INTERNAL MEDICINE

□ CASE REPORT □

Successful Treatment with Modified FOLFOX6 and Panitumumab in a Cecal Cancer Patient Undergoing Hemodialysis

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Abstract

Combination chemotherapy of mFOLFOX6 (5-fluorouracil, leucovorin, and oxaliplatin) plus panitumumab, a fully human monoclonal antibody against epidermal growth factor receptor (EGFR), is one of the standard treatments for metastatic colorectal cancer (mCRC) without *KRAS* mutation. A few reports suggested no need of dose adjustment of cetuximab, a similar chimeric anti-EGFR antibody, in patients with renal impairment. However, panitumumab combined with cytotoxic drugs for hemodialysis patients has not been reported. We herein report a case of a hemodialysis mCRC patient successfully treated with mFOLFOX6 and panitumumab combination therapy.

Key words: colorectal cancer, hemodialysis, panitumumab, mFOLFOX6

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Introduction

Panitumumab is a fully human IgG2 monoclonal antibody that binds to the extracellular domain of epidermal growth factor receptor (EGFR) and inhibits tumor cell proliferation. It is approved for the treatment of metastatic colorectal cancer (mCRC) with wild-type *KRAS*. Recent reports indicated that EGFR-targeting chemotherapy enables early tumor shrinkage and prolongs the survival (1, 2). However, there is little data on panitumumab therapy in patients undergoing chronic dialysis. We herein report the first case of a mCRC patient on hemodialysis who was successfully treated with mFOLFOX6 [a combination regimen of 5-fluorouracil (5-FU), leucovorin, and oxaliplatin] and panitumumab.

Case Report

A 62-year-old Japanese man was admitted to our hospital complaining of abdominal pain. He had been undergoing hemodialysis because of diabetic nephropathy since 53 years of age. Colonoscopy revealed a type 2 tumor located in the cecum. A tumor biopsy showed moderately differentiated adenocarcinoma. The physical examination was unremarkable. His body height was 172.0 cm and weight was 66.0 kg. A blood examination revealed mild anemia (hemoglobin 10.4 mg/dL) and elevated serum levels of blood urea nitrogen 51.3 mg/dL, creatinine 8.73 mg/dL, eGFR 5.5 mL/min/1.73 m^2 and K 5.5 mEq/L. The serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels were 23.9 ng/mL (normal <5.0 mg/mL) and 27.2 U/mL (normal <37 U/mL), respectively. The liver function test was within the normal range. A subsequent computed tomography (CT) scan revealed two metastases in the left lobe of his liver. First, an ileocecal resection with lymph node dissection was performed, and histopathology showed a moderately differentiated adenocarcinoma invading to the serosa. The clinicopathological stage was IV (T4N2M1), and direct sequencing of the tumor *KRAS* gene did not detect any mutation in exon 2 (codons 12 and 13). Next, partial hepatectomy was planned. However, new multiple liver metastases in both lobes were found in a follow-up CT examination three months after the primary operation (Fig. 1A, B). He started chemotherapy with mFOLFOX6 [oxaliplatin 85 mg/m^2 intravenously (IV),

