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Case Report

Modified FOLFOX-6 Plus Bevacizumab Chemotherapy for Metastatic Colorectal Cancer in Patients Receiving Hemodialysis: A Report of Three Cases and Review of the Literature

Chikako Funasaka[a] Yusuke Kanemasa[a] Tatsu Shimoyama[a]
Akihito Ohta[b] Yasushi Omuro[a]

[a]Department of Medical Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan; [b]Department of Nephrology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

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Colorectal cancer · Hemodialysis · Chemotherapy

Abstract
Fluorouracil plus oxaliplatin (L-OHP) (FOLFOX) plus bevacizumab (BV) therapy is commonly administered to patients with metastatic colorectal cancer. However, few reports have described L-OHP therapy in hemodialysis patients, and the efficacy and safety remain uncertain in this population. Here, we report three cases of hemodialysis patients with colorectal cancer who received a modified FOLFOX-6 (mFOLFOX-6, or FOLFOX plus folinic acid) plus BV regimen every 3 weeks. One patient, a 65-year-old man with chronic renal failure consequent to diabetic nephropathy, underwent hemodialysis 3 times/week. He exhibited a partial response after 7 cycles of mFOLFOX-6 plus BV, with the major adverse events of Grade 1 peripheral neuropathy and Grade 2 thrombocytopenia. He died of perforation-related septic shock. A 71-year-old

Chikako Funasaka
Department of Medical Oncology
Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital
3–18–22 Bunkyo-ku, Tokyo, 113–8677 (Japan)
E-Mail c-funasaka@cick.jp

man previously treated with bosutinib for chronic myelocytic leukemia received 9 cycles of mFOLFOX-6 plus BV and achieved stable disease. Chemotherapy was administered every 4 weeks, and the 5-fluorouracil dose was reduced after he developed Grade 4 neutropenia. A 71-year-old woman with chronic renal failure consequent to diabetic nephropathy underwent hemodialysis 3 times a week. She received 3 cycles of mFOLFOX-6 plus BV, but exhibited disease progression and developed Grade 4 neutropenia, which necessitated a reduced 5-fluorouracil dose. After completing FOLFOX therapy, she began second-line irinotecan/5-fluorouracil/leucovorin (FOLFIRI) plus BV therapy. In two cases, bone marrow suppression increased the difficulty of L-OHP dose escalation. We conclude that mFOLFOX-6 plus BV, with appropriate dose reduction, is acceptable for patients with chronic renal failure. Further data are needed to determine the adequate chemotherapy dose.

Introduction

The global incidence of colorectal cancer, the third leading cause of cancer-related death, continues to increase [1]. Modified FOLFOX-6 (mFOLFOX-6; oxaliplatin (L-OHP) with 5-fluorouracil (5-FU) and folinic acid) plus bevacizumab (BV) is a standard chemotherapy regimen for metastatic colorectal cancer. This treatment was reported to yield an objective response rate of 52% and median time to treatment failure of 5.8 months [2].

Although long-term hemodialysis is a significant risk factor for cancer [3], only a few reports have described the use of FOLFOX therapy in patients undergoing chronic hemodialysis. Therefore, the efficacy and safety of FOLFOX therapy in this population remains unclear. Herein, we report 3 cases involving patients undergoing chronic hemodialysis who received mFOLFOX-6 plus BV for metastatic colorectal cancer. All three received mFOLFOX-6 as described by Horimatsu et al. [4], with hemodialysis initiation immediately after L-OHP infusion. Treatment efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0.

Case Report/Case Presentation

Case 1

A 65-year-old man with chronic renal failure consequent to diabetic nephropathy had undergone hemodialysis 3 times/week at another hospital since March 2017. Screening prior to hemodialysis induction revealed a moderately/poorly differentiated adenocarcinoma in the ascending colon. The tumor was G13C *KRAS* mutation-positive but *BRAF* mutation-negative. Computed tomography (CT) revealed a 20-mm metastasis to S6/7 of the liver. The patient was diagnosed with stage IV colon cancer and underwent a right colectomy in April 2017, followed by resection of the liver metastasis in July 2017. Postoperative CT revealed multiple lung metastases, liver metastasis, lymph node metastasis, and ascites.

