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Oxaliplatin Pharmacokinetics and Pharmacodynamics in Three Metastatic Colorectal Cancer Patients with Hemodialysis

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Abstract

Aim: We investigated the safety and feasibility of L-OHP with chronic renal failure (CRF) on hemodialysis (HD) patients by examining the influence of pharmacokinetics and pharmacodynamics of oxaliplatin (L-OHP). Furthermore, we investigated.

Methods: We present the results of three patients who were treated with modified FOLFOX6 (mFOLFOX6) chemotherapy for a mCRC with chronic renal failure on HD. We measured their plasma concentration of total platinum and free platinum. We evaluated whether L-OHP dose could be safely used for these patients. Different starting dose of L-OHP and 5-fluorouracil (50% and 75%) were used in these patients. Pharmacokinetics monitoring of platinum in plasma, plasma ultrafiltrates were measured these time schedule follow as: pre-chemotherapy infusion and 4 hours (pre-HD), 6 hours (half of HD), 8 hours (post HD), 48 hours after.

Results: The 50% of peak concentrations (Cmax) was 0.27 μg·hr/mL ± 0.02 μg/mL and 75% Cmax was 0.41 μg·hr/mL ± 0.02 μg/mL. 50% of the area under the concentration versus time curve (AUC) was 14.8 μg·hr/mL ± 1.22 μg·hr/mL and 75% AUC was 22.43 μg·hr/mL ± 0.85 μg·hr/mL.

Conclusion: We recognized these free plasma concentration which 50% dose of L-OHP was similar AUC between healthy and CRF patients. L-OHP pharmacokinetics and pharmacodynamics are altered in patients with CRF, but corresponding increase in L-OHP related hematological and non-hematological toxicities is not observed. It is important for cancer patients with CRF that the feasibility and efficacy of L-OHP combined chemotherapy should be determined.

Keywords: Colorectal cancer; Chronic renal failure; Hemodialysis; Oxaliplatin

Introduction

The metastatic colorectal cancer (mCRC) is highly mortality disease in the USA, EU and Asia. Recently, we have been developing many cytotoxic agents and monoclonal antibodies such as oxaliplatin (L-OHP), irinotecan (CPT-11), 5-fluorouracil (5-FU), capecitabine (Cap), S-1, anti-VEGF antibody and anti-EGF receptor (EGFR) antibody. These combined chemotherapy are widely accepted as first-line treatment with mCRC. L-OHP is a key anti-cancer drug for gastrointestinal cancer [1-3]. L-OHP quick converts to highly reactive monochloroplatinum, dichloroplatinum and diaquoplatinum biotransformation products [4] which can immediately interact with tissue, proteins and other plasma constituents [5]. The L-OHP associated platinum in plasma ultrafiltrates is huge size (>300 L) and the kinetics of elemental platinum in plasma after L-OHP administration shows three distinct phases. First, there is a short α-phase half-life of 0.25 to 0.33 hours (hrs) followed by a longer β-phase half-life of almost 16 hrs. Finally, highly sensitive analytic methods, such as inductively coupled plasma mass spectroscopy, show measure a prolonged γ-half-life of 240 to over 600 hrs. Furthermore, initial 48 hrs after drug administration, over 50% of the administrated platinum is excreted into the urine, consist with kidneys being a main route of platinum elimination [5,6]. When we have been repeating infusion, L-OHP accumulate in erythrocytes. Finally, this intracellular binding within red blood cell is thought to be irreversible [7,8]. Actually, pharmacokinetics and pharmacodynamics in patients with hemodialysis (HD) differs from that patients with normal kidney function, chemotherapy for a hemodialysis patient should be careful to administer. We treated chemotherapy of modified FOLFOX6 (mFOLFOX6) to three mCRC patients with HD who measured oxaliplatin (L-OHP) pharmacokinetics and pharmacodynamics. We investigated a dose-escalating pharmacologic study of L-OHP in mCRC patients with chronic renal failure (CRF) on HD. In this study, 50% doses of L-OHP, 50% of 5-fluorouracil and full dose of calcium folinate administered on every 2 weeks' schedule. We did not measure two different of L-OHP concentration profile but also evaluated efficacy and drug induced adverse events. Also, more HD patients should be monitored to investigate the safety dosage, drug concentration in blood, and accumulated toxicities. This dose escalation study is very important of mCRC chemotherapy with CRF on HD.