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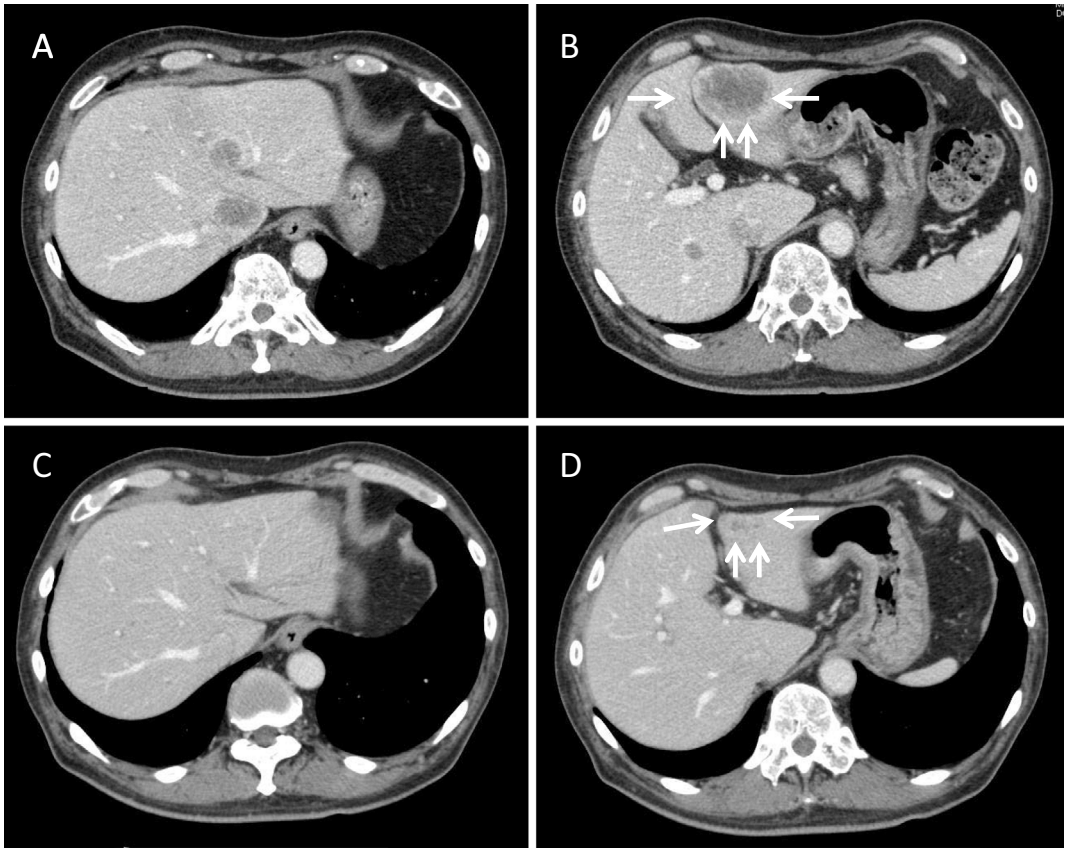

Figure 1. **Abdominal computed tomography before chemotherapy (A, B). Multiple metastatic lesions were observed in both lobes of the liver. The biggest lesion was approximately 5 cm in the left lateral segment (arrows). After chemotherapy (C, D), liver metastases in the right lobe disappeared, and metastases of the left lobe were markedly reduced in size (arrows).**

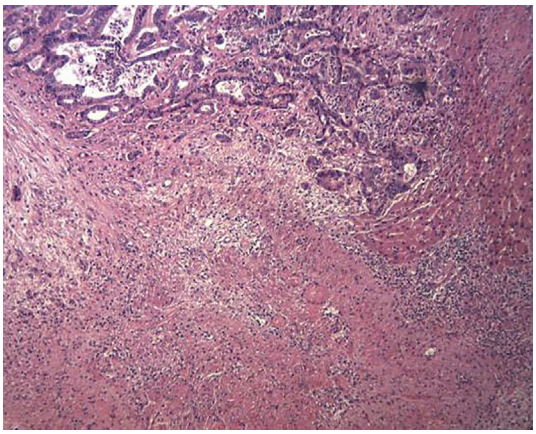

Figure 2. **Histology of the liver metastatic lesion resected after chemotherapy. Most of the tumor was displaced with necrotic tissue or fibrotic tissue. Degenerating tumor cells partly remained (Hematoxylin and Eosin staining, 100×).**

