Cancer Chemother Pharmacol (2011) 68:263–266
DOI 10.1007/s00280-011-1633-9

SHORT COMMUNICATION

Pharmacokinetics of oxaliplatin in a hemodialytic patient treated with modified FOLFOX-6 plus bevacizumab therapy

Takahiro Horimatsu · Shin'ichi Miyamoto · Shuko Morita · Yoko Mashimo · Yasumasa Ezoe · Manabu Muto · Tsutomu Chiba

Received: 14 February 2011 / Accepted: 22 March 2011 / Published online: 16 April 2011

Abstract
Purpose To establish an appropriate administration schedule for oxaliplatin in FOLFOX plus bevacizumab therapy for a hemodialytic patient.
Methods A 50-year-old man on chronic hemodialysis was treated for colon cancer and synchronous hepatic metastasis with modified FOLFOX-6 plus bevacizumab therapy every 3 weeks. The plasma concentration of free platinum was measured at eight points, before and within the first 50 h after oxaliplatin administration. A dose escalation study of oxaliplatin was performed at doses of 60, 70, and 85 mg/m^2. A 4-h dialysis session was begun at the end of the oxaliplatin treatment.
Results The pharmacokinetics of free platinum showed a bimodal pattern at each dose: The serum concentration decreased rapidly soon after dialysis, then increased, and remained at a high level for 24 h. The areas under the curves (AUC) for free platinum were 17.6, 23.6, and 32.6 μg h/mL after doses of 60, 70, and 85 mg/m^2 oxaliplatin, respectively. These exceeded the AUC when 90 mg/m^2 was given to a patient with normal renal function (7.9 μg h/mL). Treatment was safely continued for 6 months without severe toxicity.
Conclusion FOLFOX plus bevacizumab therapy can be given safely to hemodialytic patients with no reduction in the dose of oxaliplatin if hemodialysis is performed soon after the administration of oxaliplatin and the dosing interval is extended to 3 weeks.

Keywords Colorectal cancer · Renal failure · Hemodialysis · FOLFOX plus bevacizumab · Oxaliplatin

T. Horimatsu · S. Miyamoto (✉) · S. Morita · Y. Mashimo · M. Muto · T. Chiba
Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, 54 Shogoinkawaharacho, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: shmiyamo@kuhp.kyoto-u.ac.jp

Y. Ezoe
Department of Multidisciplinary Cancer Treatment, Kyoto University Graduate School of Medicine, 54 Shogoinkawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

Introduction

The number of long-lived hemodialytic patients has been increasing with improvements in dialysis treatments. However, hemodialytic patients 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 [1].

Colorectal cancer is the third leading cause of cancer deaths, and its incidence is also increasing yearly in Japan [2]. FOLFOX plus bevacizumab is a chemotherapeutic regimen consisting of oxaliplatin and infusional 5-Fluorouracil (5-FU)/levofolinate plus bevacizumab and is accepted widely as an initial treatment for unresectable colorectal cancer, with an objective response in up to 50% of patients treated [3]. However, there have been few reports of the use of oxaliplatin in hemodialytic patients [4–6], and little is known about the safety/efficacy of FOLFOX plus bevacizumab therapy or its optimum dosage in this patient population. Here, we report the case of a hemodialytic patient with metastatic colon cancer, successfully treated with modified FOLFOX-6 plus bevacizumab therapy.

Materials and methods

A 50-year-old Japanese man with gouty nephropathy had been maintained on hemodialysis since 2006. A computed tomography (CT) scan showed more than 20 metastases (up to 3 cm in diameter) scattered throughout both lobes of his liver. A colonoscopy showed a protuberant type of tumor located on the sigmoid colon. After the surgical resection of the primary tumor to prevent intestinal obstruction and bleeding, the patient received systemic chemotherapy. Chemotherapy was initiated with the modified FOLFOX-6 (mFOLFOX-6) regimen plus bevacizumab, given every 3 weeks. After bevacizumab was administered by infusion over 90 min, oxaliplatin and levofolinate were administered simultaneously for 2 h. 5-FU was then administered as a bolus injection, followed by its continuous infusion for 46 h with a pump after a 4-h dialysis session (Fig. 1). The starting dose of oxaliplatin was 60 mg/m^2 (70% of the standard dose of 85 mg/m^2) because oxaliplatin is known to be primarily excreted in the urine and was expected to be eliminated by hemodialysis alone in this patient [7]. The dose of oxaliplatin was increased to 70 and 85 mg/m^2, while possible adverse events were monitored. The starting dose of 5-FU was set at the standard dose, because 5-FU is largely (80%) eliminated by the hepatic metabolism and secreted into the bile [8]. Many previous reports have shown that there is no need to adjust its dose in dialysis patients [9]. During each course of mFOLFOX-6 plus bevacizumab therapy, a 4-h dialysis session was begun immediately after the administration of oxaliplatin, using a polysulfonate hollow-fiber dialyzer (APS-21SA) and acetic acid-free dialysate (Carbostar P). The blood flow rate was set at 250 mL/min and the dialysate flow rate at 600 mL/min. The patient's free platinum levels were measured. Blood samples were collected at the following eight points: before the start of oxaliplatin administration, 2 (just before dialysis), 2.25, 2.5, 3, 6, 26, and 50 h after oxaliplatin administration (the last collection was just before the second dialysis session). The blood samples were immediately centrifuged at 1,700×g for 10 min, and the serum thus obtained was further centrifuged at 1,700×g for 20 min in an ultrafiltration tube. The ultrafiltrate sample was then stored in a freezer until the platinum concentration was assayed by flameless atomic absorption spectrometry (NAC Co., Ltd, Tokyo, Japan). The area under the curve (AUC) for platinum in the ultrafiltrate was calculated from time 0 to 50 h after the start of oxaliplatin administration, using the trapezoidal method.

