

[CASE REPORT]

Treatment of Gastric and Gastroesophageal Cancer Patients with Hemodialysis by CapeOX

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Abstract:

Two patients underwent hemodialysis. Case 1 with stage IV gastric cancer was treated with reduced doses of capecitabine (1,000 mg/m²/day, days 1 to 14) and oxaliplatin (65 mg/m², day 1). Although grade 1 thrombocytopenia occurred in the first cycle, grade 3 thrombocytopenia developed in the second cycle because of increasing dosage. After the dosage was reduced, chemotherapy was continued safely. Case 2 with stage IA gastroesophageal cancer was treated with radiotherapy followed by chemotherapy. Treatment with the same dose of CapeOX therapy as in case 1 resulted in no severe toxicity. We conclude that a half-dose of the CapeOX regimen is safe for gastric cancer patients undergoing hemodialysis.

Key words: gastric cancer, capecitabine, oxaliplatin, hemodialysis, CapeOX

(Intern Med 58: 2791-2795, 2019)

(DOI: 10.2169/internalmedicine.2718-19)

Introduction

The number of hemodialysis patients has increased because the Japanese population is aging and hemodialysis treatment is improving. As a result, the number of cancer patients receiving hemodialysis due to chronic renal failure has also increased. Gastric cancer is the second leading cause of cancer and the third leading cause of death among cancers in Japan (1).

The first-line standard chemotherapy for unresectable advanced gastric cancer is a combination of platinum plus fluorouracil (2). Platinum includes cisplatin and oxaliplatin, and fluorouracil includes 5-fluorouracil and prodrugs of fluorouracil (e.g., S-1 and capecitabine). Although platinum, S-1, and capecitabine are all contraindicated for patients with severe chronic renal failure, several case reports describing chemotherapy including those drugs, either in combination or alone, have been published (3-6). However, none of these regimens are standard for first-line treatment.

We herein report two patients undergoing hemodialysis who were safely treated with reduced doses of capecitabine plus oxaliplatin (CapeOX) for advanced gastric and gastroesophageal cancers.

Case Reports

Choice of regimen and doses

No cases of hemodialysis patients receiving any standard regimen of first-line chemotherapy for advanced gastric cancer have been reported. We decided to administer the CapeOX regimen to our gastric cancer patients undergoing hemodialysis based on a case report of a previous CapeOX regimen [capecitabine 1,250 mg/m²/day (full dose: 2,000 mg/m²/day) from days 1 to 14 plus oxaliplatin 70 mg/m² (full dose: 130 mg/m²) on day 1] in colorectal cancer patients undergoing hemodialysis (7). After referencing published pharmacokinetic data and case reports, we decided to commence hemodialysis 1 hour after the completion of oxaliplatin administration and to continue hemodialysis for as long as is routine (8, 9).

Case 1

A 62-year-old Japanese man had been on hemodialysis for 15 years due to chronic renal failure caused by chronic glomerulonephritis. He underwent screening upper gastrointestinal endoscopy, and a large type 2 tumor was found on

