treatment for SCLC have been reported. A previous study demonstrated both safety and efficacy of chemotherapy with carboplatin (300 mg/m²) on day 1 and etoposide (50 mg/m²²) on days 1 and 3 followed by HD 1 h after administration each day (3). Our patient received chemotherapy with carboplatin and etoposide following this report and achieved PR. Amrubicin is metabolized in the liver and rarely affected by renal function. Previous Japanese reports have indicated that HD rarely affected the pharmacokinetics of amrubicin (8–10). In our case, although we did not investigate the pharmacokinetics of amrubicin, she achieved PR without serious toxicity.

Irinotecan unexpectedly causes severe toxicity of leukopenia or diarrhea. It is metabolized to form active SN-38 (100–1000 times greater than the parent drug), which is converted to the inactive SN-38G by UGT1A1. Patients with haplotypes harboring UGT1A1*6 or *28 had significantly increased SN-38, and the homozygotes and double heterozygotes of *6 and *28 (*6/*6, *28/*28 and *6/*28) were significantly associated with severe neutropenia (11–13). According to the product label, a reduction in the starting dose by at least one level of irinotecan should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction is not known (14). In addition, recent data suggested a relationship between renal function and irinotecan-induced neutropenia (15). Then, in this case, since the patient had UGT1A1*28/*28 and considering her renal function, the dose was decreased to 50 mg/m². Even with a reduced dose on day 1, she had severe neutropenia (grade 4). Although the maximal plasma concentration (Cmax) of SN-38 was similar to the data of a Japanese phase-I study, AUC0–last of SN-38 was much higher and the elimination of SN-38 was delayed (4). In one study, no significant difference in AUC of SN-38 was observed between patients undergoing HD and control (16). In other studies, however, delayed elimination of SN-38 was observed in patients undergoing HD like our case. Although the definite reason remains unclear, one potential explanation includes that uremic toxins can affect SN-38 elimination by inhibiting uptake into hepatocytes (17,18). Overall, 76% of irinotecan and 65% of SN-38G remained in the plasma during HD; however, the plasma concentration of SN-38 after HD was higher than that before HD, which might be explained by hemococoncentration. Since the binding of SN-38 to human plasma proteins was very high (99%), most plasma SN-38 seemed not to be dialyzed (19).

In this article, we presented a case of ED-SCLC with ESRF undergoing HD who survived more than 2 years by receiving multiple lines of chemotherapy. Although further studies are needed, chemotherapy for SCLC patients should not be withheld just because they are undergoing HD; however, chemotherapy should be performed even more carefully because more severe toxicities can occur than expected.

Conflict of interest statement
None declared.

References