Results

Table 1 shows the C_{max} and AUC data for free platinum in the serum of a hemodialytic patient receiving mFOLFOX-6 plus bevacizumab therapy. Figure 2 shows the time course of the free platinum concentration. The level of free platinum, which is related to the antitumor activity and toxicity of oxaliplatin, decreased soon after dialysis. It subsequently increased for 26 h after the administration of oxaliplatin and thereafter remained at the same level for 24 h. These findings differ considerably from those previously reported for patients with normal renal function who received 90 mg/m^2

Table 1 Pharmacokinetic parameters of platinum in plasma ultrafiltrate

	60 mg/m^2 $n = 1$	70 mg/m^2 $n = 1$	85 mg/m^2 $n = 3$	90 mg/m^2 ($n = 3$*)
C_{max} (ng/mL)	500	600	863	963.3
AUC_{0-50} (μg h/mL)	17.6	23.6	32.6	7.9

AUC area under the plasma concentration–time curve

* Shirao et al. [10]

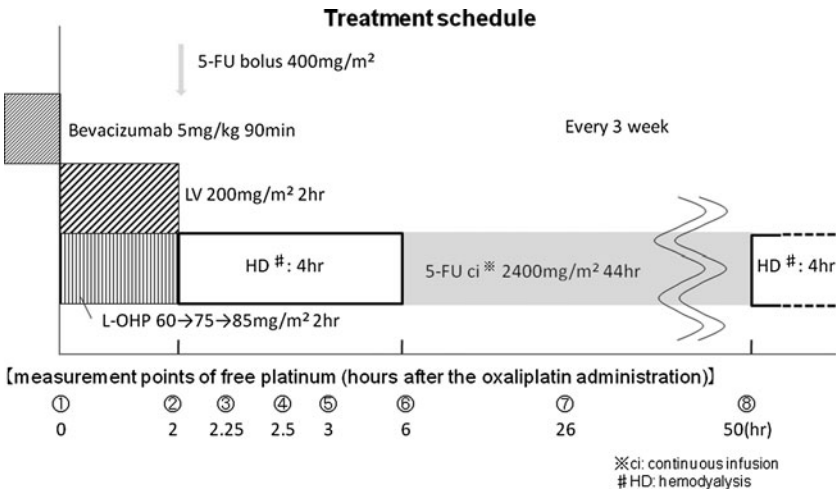

Fig. 1 Treatment schedule

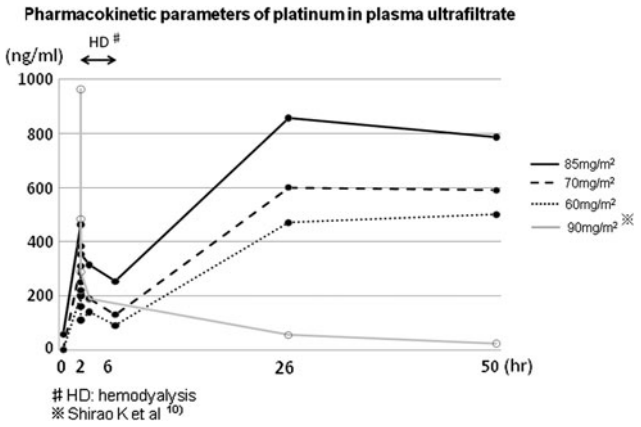

Fig. 2 Concentration of platinum in plasma ultrafiltrate

oxaliplatin (free platinum C_{max} was 963.3 ng/mL and AUC was 7.9 μg h/mL) [10]. The tolerability data and pharmacokinetic profiles obtained during each cycle were used to optimize the dose of each drug and the dosing intervals for the subsequent cycles. The free platinum AUCs were 17.6, 23.6, and 32.6 μg h/mL at doses of 60, 70, and 85 mg/m^2, respectively, which are about 2–4 times greater than that obtained with 90 mg/m^2 oxaliplatin in patients with normal renal function [11]. Therefore, a longer dose interval of 3 weeks was set for the subsequent cycles, instead of the standard interval of 2 weeks for mFOLFOX-6 plus bevacizumab therapy. The free platinum C_{max} values measured in this patient were 500, 600, and 863 ng/mL at oxaliplatin doses of 60, 70, and 85 mg/m^2, respectively, which are about 50–90% of that obtained with a dose of 90 mg/m^2 oxaliplatin in patients with normal renal function [10]. Therefore, a standard dose of 85 mg/m^2 was given during the subsequent five cycles. In all, eight courses of mFOLFOX-6 plus bevacizumab therapy (a total of 815 mg/m^2 oxaliplatin) were completed, although grade 1 peripheral neuropathy by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3) criteria was observed. A CT scan showed no changes in the number or sizes of the metastatic liver tumors.

Discussion

To the best of our knowledge, this is the first report of a hemodialytic patient with metastatic colon cancer successfully treated with mFOLFOX-6 plus bevacizumab therapy. In the patient reported here, the free platinum level showed a bimodal pattern, with peaks appearing at 2 and 26 h after the start of oxaliplatin administration. The second peak was as high as the first peak. In patients treated with oxaliplatin, the serum-free platinum concentration reflects the biological activity of the drug, i.e., it determines both its antitumor activity and its toxicity [11, 12]. Previous studies have shown that most circulating platinum molecules derived from oxaliplatin are immediately bound to plasma proteins (primarily albumin) and irreversibly inactivated [13, 14]. The free platinum in the blood is serially excreted by the kidneys, and its excretion is delayed in patients with impaired renal function [15]. A second peak in the free platinum concentration between hemodialyses has also been observed in hemodialytic patients treated with cisplatin [16]. This might be caused by the dissociation of the platinum bound to plasma proteins and blood cells or by platinum in the tissues returning to the blood [17]. In patients with normal renal function, it is likely that free platinum is rapidly eliminated by renal excretion, so no second peak is observed [10].