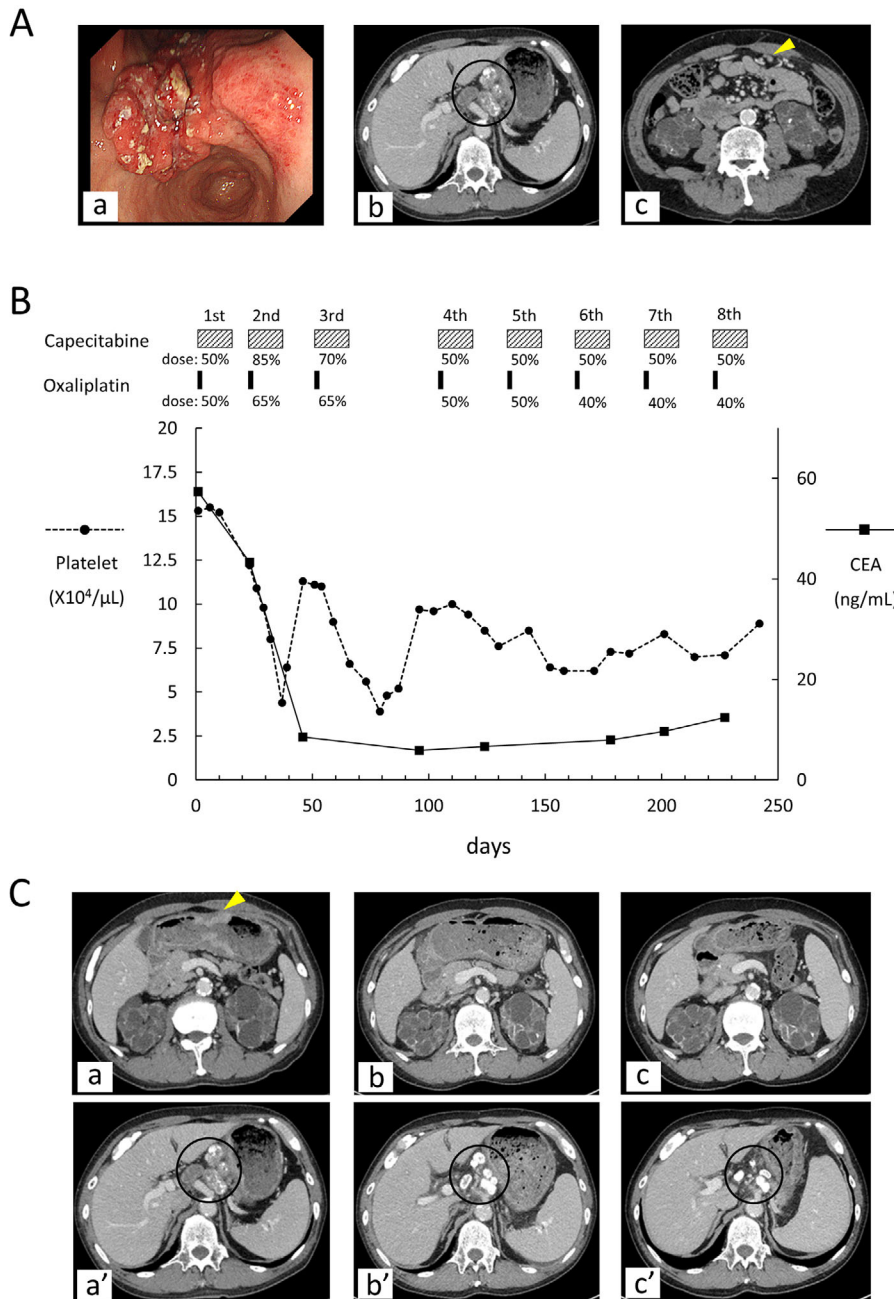


Figure 1. Treatment, adverse effects, and images of case 1. **A:** Endoscopic and computed tomography (CT) images taken prior to treatment. The circles indicate lymph nodes. The arrow indicates the disseminated peritoneal nodule. **B:** Course of chemotherapy and platelet and carcinoembryonic antigen (CEA) levels. **C:** Upper abdominal computed tomography images (a) before treatment, (b) after three courses, and (c) after six courses. The arrow indicates the thick stomach wall with the primary tumor. The circles indicate lymph nodes.

the lesser curvature between the cardia and antrum of the stomach (Fig. 1Aa).

A tumor biopsy showed a moderately differentiated tubular adenocarcinoma, and the human epidermal growth factor receptor (HER) 2 status was negative. Computed tomography (CT) revealed multiple lymph node metastases (Fig. 1Ab) and peritoneal dissemination (Fig. 1Ac). The patient was therefore diagnosed with gastric cancer cT4aN3aM1, stage IV.

A half-dose of CapeOX chemotherapy (capecitabine 1,000

mg/m²/daily for 14 days and oxaliplatin 65 mg/m², intravenous drip for 2 hours on day 1, every 3 weeks) was initiated (Fig. 1B). On day 1, hemodialysis was performed 1 hour after the completion of oxaliplatin administration. No significant adverse effects other than common terminology criteria for adverse events (CTCAE) grade 1 thrombocytopenia were observed during the first cycle of chemotherapy. When the doses of both drugs were increased (85% of capecitabine and 65% of oxaliplatin compared to full doses during the second cycle), grade 3 thrombocytopenia occurred. These