Patients and Methods

From 2008 until 2012, mFOLFOX6 was treated to three patients of mCRC with HD as the initial chemotherapy. The patient characteristics was shown in Table 1. Patients who confirmed adenocarcinoma of colorectal cancer, and who met the following inclusion criteria 1 to 7 were included. 1) no age restrictions; 2) major organ function preserved ([i] leukocyte count: ≥4,000/mm^3; [ii] blood platelet count: ≥100,000/mm^3; [iii] total bilirubin value: ≤1.5 mg/dL; [iv] aspartate aminotransferase (AST), alanine aminotransferase (ALT): <2.5 times upper limit of normal; 3) Eastern Cooperative Oncology Group

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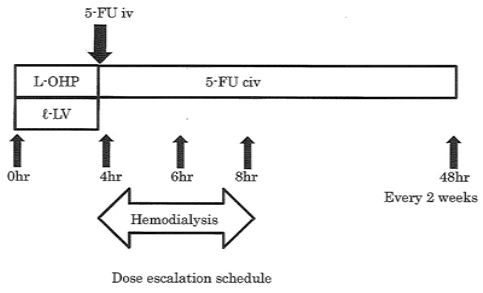
	Patient 1	Patient 2	Patient 3
Age, Gender	81, M	65, M	60, F
ECOG PS	1	1	1
Primary site	Rectum	Rectosigmoid	Ascending
Metastatic site	Liver	Liver	Liver
	Lymph node	Lymph node	Lymph node

M: Male, F: Female, ECOG PS: Eastern Cooperative Oncology Group Performance Status

Table 1: Patient characteristics.



Dose escalation schedule

Step	Oxaliplatin (85mg/m²)	iv 5FU (400mg/m²)	civ 5FU (2,400mg/m²)
1	50%	50%	50%
2	75%	75%	75%

Dialysis time	4 hours
Blood flow	150ml/min
Dialysis flow	500ml/min
Dialysate	Lympack TA1®
Dialysis machine	APS-15MD®

Note: 5-FU: 5-Fluorouracil, L-OHP: Oxaliplatin, l-LV: l-leucovorin, hr: hour, iv: intravenous infusion, civ: continuous intravenous infusion

Figure 1: Schema of sampling processing and dose escalation schedule.

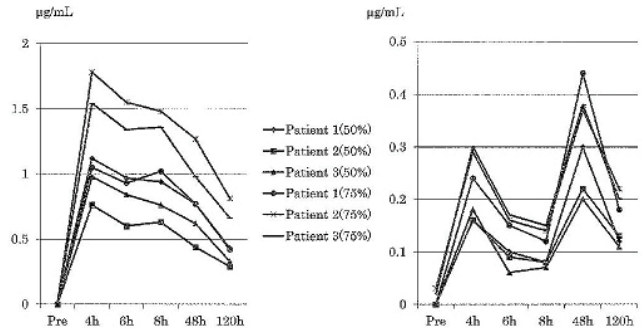


Figure 2A and 2B: (A)The total platinum concentrations. Each dose revealed two peaks pattern of total platinum concentrations respectively. (B) The protein-free platinum concentrations. The each dose revealed two peaks pattern of protein-free platinum concentrations respectively.

(ECOG) Performance status (PS) score: 0-2; 4) no active multiple primary cancers; 5) no serious complications (intestinal obstruction, hypertension and thrombus); 6) provided written consent based on informed consent.

Sampling processing and analysis methodology

Every patients received HD three times per week. A 4 hours HD session was started at the end of L-OHP infusion using polysulfone membrane (AsahiKASEI, Tokyo, Japan). The dialysis setting follow as; dialysis machine: PS-15MD®, blood flow: 150 mL/min, dialysis flow: 500 mL/min and dialysate: Lympack TA1®. Blood sampling for plasma and plasma ultrafiltrate platinum concentrations were obtained during cycles 50% dose of L-OHP and 75% dose of L-OHP at the following times: pre-chemotherapy infusion and 4 hours (pre-HD), 6 hours (half of HD), 8 hours (post HD), 48 hours after start of chemotherapy as shown in Figure 1. Eight milliliter blood got into centrifuge tube, and centrifuged within 10 minutes 3,000 rpm and isolated plasma re-centrifuged within 20 minutes 3,000 rpm at 4°C. The protein-free ultrafiltrate and plasma sampling were frozen and stored at -20°C. L-OHP concentrations were measured by NAC Company Tokyo, Japan.

This study was carried out according to the regulation of local ethics committee of our hospital and according to the Declaration of Helsinki.

Patient's backgrounds

Case 1: A 81-year-old man who treated HD due to gout kidney from 2008. A year later, he had progression of anemia due to rectal cancer. He performed light colectomy on 2009/5/12: The pathological finding following as; Locus transverse, Type 2, 5.5 cm × 6.0 cm, pSS, N1 (LN221 2/7), ly2, v1, CE(-), M1 (liver). He performed two courses of 50% and four courses of 75% mFOLFOX6 every 2weeks for liver metastasis which best response was stable disease (SD).

Case 2: A 65-year-old man who treated HD due to diabetic nephropathy from 2008. A year later, he diagnosed to liver metastasis due to rectal cancer by screening examination. He performed Miles operation on 2009/7/14: The pathological finding following as; Locus Rectosigmoid, Ip, 2 × 2 cm, pSM, N1(2/10), ly1, v2, M1(liver). He performed two courses of 50% and five courses of 75% mFOLFOX6 every 2weeks for liver metastasis which best response was SD.

Case 3: A 60-year-old woman who treated HD due to diabetic nephropathy from 2010. Two years later, she diagnosed to liver metastasis due to ascending colon cancer by screening examination. She performed light colectomy on 2012/11/12: The pathological finding following as; Locus Ascending, Type 2, 7.0 × 5.5 cm, pSE, N2(4/18), ly2, v1, CE (-), M1(liver). She performed two courses of 50% and eight courses of 75% mFOLFOX6 every 2 weeks for liver metastasis which best response was SD.