In our patient, who was given 60 mg/m^2 oxaliplatin, the AUC of free platinum was about twofold greater than that observed after an oxaliplatin dose of 90 mg/m^2 in patients with normal renal function. Although the relationship between the AUC of free platinum and the antitumor activity of oxaliplatin is poorly understood, it has been reported that the antitumor activities of cisplatin and carboplatin correlate with the AUC of free platinum [12]. Takimoto et al. [9] reported that reductions in the dose of single-agent oxaliplatin are unnecessary, even in patients with impaired renal function, suggesting that the AUC of free platinum does not correlate with the toxicity of oxaliplatin, regardless of the patient's renal function. They proposed the hypothesis that after the administration of oxaliplatin, the majority of free platinum is in the inactive form in low molecular weight conjugates, which are cleared by glomerular filtration. Therefore, the increase in systemic platinum exposure associated with renal impairment does not increase the drug-related toxicity [18].

Giacchetti et al. [19] compared the antitumor activity and hematological toxicity of oxaliplatin in two regimens: four daily doses versus continuous infusion for 48 h. They reported that hematological toxicity was three times more frequent with the former regimen than with the latter regimen, whereas a similar tumor response was achieved with both regimens. These findings suggest that the antitumor activity of oxaliplatin does not correlate with the AUC of free platinum, whereas its hematological toxicity correlates with its C_{max}.

In our patient, treatment with the standard dose of oxaliplatin in the mFOLFOX-6 plus bevacizumab regimen resulted in a larger AUC with a lower C_{max} for free platinum than those observed with the standard dose of oxaliplatin in patients with normal renal function. This pharmacokinetic profile might explain the significant tumor response achieved with relatively mild toxicity.

Recently, Kawazoe et al. reported that long-term FOLFOX-6 therapy given every 2 weeks with the standard dose of oxaliplatin in patients with mild renal dysfunction led to

accumulated renal toxicity, and the patients were forced to undergo dialysis [20]. However, in the patient reported here, the concentration of free platinum before the administration of oxaliplatin increased gradually (<30, 40, 50, and 80 ng/mL in the second, third, fifth, and seventh courses, respectively). The 3-week dosing interval set for this patient may have been optimal, but it is essential to monitor the serum concentration of free platinum before the administration of oxaliplatin in each course.

In contrast, it has been reported that the clearance rate of bevacizumab by hemodialysis was 0 mL/min and that the pharmacokinetic parameters in hemodialytic patients were similar to those in patients with normal renal function [21].