over 90 minutes, with folinic acid 400 mg/m^2, over 120 minutes, followed by 5-FU 400 mg/m^2 IV bolus, then 2,400 mg/m^2 IV infusion, over 46 hours] plus panitumumab (5 mg/kg IV infusion over one hour) every two weeks. Hemodialysis was performed one hour after the administration of oxaliplatin on day 1 and repeated three times a week. On day 1 after chemotherapy, he developed CTCAE (Common Terminology Criteria for Adverse Events, ver. 4, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40) grade 3 nausea and encephalopathy associated with hyperammonemia. Brain CT showed no significant abnormal findings and the blood laboratory data, except for ammonia, did not change. Therefore, the cause of the coma was considered to be 5-FU-related hyperammonemic encephalopathy. Two days later, his consciousness level improved after the administration of branched-chain amino acid solutions and hemodialysis. The dose of 5-FU was reduced up to 60% and branched-chain amino acid solutions was used during 5-FU administration from the next cycle. These adverse events were completely controlled by the treatment management. After cycle two, he also developed grade 1 skin acneiform eruption associated with panitumumab. However, it was manageable by the administration of oral antibiotics and steroid ointments. The patient accomplished nine cycles without treatment delay. His metastatic liver tumors showed a good partial response (Fig. 1C, D) and the lesions in the right lobe disappeared. Then, left hepatectomy was performed. The pathological findings showed semi-curative effects (Fig. 2). The follow-up CT four months after hepatectomy showed cancer recurrence of his liver. Chemotherapy with mFOLFOX6 and panitumumab

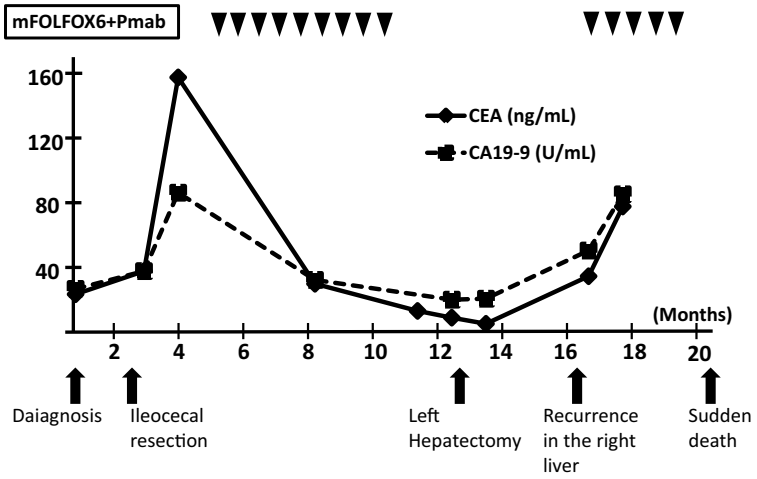

Figure 3. **Clinical course of the patient.**

Table. **Past Reports on Cetuximab in Patients with Hemodialysis.**

Cancer	Age	Gender	Regimen	Line	Dose of cetuximab	Efficacy	Adverse events related with cetuximab	Reference
head and neck cancer	65	male	cetuximab and radiotherapy	first line	full doses	not described	grade 1 acneiform rash	4
colorectal cancer	68	male	cetuximab and CPT-11	third line	full doses	partial response	not described	5
colorectal cancer	66	male	cetuximab monotherapy	first line	full doses	partial response	not described	6

was reinitiated. Although disease progression was not observed for four months during chemotherapy, he suddenly died from acute cardiac failure two days after the last mFOLFOX6 and panitumumab administration. Fig. 3 shows the patient's clinical course.

