Case Report

Hepatic Arterial Infusion of Oxaliplatin for a Patient with Hepatic Metastases from Colon Cancer Undergoing Hemodialysis

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There has been no previous report of oxaliplatin administration in patients undergoing hemodialysis. A 65-year-old female with end-stage renal disease who was undergoing hemodialysis presented with anemia in August 2005. She was diagnosed with colon cancer with multiple liver metastases. After colectomy, hepatic arterial infusion chemotherapy of 5-fluorouracil was initiated and systemic administration of irinotecan was later added. After 3 months of treatment, liver metastases were strikingly reduced in size, and the carcinoembryonic antigen level decreased from 336 to 14.2 ng/ml. Eight months after treatment initiation, liver metastases increased in size with higher levels of carcinoembryonic antigen, therefore hepatic arterial infusion of oxaliplatin 60 mg was initiated. Hepatic arterial infusion was performed biweekly during hemodialysis and blood platinum concentrations were assessed. At the first cycle, the area under the curve of total platinum was 19.39 μg h/ml and that of free platinum was 5.51 μg h/ml. After six treatment cycles, the carcinoembryonic antigen level declined from 335 to 123 ng/ml. After eight treatment cycles, she experienced transient fever and impaired consciousness as a result of cholangitis, which improved following administration of antibiotics. We propose that limited cycles of hepatic arterial infusion of oxaliplatin are feasible in patients undergoing hemodialysis and this may become a strategy for treating hepatic metastases from colon cancer in patients undergoing hemodialysis.

Key words: oxaliplatin – hepatic arterial infusion – hemodialysis

INTRODUCTION

In recent years, improvement in the management of patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD) has led to an increased prevalence of elderly patients with ESRD. As a result, the number of patients with both cancer and ESRD is also increasing (1). However, treatment of advanced cancer patients undergoing HD with chemotherapy remains difficult, as pharmacokinetic and pharmacodynamic data for most anticancer drugs in patients undergoing HD are insufficient (2).

At first diagnosis, 19% of colorectal cancer (CRC) cases are metastatic, and the overall 5-year survival rate is 10% or less in such settings (3,4). Three cytotoxic drugs are primarily used in the treatment of advanced CRC: 5-fluorouracil (5-FU) with leucovorin (LV), irinotecan (CPT-11) and oxaliplatin (5). Oxaliplatin is a novel diaminocyclohexane (DACH) platinum derivative with activity in CRC cell lines that are resistant to cisplatin and carboplatin (6). Oxaliplatin was recently approved in Japan for patients with advanced CRC. While the use of oxaliplatin in patients with mild renal impairment has been reported (7), there has been no report of oxaliplatin use in patients undergoing HD to date. Here we report a case of patient with advanced colon cancer with unresectable liver metastasis undergoing HD, who
received hepatic arterial infusion (HAI) of oxaliplatin as salvage treatment after failure of combination 5-FU HAI/systemic CPT-11 chemotherapy.

**CASE REPORT**

A 65-year-old female with ESRD as a result of chronic nephritis, who had undergone HD 3 times/week for 2 years, underwent colonoscopy in August 2005 because of aggravated anemia. Colonoscopy results revealed type 2 advanced colon cancer with stenosis at the transverse colon. Biopsy specimens of the lesion revealed well differentiated adenocarcinoma. Computed tomography (CT) of the abdomen showed five liver metastases at bilateral lobes with a maximum size of 55 mm. Because of anemia and stenosis, transverse colectomy was performed on 27 September. On the 14th post-operative day, she experienced right upper abdominal pain with tenderness that necessitated opioid injection. Abdominal CT showed slightly enlarged liver metastases, with a maximum size of 65 mm (Fig. 1a). Her carcinoembryonic antigen (CEA) level was 336 ng/ml. The patient agreed with our decision to treat her with chemotherapy via HAI. Angiography was performed, which revealed the right hepatic artery arising from the superior mesenteric artery. The accessory left hepatic artery arose from the left gastric artery, which was embolized with a platinum coil. A catheter with a side hole was inserted, and the tip of the catheter was placed in the right hepatic artery. The proximal end of the catheter was connected with a port and implanted subcutaneously. HAI of 5-FU 700 mg/m^2 for 4 h was performed through the implanted port system starting on 2 October. Because no side effects were observed with HAI, systemic CPT-11 50 mg/m^2 infusion for 1.5 h was added beginning on 19 October. HAI was performed weekly, and CPT-11 was given biweekly. HD was performed 24 h after chemotherapy, as has been previously reported (8).

Responses were evaluated using the Response Evaluation Criteria in Solid Tumor (RECIST) guidelines every 4 weeks. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0.