The patient began receiving chemotherapy at our hospital in November 2017. At that time, his ECOG performance status, body surface area (BSA), and body weight were 1, 1.88 m^2,

and 76.9 kg, respectively. He began receiving mFOLFOX-6 (L-OHP: 60 mg/m^2 [112 mg], l-LV: 200 mg/m^2 [375 mg], bolus 5-FU: 400 mg/m^2 [751 mg], 46-hr injection of 5-FU: 2,400 mg/m^2 [4,500 mg]) plus BV (5 mg/kg [384 mg]) in December 2017. He received 7 cycles of this therapy over a period of 4.7 months, with L-OHP dose escalation in the fifth cycle. His serum platinum concentration over time is shown in Figure 1. This patient achieved a partial response and developed the major adverse events of Grade 1 peripheral neuropathy and Grade 2 thrombocytopenia. He died of perforation-related septic shock at the other hospital.

Case 2

A 71-year-old man with chronic renal failure consequent to diabetic nephropathy had undergone hemodialysis 3 times/week since February 2017. He had a history of chronic myelocytic leukemia for which he had received bosutinib in the hematology department of our hospital. An examination revealed anemia, and a colonoscopy identified a *KRAS* and *BRAF* mutation-negative type 2 adenocarcinoma (tub1/ tub2) in the rectum. He underwent laparoscopic colectomy and partial resection of the intestine, which led to a diagnosis of stage IIIa rectal adenocarcinoma. No adjuvant chemotherapy was administered.

In April 2018, CT revealed multiple liver metastases and evidence of local recurrence. At that time, his performance status, BSA, and body weight were 0, 1.7 m^2, and 55.9 kg, respectively. He began receiving mFOLFOX-6 (L-OHP: 60 mg/m^2 [100 mg], l-LV: 200 mg/m^2 [334 mg], bolus 5-FU: 400 mg/m^2 [669 mg], 46-h injection of 5-FU: 2,400 mg/m^2 [4,015 mg]) plus BV (5 mg/kg [279 mg]) in May 2018 and received a total of 9 chemotherapy cycles in 7.7 months. He achieved stable disease but developed Grade 4 bone marrow suppression, necessitating a 5-FU dose reduction (bolus 5-FU: 320 mg/m^2 [534 mg], 46-h injection of 5-FU: 1,920 mg/m^2 [3,200 mg]) from the second treatment course and a decrease in the chemotherapy frequency to every 4 weeks. His serum platinum concentration over time is shown in Figure 2. The patient developed the major adverse events of Grade 4 neutropenia and Grade 3 leukopenia. No non-hematological adverse events were observed. He continues to receive treatment.

Case 3

A 71-year-old woman with chronic renal failure consequent to diabetic nephropathy had undergone hemodialysis 3 times/week since August 2017. She presented with anemia, and a colonoscopy revealed a G12D *KRAS* mutation-positive, *BRAF* mutation-negative type 2 adenocarcinoma (tub2 > por2) in the transverse colon. As CT revealed a liver metastasis, the patient was diagnosed with Stage IV colorectal cancer and underwent a laparoscopic right colectomy in September 2017, followed by a resection of the liver metastasis in December 2017.