Discussion

Recent reports demonstrated that chemotherapy with anti-EGFR antibodies yielded high response rates and led to significantly increased resectability of metastatic lesions in mCRC patients with wild-type *KRAS* (3). Panitumumab has been considered equally effective and similarly safe to another anti-EGFR antibody, cetuximab, and its survival benefit was shown in the first-line treatment when combined with FOLFOX. According to these findings, we selected mFOLFOX6 plus panitumumab, expecting hepatectomy after tumor shrinkage. Although the number of patients undergoing hemodialysis has been increasing to date, the guidelines regarding the management of chemotherapy in cancer patients undergoing hemodialysis have not yet been established. Three previous case reports of hemodialysis cancer patients treated with cetuximab suggested its safety, efficacy and no necessity for dose reduction (Table) (4-6). Another report analyzing the pharmacokinetics of cetuximab showed that it could be safely used in patients with renal impairment without dose adjustment (7). Although the administration of panitumumab in patients with renal impairment has not yet been reported, its pharmacokinetic behavior appears similar to cetuximab. These antibodies are transported into the cells after binding to EGFR and degraded in the lysosomal system. When binding to EGFR is saturated, these antibodies are hydrolyzed in the endothelial system, similar to endogenous IgG1 or IgG2 (4, 8). It has been considered that renal dysfunction had no apparent impact on the pharmacokinetics of these drugs. However, panitumumab clearance in hemodialysis has not yet been analyzed (8). In our case, panitumumab was administered without dose reduction, and adverse events observed relative to panitumumab included only a slight skin rash. Panitumumab may be used safely in patients with renal impairment, however, further investigations involving drug clearance are needed.

The safety of 5-FU and oxaliplatin in dialysis patients has been widely studied. Approximately 80% of 5-FU is inactivated by dihydropyrimidine dehydrogenase (DPD) in the liver, and it is considered that dose reduction is not necessary in dialysis patients. The plasma 5-FU level decreases rapidly after the start of dialysis, but remains constant in the case of continuous 5-FU infusion (9). We started the standard dose of 5-FU, however, our patient experienced 5-FU-related hyperammonemic encephalopathy caused by the continuous infusion of 5-FU. 5-FU-related hyperammonemic encephalopathy may be caused by a large amount of infusional 5-FU, regardless of hemodialysis. Two previous reports showed that a dose reduction of 5-FU up to 60-80% with other supportive treatments prevented the recurrence of

encephalopathy (10, 11). We provided a relevant explanation regarding the risk of hyperammonemic encephalopathy, but our patient wished to continue mFOLFOX6 with panitumumab chemotherapy. We reduced the dose of 5-FU up to 60% and administered branched-chain amino acid solutions. Indeed, encephalopathy did not recur by reducing 5-FU dose to 60% in our patient. The dialysis removal rate of free platinum was reported to be 84% (12). We could safely administer oxaliplatin without dose reduction by performing hemodialysis one hour after the administration of oxaliplatin. However, an analysis of the pharmacokinetics of oxaliplatin in mFOLFOX6 plus bevacizumab therapy under hemodialysis was reported to show a larger AUC with a lower Cmax for free platinum than those in patients with normal renal function (13). Therefore, the safety and efficacy of FOLFOX in dialysis patients must be further clarified, including the pharmacokinetics.

The association between the sudden death of our patient and mFOLFOX6 plus panitumumab chemotherapy is unknown. The frequency is rare, however, sudden death is always observed in chemotherapy for advanced cancer patients and hemodialysis patients. Our patient is suspected to have died of acute cardiac failure. Cardiac toxicities are also rare, however, significant complications are associated with 5-FU therapy and EGFR monoclonal antibodies (14). 5-FU associated cardiotoxicity is reported in 1.2-7.6% of patients (15). A Japanese postmarketing survey of panitumumab revealed that cause-unidentified death occurred in 0.03% (1/3,085), death caused by cardiac failure occurred in 0.03% (1/3,085) and cardiac disorders occurred in 0.23% (7/3,085) of patients (16). Other side effects include hypertension, thrombosis and arrhythmias. It is not yet clear to what extent mFOLFOX6 plus panitumumab chemotherapy increases the risk of sudden death in patients on hemodialysis, but the accumulation of such cases is necessary.

In conclusion, this case report indicates that combination chemotherapy with panitumumab appeared to be safe and effective for a patient with chronic kidney disease undergoing hemodialysis.

Author's disclosure of potential Conflicts of Interest (COI).

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