After 3 months of treatment, multiple metastases were reduced in size (maximum tumor size, 38 mm; degree of reduction, 41.5%; diagnosed as partial response) (Fig. 1b) and the CEA level decreased to 14.2 ng/ml. Although this combination was well tolerated with grade 2 neutropenia for 7 months, grade 4 neutropenia (without infection) was observed 8 months after treatment initiation, which improved in 4 days following administration of granulocyte-colony stimulating factor. After resolution of neutropenia, CEA levels increased to 335 ng/ml and CT showed slightly enlarged liver metastases with calcification (Fig. 1c). We decided to discontinue HAI of 5-FU and systemic CPT-11. Since no extrahepatic sites were yet apparent and hepatic metastases were considered to be the primary prognostic factor, HAI of oxaliplatin was suggested. The patient and her family agreed with this treatment plan by written informed consent. This treatment was approved by the institutional review board in our hospital. The initial dose of oxaliplatin was 60 mg, which represented half of the reported dose of oxaliplatin HAI (100–130 mg) (9–12). Oxaliplatin 60 mg (12 ml) was dissolved in sterile 5% glucose (total volume, 20 ml), which was administered by infuser pump. HAI of hydrocortisone 100 mg in 20 ml normal saline was performed prior to HAI of oxaliplatin. Oxaliplatin HAI was initiated in conjunction with HD on 31 July 2006, and was performed for 4 h during 5 h of HD. Laboratory values prior to oxaliplatin HAI are shown in Table 1. Blood was collected to determine the ultrafiltrate platinum (free platinum) in plasma and the total platinum concentration (sum of ultrafiltrate platinum and plasma-bound platinum in plasma) every hour during the first 6 h of oxaliplatin HAI, and at 9, 16, 24, 48, 96, 168 and 336 h. Because both free and total platinum concentrations were low at 336 h, treatment was repeated every 2 weeks, which was considered a single cycle. The peak total platinum concentration was 1100 ng/ml; and that of plasma-free platinum was 500 ng/ml. The area under the curve of total platinum was 19.39 μg·h/ml and that of free platinum was 5.51 μg·h/ml (Fig. 2), which was lower than that of intravenously administered oxaliplatin in Japanese patients (13).

Because the first three cycles were performed without side effects, the dose of oxaliplatin was escalated to 70 mg. After six cycles of treatment, the CEA level dropped from 335 to 123 ng/ml, although the size of the liver metastases did not change (Fig. 1d). The total and free platinum concentration was low prior to the sixth treatment cycle (total, 200 ng/ml; free, 50 ng/ml), and no hematological toxicity or neuropathy
Table 1. Laboratory values

<table>
<thead>
<tr>
<th></th>
<th>Prior to HAI</th>
<th>2 days after 6 cycles</th>
<th>2 days after 8 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (µl)</td>
<td>8080</td>
<td>5660</td>
<td>133 800</td>
</tr>
<tr>
<td>Hb (mg/dl)</td>
<td>9.2</td>
<td>9.6</td>
<td>8.8</td>
</tr>
<tr>
<td>Pt (µl)</td>
<td>24.6 × 104</td>
<td>25.7 × 104</td>
<td>22.7 × 104</td>
</tr>
<tr>
<td>T-bil (mg/dl)</td>
<td>0.14</td>
<td>0.33</td>
<td>1.35</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>29</td>
<td>29</td>
<td>81</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>20</td>
<td>25</td>
<td>94</td>
</tr>
<tr>
<td>LDH (IU/l)</td>
<td>341</td>
<td>219</td>
<td>1002</td>
</tr>
<tr>
<td>γ-GTP (IU/l)</td>
<td>109</td>
<td>134</td>
<td>245</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>49.7</td>
<td>50.4</td>
<td>88.7</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>7.0</td>
<td>6.8</td>
<td>6.7</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>1.3</td>
<td>0.3</td>
<td>17.2</td>
</tr>
<tr>
<td>PT (%)</td>
<td>96.0</td>
<td>98.0</td>
<td>91.0</td>
</tr>
<tr>
<td>CEA (ng/ml)</td>
<td>335</td>
<td>123</td>
<td>142</td>
</tr>
</tbody>
</table>

HAI, hepatic arterial infusion; L-OHP, oxaliplatin; WBC, white blood cell count; Hb, hemoglobin; Pt, platelet; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyl transpeptidase; BUN, blood urea nitrogen; CRP, C-reactive protein; PT, prothrombin time; CEA, carcinoembryonic antigen.

was observed until the seventh cycle of treatment. Two days after the eighth treatment cycle, the patient experienced transient fever and impaired consciousness due to cholangitis (Table 1), which improved following administration of antibiotics. On 20 December 2006, a CT scan revealed that liver metastases had increased in size and HAI of oxaliplatin was discontinued. The time to progression associated with HAI of oxaliplatin in this patient was considered to be 5 months. HAI of 5-FU was resumed on 28 December 2006, but discontinued after one month because of peritonitis carcinomatosis. She died on 22 April 2007, which was 18 months since initiation of chemotherapy.

DISCUSSION

The current standard first-line chemotherapy regimens for metastatic CRC include FOLFOX (infusional 5-FU/LV with oxaliplatin) and FOLFIRI (infusional 5-FU/LV with CPT-11) with or without molecular targeted agents (e.g. bevacizumab) (14). Chemotherapy administered via HAI has been reported as effective for unresectable hepatic metastases in patients with CRC (15). A higher concentration of infused drugs in the liver can be achieved with HAI compared to systemic chemotherapy, with fewer side effects (16). HAI of oxaliplatin has already been reported with oxaliplatin doses ranging from 100 to 130 mg (9–12). Infusion times also vary, from 2 to 6 h (9–12). Guthoff et al. reported HAI of oxaliplatin, 5-FU, and mitomycin-C in patients with colorectal liver metastases, which resulted in a response rate of 59% (10). These investigators estimated a liver extraction ratio of 0.47 for oxaliplatin, with some portion of the oxaliplatin considered to efflux from liver (10). Neuropathy occurred in 47–69%, which is indicative of systemic efflux of oxaliplatin (9–12). Based on these results, we administered oxaliplatin via HAI during HD. Although oxaliplatin use has not been reported in HD patients, it is known to bind to plasma protein in a similar manner as cisplatin, which may thereby render oxaliplatin difficult to remove via HD (6,17,18). In our case, the systemic platinum concentration was low, and no systemic toxicities were observed. HAI of oxaliplatin in conjunction with HD in our case was well tolerated, with antitumor activity noted as declined CEA, although the metastases did not appear to diminish in size. HAI of oxaliplatin may become an important treatment option for patients with hepatic metastasis from colorectal cancer and warrant further investigation.

Conflict of interest statement

None declared.

References