Results

Pharmacokinetics study

Our study was performed in three patients as shown in Table 1. The total platinum concentrations immediately elevated after L-OHP infusion and reduced gradually as shown in Figure 2A. Otherwise, the protein-free platinum concentrations recognized two peak curves which pattern was observed in all patients despite the HD condition as shown in Figure 2B. The first protein-free platinum concentration peak immediately reduced due to HD. Surprisingly, the protein-free platinum concentrations increased after HD and reached similar maximum level of the day (Cmax). The 50% dose and 75% dose of L-OHP of area under the curve (AUC) revealed similar as 16.4 μg·h/mL ± 5.02 μg·h/mL that was AUC of patients with normal renal function [9].

Safety

We showed their adverse events on Table 2. The hematological and non-hematological toxicities were tolerable. We did not recognize any serious adverse events Step 1(50% dose of L-OHP) and Step 2(75% dose of L-OHP) respectively. It can be performed safely mFOLFOX6 chemotherapy by following the dialysis schedule in Figure 1.

	Neutropenia		Leukopenia		Thrombocytopenia		Anorexia		Peripheral neuropathy	
Step	1	2	1	2	1	2	1	2	1	2
Patient 1	0	2	0	1	0	0	1	1	1	1
Patient 2	1	1	1	1	1	1	0	1	1	1
Patient 3	1	1	1	1	0	1	0	1	1	1
Step 1: 50% dose of L-OHP, Step 2: 75% dose of L-OHP										

Table 2: Adverse events (CTCAE version 4.0 Grade).

Discussion

Chronic renal failure patients have been increasing because of diabetes. Currently, the Japanese hemodialysis patients is about 31 million people in conjunction with peritoneal dialysis.

Diabetes is a one of risk factor for cancer. Therefore, the establishment of cancer chemotherapy for hemodialysis patients and HD patients has been desired. The mFOLFOX6 chemotherapy [10,11] is a combination chemotherapy that is central in metastatic colorectal cancer patients. We often choose L-OHP as a first line chemotherapy in Japan. L-OHP in the anti-cancer agent of the platinum complex system which is a molecular weight of about 397. L-OHP binds at a high rate with plasma proteins when administered, the antitumor activity is lost. Protein binding rate of L-OHP is reported as 57% to 85% in about 2 hours after administration [12]. L-OHP since urinary excretion is about 50%, nephrotoxicity has been reported as minor [12]. Here we were administered mFOLFOX6 therapy in HD patients three cases, it was measured a free platinum concentration and blood in the total platinum concentration of L-OHP. While considering these results, we did dose escalation study gradually and evaluated safety and efficacy. The total platinum concentration and free platinum concentration that can be placed HD patients is reduced efficiently by HD. But free platinum occurs again rise from the plasma protein after HD terminated by transfer from it and organizations to liberate the free platinum. The concentration of the protein-free platinum have been reported with the bimodal [13-15]. 50% dose of the L-OHP amounts in all cases who measured similar AUC substantially. CRF patients the protein binding capacity is reduced to a drug when compared with normal renal function [16]. Even L-OHP are considered similar reasons. Antitumor effect of cisplatin mainly AUC of CRF patients in order to allow the AUC and the correlation of the free platinum concentration is increased. Adverse events are dependent mainly on the C_{max}. We obtained almost similar AUC which compared with normal renal function in 50% dosage of L-OHP in all three cases as same as these reports [17,18]. C_{max} was low value in 75% and 50% dosage of L-OHP when compared with normal renal function patients. If these patients revealed equivalent AUC who obtained similar anti-tumor effect and less adverse events compared with normal renal function patients. Regardless they obtained less toxicities, they did not obtain tumor reduction. For the administration of L-OHP for dialysis patients, it is necessary to observe carefully the course because it has not been established safety. We obtained to similar AUC of L-OHP in CRF patients compare with normal renal function patients despite was reduced to L-OHP in this report. But it was lower with respect to C_{max}. It is necessary to consider the timing of the optimum dosage and HD by accumulation of cases in the future.

Conclusion

In three HD patients with metastatic colorectal cancer underwent mFOLFOX6 chemotherapy. When they received chemotherapy to measure the pharmacokinetics and pharmacodynamics of L-OHP was examined the context of the efficacy and safety. The mFOLFOX6 chemotherapy with metastatic colorectal cancer was safe under measure the pharmacokinetics and pharmacodynamics of L-OHP. Regardless we obtained less toxicities and similar AUC despite dose reduction of L-OHP, we did not obtained similar tumor reduction compare with normal renal function patients. Molecular target drug combined chemotherapy is desired even for HD patients with cancer. Finally, it is necessary to build a chemotherapy of HD patients with cancer in the future.

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Conflict of Interest Statement

The author of this manuscript has no conflict of interest statement.

Ethical Standard

Human rights statement and informed consent.

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