In May 2018, a postoperative CT examination revealed multiple lung metastases and a recurrence of the liver metastasis. At that time, her performance status, BSA, and body weight were 2, 1.4 m^2, and 52.8 kg, respectively. She began receiving mFOLFOX-6 (L-OHP: 60 mg/m^2 [86 mg], l-LV: 200 mg/m^2 [288 mg], bolus 5-FU: 400 mg/m^2 [576 mg], 46-h injection of 5-FU: 2,400 mg/m^2 [3,400 mg]) plus BV (5 mg/kg [264 mg]). However, she developed Grade 4 bone marrow suppression which necessitated a 5-FU dose reduction (bolus 5-FU: 320 mg/m^2 [460 mg], 46-h injection of 5-FU: 1,920 mg/m^2 [2,720 mg]) from the second chemotherapy course. She received 3 cycles of mFOLFOX-6 therapy over a period of 2.2 months but exhibited progressive disease with major adverse events of Grade 4 neutropenia, Grade 3 thrombocyto-

penia, and Grade 1 fatigue. Her serum platinum concentration over time is shown in Figure 3. FOLFOX therapy was discontinued, and irinotecan/5-fluorouracil/leucovorin (FOLFIRI) plus BV therapy was initiated as a second-line treatment.

Discussion/Conclusion

In this case series, we have demonstrated the acceptability of mFOLFOX-6 plus BV for colorectal cancer in patients undergoing chronic hemodialysis. However, two patients developed severe hematological adverse events such as bone marrow suppression, which presented challenges with respect to L-OHP dose escalation.

Table 1 lists the published cases involving FOLFOX therapy for colorectal cancer in patients receiving chronic hemodialysis [4, 5–13]. In all listed cases, the L-OHP dose was reduced to 50–80% of the standard dose (85 mg/m^2) and in most, hemodialysis was initiated immediately after L-OHP infusion. In all previously reported cases, FOLFOX therapy was administered safely without any severe adverse events and although the efficacy of this treatment is unclear, tumor progression was not observed in most cases. In our cases, the starting L-OHP dose was 60 mg/m^2, with the intent to escalate to 85 mg/m^2. However, this was difficult due to myelosuppression. Major hematological adverse events, such as thrombocytopenia and neutropenia, were observed. Although Grade 4 neutropenia occurred in two patients aged >70 years, febrile neutropenia was not observed. These adverse events were managed adequately by appropriate dose reductions and increased intervals between subsequent chemotherapy cycles. No severe non-hematological toxicities (e.g., peripheral neuropathy) were observed in our three patients.

The pharmacokinetic data in previous reports demonstrate that free platinum levels follow a bimodal pattern, with peaks appearing at 2 and 26 h after the start of L-OHP administration. The second peak appears after the first hemodialysis session and is attributed to the dissociation of platinum bound to plasma proteins and blood cells or to the return of platinum from the tissues to the blood. In patients receiving hemodialysis, this second peak has a greater influence on the area under the curve than that observed with FOLFOX therapy in patients with normal renal function. Therefore, patients receiving hemodialysis generally are generally treated at intervals of 3 weeks, which is longer than the interval used for FOLFOX therapy in patients with normal renal function.

A previous study by Giacchetti et al. reported differences in hematological toxicity between patients treated with FOLFOX-2 and a chronomodulated infusion of L-OHP, 5-FU, and leucovorin (chronoFLO4) and suggested that hematological toxicity correlates with the C_{max} of L-OHP [13]. In our three patients, the C_{max} for a L-OHP dose of 60 mg/m^2 was approximately 50–94% of that observed with for a L-OHP dose of 90 mg/m^2 in patients with normal renal function [14]. Although the C_{max} values of serum platinum concentrations in our cases were similar to those in other reports, our patients exhibited more severe hematological toxicities.

Moreover, the plasma platinum concentrations before L-OHP administration and the platinum C_{max} increased gradually in our patients with each treatment course, and hematological adverse events occurred from the first therapy cycle. In other words, we did not observe a relationship between C_{max} and the severity of hematological toxicity, possibly because we administered appropriate doses of 5-FU. Our findings may be consistent with other reports that

did not suggest a relationship between the C_{max} of L-OHP and hematological toxicity. An understanding of the correlation between toxicity and L-OHP pharmacokinetics in hemodialysis patients should also consider concentrations of other drugs in the combination regimen.