In conclusion, mFOLFOX6 plus bevacizumab therapy can be used safely for hemodialytic patients, with no dose reduction in oxaliplatin, if hemodialysis is performed soon after the administration of oxaliplatin and the dosing interval is extended to 3 weeks. The cumulative toxicities and long-term outcomes remain to be established. Larger studies of hemodialytic patients with longer follow-up periods are required.

Acknowledgments We thank Dr. Shigemi Matsumoto, Dr. Takafumi Nishimura, and Dr. Yoshiharu Sakai for their invaluable support in the conduct of this study.

References

1. Maisonneuve P, Agodoa L, Gellert R et al (1999) Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 354:93–99
2. Hyodo I, Suzuki H, Takahashi K et al (2010) Present status and perspectives of colorectal cancer in Asia: colorectal cancer working group report at the 30th Asia-Pacific cancer conference. Jpn J Clin Oncol 40(Suppl 1):i38–i43
3. Hochster HS, Hart LL, Ramanathan RK et al (2008) Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 26:3523–3529
4. Shitara K, Munakata M, Muto O et al (2007) Hepatic arterial infusion of oxaliplatin for a patient with hepatic metastases from colon cancer undergoing hemodialysis. Jpn J Clin Oncol 37:540–543
5. Matoba S, Sawada T, Toda S et al (2008) Modified FOLFOX6 in a patient on hemodialysis with metastatic colorectal cancer. Gan To Kagaku Ryoho 35:673–675 (in Japanese)
6. Watayo Y, Kuramochi H, Hayashi K et al (2010) Drug monitoring during FOLFOX6 therapy in a rectal cancer patient on chronic hemodialysis. Jpn J Clin Oncol 40:360–364
7. Takimoto CH, Remick SC, Sharma S et al (2003) Administration of oxaliplatin to patients with renal dysfunction: a preliminary report of the National Cancer Institute Organ Dysfunction Working Group. Semin Oncol 30:20–25
8. Heggie GD, Sommadossi JP, Cross DS, Huster WJ, Diasio RB (1987) Clinical pharmacokinetics of 5-fluorouracil and its metabolites in plasma, urine, and bile. Cancer Res 47:2203–2206
9. Takimoto CH, Remick SC, Sharma S et al (2003) Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute Organ Dysfunction Working Group Study. J Clin Oncol 21:2664–2672
10. Shirao K, Matsumura Y, Yamada Y et al (2006) Phase I study of single-dose oxaliplatin in Japanese patients with malignant tumors. Jpn J Clin Oncol 36:295–300
11. Schellens JHM, Ma J, Planting AST et al (1996) Relationship between the exposure to cisplatin, DNA-adduct formation in leucocytes and tumour response in patients with solid tumours. Br J Cancer 73:1569–1575
12. Jodrell DI, Egorin MJ, Canetta RM et al (1992) Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol 10:520–528
13. Graham MA, Lockwood GF, Greenslade D et al (2000) Clinical pharmacokinetics of oxaliplatin: a critical review. Clin Cancer Res 6:1205–1218
14. Calvert H, Judson I, van der Vijgh WJ (1993) Platinum complexes in cancer medicine: pharmacokinetics and pharmacodynamics in relation to toxicity and therapeutic activity. Cancer Surv 17:189–217
15. Massari C, Brienza S, Rotarski M et al (2000) Pharmacokinetics of oxaliplatin in patients with normal versus impaired renal function. Cancer Chemother Pharmacol 45:157–164
16. Watanabe R, Takiguchi Y, Moriya T et al (2003) Feasibility of combination chemotherapy with cisplatin and etoposide for haemodialysis patients with lung cancer. Br J Cancer 88:25–30
17. Levi F, Metzger G, Massari C, Milano G (2000) Oxaliplatin: pharmacokinetics and chronopharmacological aspects. Clin Pharmacokinet 38:1–21
18. Takimoto CH, Graham MA, Lockwood G et al (2007) Oxaliplatin pharmacokinetics and pharmacodynamics in adult cancer patients with impaired renal function. Clin Cancer Res 13:4832–4839
19. Giacchetti S, Bjarnason G, Garufi C et al (2006) Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy group. J Clin Oncol 24:3562–3569
20. Kawazoe H, Sugishita H, Watanabe S et al (2010) Nephrotoxicity induced by repeated cycles of oxaliplatin in a Japanese colorectal cancer patient with moderate renal impairment. Gan To Kagaku Ryoho 37:1153–1157
21. Garnier-Viougeat N, Rixe O, Paintaud G et al (2007) Pharmacokinetics of bevacizumab in haemodialysis. Nephrol Dial Transplant 22:975