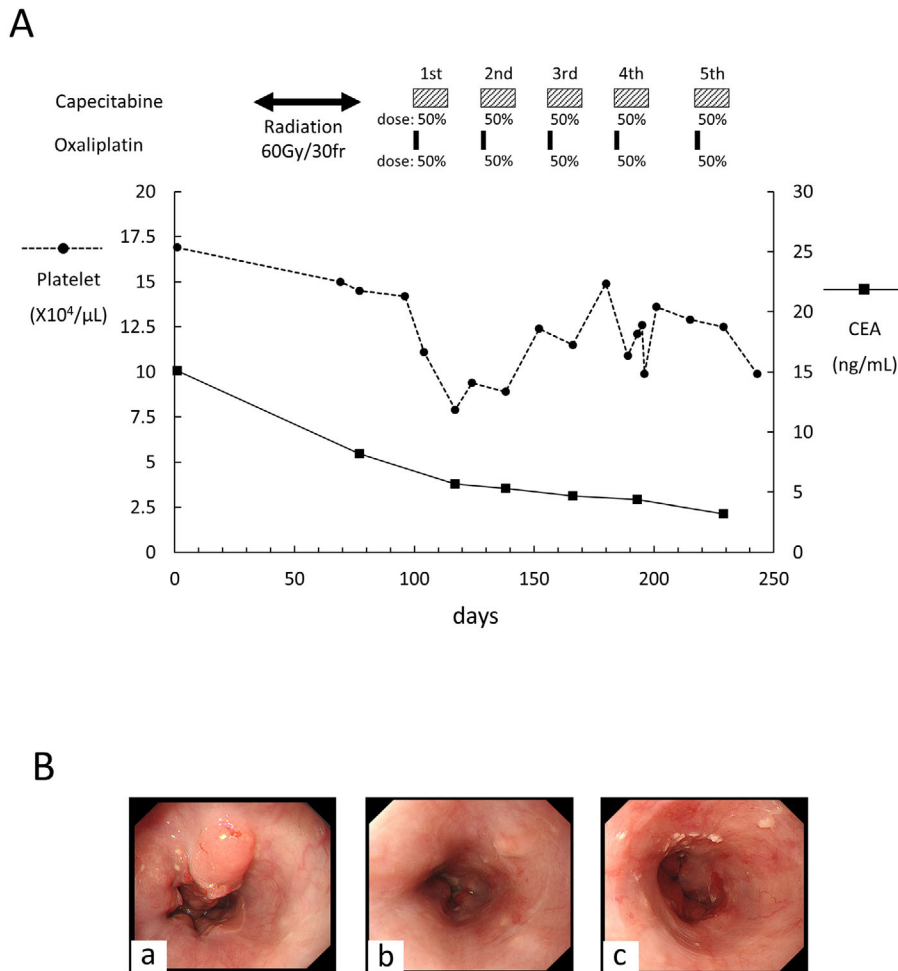


Figure 2. Clinical course and images of case 2. **A:** Course of radiation and chemotherapy as well as platelet and CEA levels. **B:** Endoscopic findings at the esophagogastric junction (a) before treatment, (b) after radiation and two courses of chemotherapy, and (c) after four courses of chemotherapy.

doses were reduced again and adjusted according to the adverse effects (Fig. 1A). After chemotherapy, the primary lesion could not be detected (Fig. 1C, upper images), and the lymph nodes had decreased in size (Fig. 1C, lower images). The serum carcinoembryonic antigen (CEA) level had also decreased (Fig. 1B). The antitumor effect was considered a partial response.

Case 2

A 65-year-old Japanese man had been on hemodialysis for 20 years due to chronic renal failure caused by IgA glomerulonephritis. He had a history of malignant pleural mesothelioma five years prior and comorbidities of angina pectoris, hypertension, and diabetes mellitus.

An elevated serum CEA level was detected on a follow-up blood test. He underwent upper gastrointestinal endoscopy, and a type 0-IIa+IIc lesion was found at the esophagogastric junction. Endoscopy further revealed that the tumor had invaded at least the submucosa, eliminating the possibility of treatment with endoscopic submucosal dissection (ESD). A tumor biopsy showed a moderately differentiated tubular adenocarcinoma, and the HER2 status was

negative. No lymph node swelling or distant metastasis was detected by CT. The patient was therefore diagnosed with gastroesophageal cancer cT1bN0M0, stage 1A.

As ESD was not indicated, and tumor stenosis was expected, we planned radiotherapy followed by chemotherapy instead of surgery because he had a history of malignant pleural mesothelioma, multiple comorbidities of diabetes mellitus and angina pectoris, and had undergone coronary artery bypass grafting. Radiotherapy caused grade 2 esophagitis. After 60 Gy of radiation in 30 fractions, CapeOX chemotherapy with a half-dose of each drug was initiated, as in case 1. Although only grade 1 thrombocytopenia was observed during the first cycle of chemotherapy, we did not increase the doses because we experienced grade 3 thrombocytopenia in case 1. Grade 2 peripheral neuropathy and grade 1 hand-foot syndrome were also observed during five cycles. The doses of the drugs were not changed throughout treatment.