In conclusion, our cases demonstrate the acceptability of the mFOLFOX-6 plus BV regimen for the treatment of advanced colorectal cancer in patients receiving hemodialysis. However, it is necessary to monitor toxicity carefully in these patients, given the tendency of adverse events to be severe and the consequent need for L-OHP dose reduction. Further investigations should aim to clarify the dose and chemotherapy intervals to allow adjustments according to plasma platinum pharmacokinetics and the occurrence of adverse events.

Statement of Ethics

We have reported these cases in compliance with the Declaration of Helsinki. General consent for the publication and presentation of case data were obtained from the patients when they provided informed consent to undergo treatment.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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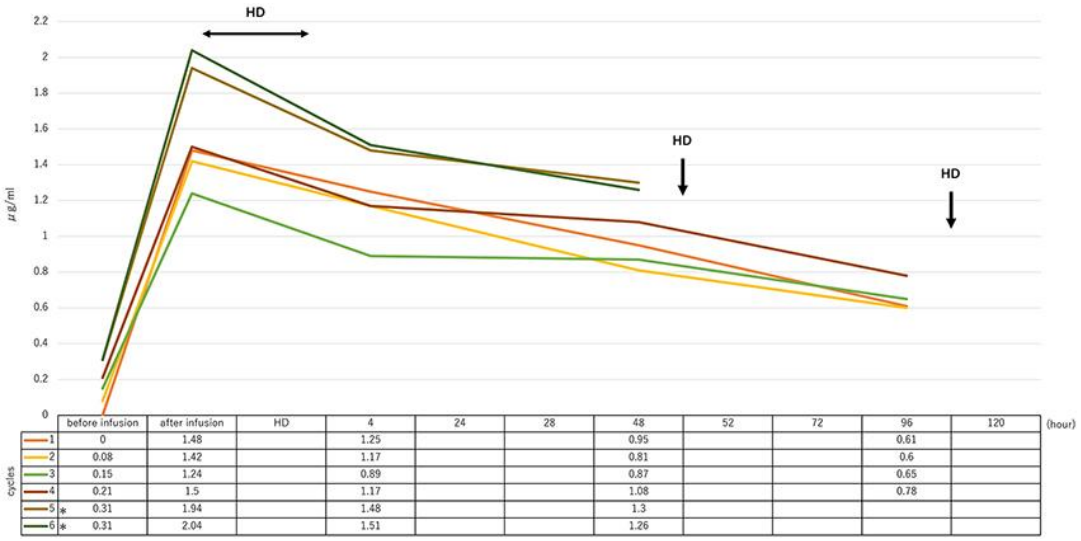
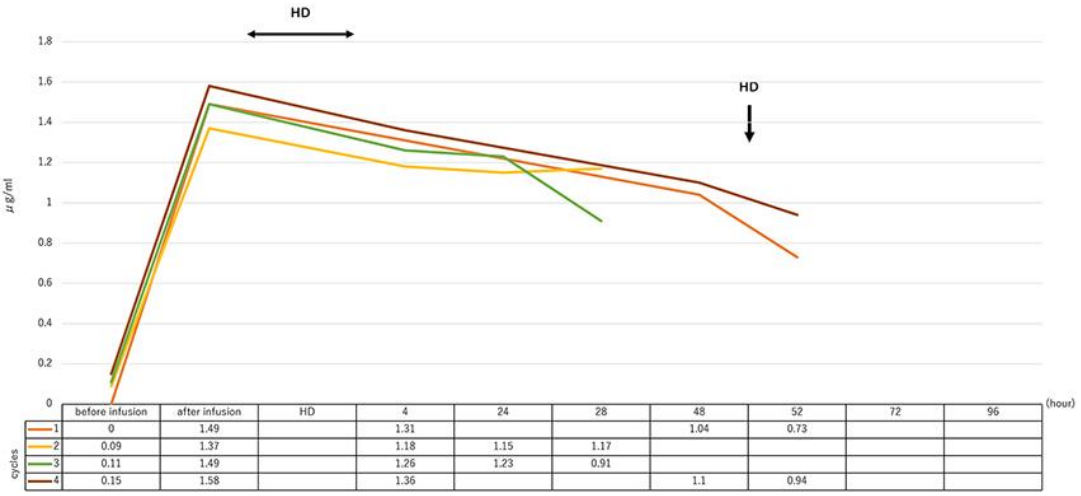


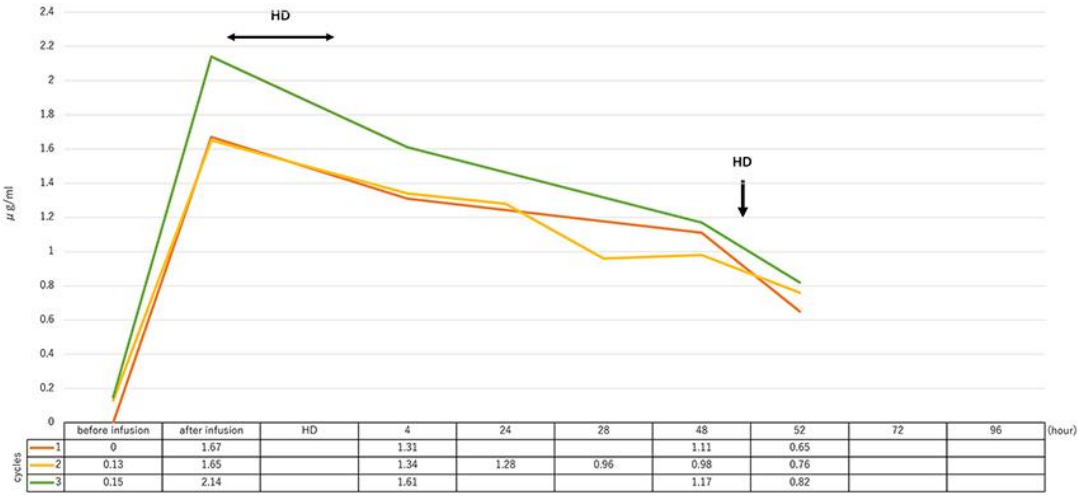
cycles	before infusion	after infusion	HD	4	24	28	48	52	72	96	120	(hour)
1	0	1.48		1.25			0.95			0.61		
2	0.08	1.42		1.17			0.81			0.6		
3	0.15	1.24		0.89			0.87			0.65		
4	0.21	1.5		1.17			1.08			0.78		
5	* 0.31	1.94		1.48			1.3					
6	* 0.31	2.04		1.51			1.26					

Fig. 1. Serum platinum concentrations over time in Case 1. * Oxaliplatin dose of 70 mg/m2. HD, hemodialysis.



cycles	before infusion	after infusion	HD	4	24	28	48	52	72	96	(hour)
1	0	1.49		1.31			1.04	0.73			
2	0.09	1.37		1.18	1.15	1.17					
3	0.11	1.49		1.26	1.23	0.91					
4	0.15	1.58		1.36			1.1	0.94			

Fig. 2. Serum platinum concentrations over time in Case 2. In cycles 2 and 3, temporary hemodialysis was performed 24 h after oxaliplatin infusion because of insufficient drainage. HD, hemodialysis.



cycles	before infusion	after infusion	HD	4	24	28	48	52	72	96
1	0	1.67		1.31			1.11	0.65		
2	0.13	1.65		1.34	1.28	0.96	0.98	0.76		
3	0.15	2.14		1.61			1.17	0.82		

Fig. 3. Serum platinum concentrations over time in Case 3. In cycle 2, temporary hemodialysis was performed 24 h after oxaliplatin infusion because of insufficient drainage. HD, hemodialysis.