After five cycles of treatment, the serum CEA level was found to have decreased, and the lesion had been replaced with regenerative epithelium according to endoscopy (Fig. 2). The tumor was well controlled during chemother-

apy.

Discussion

We safely treated two patients with gastric and gastroesophageal cancer undergoing hemodialysis with half-doses of CapeOX without severe toxicities. When the doses of capecitabine and oxaliplatin were increased by more than 50%, grade 3 thrombocytopenia occurred in case 1. Both patients received more than five courses of chemotherapy, resulting in good disease control.

Cancer is one of major causes of death in hemodialysis patients (10, 11). Due to the increasing number of patients with hemodialysis, the number of such patients undergoing chemotherapy for advanced cancer has also increased. However, neither guidelines nor evidence supporting cancer chemotherapy in patients with hemodialysis exist.

A retrospective study of chemotherapy in hemodialysis patients was conducted in France (12). This study reported the anticancer drugs prescribed and dosage adjustment in hemodialysis patients but did not mention the recommended dosages of the prescribed anticancer drugs. A nationwide survey of chemotherapy in cancer patients undergoing hemodialysis was also conducted in Japan (13). Among 107 patients with unresectable cancer, only 44 (41%) underwent chemotherapy, 36 (34%) received the best supportive care, and 27 (25%) underwent other therapies. The dosage and timing of the drugs depended on each institution. Three patients (6.8%) died of treatment-related death, and 9 (20%) died of a cause other than cancer among the 44 patients who received chemotherapy. That study suggested that the risks of chemotherapy were high and that the indication chemotherapy should be considered carefully in cancer patients undergoing hemodialysis. Although the use of pharmacokinetic data to adjust anticancer drug doses would be ideal, mass spectrometry is time-consuming and expensive.

The standard first-line chemotherapy regimen for gastric cancer consists of cisplatin and S-1 (SP), cisplatin and capecitabine (XP), oxaliplatin and S-1 (SOX), CapeOX, and FOLFOX (2). To select the optimum regimen and drug doses for our gastric cancer patients, we searched the literature, as these drugs are secreted by the kidney, and severe adverse events reportedly occur in patients with renal impairment. Among the standard regimens, CapeOX and FOLFOX had been reported useful in colorectal cancer patients receiving hemodialysis, but their efficacy and safety in gastric cancer patients was not mentioned (7, 14). The FOLFOX regimen is generally used in colorectal cancer patients with hemodialysis but requires the placement of a central vein catheter. Since hemodialysis may increase the risk of complications with a central vein catheter, we chose the CapeOX regimen for our gastric cancer patients with hemodialysis, as no catheter was needed.

Capecitabine is an orally administered precursor of 5'-deoxy-5-fluorouridine (5'-DFUR), which is preferentially activated to 5-fluorouracil in tumors. A previous report rec-

ommended capecitabine not be used in patients with severe renal impairment because such impairment leads to an increased area under the curve of 5'-DFUR and treatment-related grade 3 or 4 adverse effects (15). However, another retrospective study indicated capecitabine to be safe to use with a dose reduction in patients with end-stage renal disease on hemodialysis (16). The dose of capecitabine could be safely increased to 50% in patients with hemodialysis.

Oxaliplatin is a platinum drug that is mainly secreted from the kidney and, therefore, generally contraindicated in patients with severe renal impairment. Pharmacokinetic studies have revealed no accumulation of free platinum detectable in patients with hemodialysis (8). The FOLFOX regimen, which includes a dose of 70 mg/m² oxaliplatin, is effective and safe in colorectal cancer patients with hemodialysis (8). Based on these previous and present findings, we conclude that a half-dose of the CapeOX regimen is optimal for gastric cancer patients on hemodialysis.

In conclusion, we herein report two hemodialysis cancer patients treated with half-doses of the CapeOX regimen who achieved good disease control without severe toxicities. Dose modifications (reductions of up to 50% of each drug) are optimal for gastric cancer patients undergoing hemodialysis.

The authors state that they have no Conflict of Interest (COI).

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