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Table 1. Summary of data from previous case reports

	Onishi et al. [5], 2007	Matoba et al. [6], 2008	Katumata et al. [7], 2008	Hujita et al. [8], 2009	Watayo et al. [9], 2010	Kuwahara et al. [10], 2011	Horimatsu et al. [4], 2011	Gori et al. [11], 2014	van Berlo et al. [12], 2017	Our patients		
										case 1	case 2	case 3
Sex	68	50	65	77	58	58	50	55	77	65	71	71
Age, years	Female	Female	Male	Female	Male	Female	Male	Male	Male	Male	Male	Female
Performance status	1									1	1	1
Treatment	FOLFOX4	mFOLFOX6	mFOLFOX6	mFOLFOX6	mFOLFOX6	mFOLFOX6	mFOLFOX6 + BV	FLOX	mFOLFOX6 + BV	mFOLFOX6 + BV	mFOLFOX6 + BV	mFOLFOX6 + BV
Oxaliplatin body surface area adjusted dose, mg/m^2	40	40–50–60–7–85	40	60–70–85	40–50–85	60	60–70–85	42.5	70	60–70	60	60
Total dose, mg			63		68–85			85		112	100	86
Interval, weeks	3		3	3	3	2–3	3	3	3	3	4	4
Hemodialysis start time	1 h after infusion	Immediately after infusion	30 min after infusion	Immediately after infusion	Immediately after infusion	1 h after infusion	Immediately after infusion	1.5 h after infusion	Immediately after infusion	Immediately after infusion	Immediately after infusion	Immediately after infusion
Blood flow rate, mL/min	180	200	200	200	200	150	200	220	300	220	220	220
Hemodialysis duration	4	4	3	4	4	4	4	3.5	4	3.5-4	4	4
Number of platinum pharmacokinetics	1	5	1	3	3	2	3	1	3	6	4	3
Free platinum Cmax, ug/mL (adjusted dose, mg/m^2)	0.2 (40)		0.42 (40)	Not evaluated	0.27 (40) 0.22 (40) 0.39 (50)	1.78* (60) 2.19* (60)	0.50 (60) 0.60 (70) 0.86 (85)	0.53 (42.5)	1.3 (70) 1.3 (70) 2.2 (70)	1.48* (60) 1.42* (60) 1.24* (60) 1.5* (60) 1.94* (70) 2.04* (70)	1.49* (60) 1.37* (60) 1.49* (60) 1.58* (60)	1.67* (60) 1.65* (60) 2.14* (60)
Free platinum AUC 0–48 h, ug/h/mL (adjusted dose, mg/m^2)	Not evaluated	5.67** (40) 14** (50) 10.21** (60) 10.14** (70) 8.15** (85)	Not evaluated	26.2 (60) 28.1 (70) 39.9 (85)	15.65 (40) 12.46 (40) 21.48 (50)	Not evaluated	17.6 (60) 23.6 (70) 32.6 (85)	19.5 (42.5)	24.3 (70) 24.7 (70) 25.8 (70)			
Efficacy	PD	PR	No tumor progression		SD		SD	SD	PR	PR	SD	PD
Duration of treatment, cycles (months)	4				11 (8)	10	8	4	3	7 (4.7)	9 (7.6)	3 (2.2)
Major adverse events	Gr1 leukopenia, Gr2 nausea, Gr3 neutropenia, Gr3 anorexia	Few events occurred	Gr2 constipation, Gr3 anorexia, fatigue	Gr2 neutropenia, Gr3 anemia	Gr2 leukopenia, neutropenia and thrombocytopenia	No adverse events	Gr1 peripheral neuropathy	No adverse events	Not listed	Gr 1 peripheral neuropathy, Gr 2 thrombocytopenia	Gr 3 leukopenia, Gr 4 neutropenia	Gr 1 fatigue, Gr 3 thrombocytopenia, Gr 4 neutropenia

* Plasma total platinum Cmax, ** AUC: 0–26 h. Gr, Grade; AUC, area under the curve; PR, partial response; SD, stable disease; PD, progressive disease.