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CASE REPORT

Concentrations of Irinotecan and SN-38 in the Ascites and the Fluid Product of Cell-Free and Concentrated Ascites Reinfusion Therapy 9 Days After Administration of Irinotecan in a Patient with Gastric Cancer: A Case Report

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Introduction: Cell-free and concentrated ascites reinfusion therapy (CART) is frequently used to relieve the symptoms caused by massive ascites due to peritoneal metastasis of gastric cancer, especially in the later stages of its clinical course. Irinotecan (CPT-11) is recommended for third- or later-line chemotherapy according to gastric cancer treatment guidelines. However, the concentrations of anti-cancer drugs in the ascites and the product of CART are not well known, it is considered that some amounts of anti-cancer drugs contained in the product of CART may be readministered and induce severe adverse reactions.

Case Presentation: A 66-year-old female with gastric cancer and massive ascites received third-line chemotherapy with CPT-11 (150 mg/m^2) and ramucirumab (8 mg/kg). On day 7, the laboratory test showed a white blood cell count of 1,290/μL and neutrophil count of 480/μL. On day 9, the patient underwent CART, and the concentrations of CPT-11 and its active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38) were 1.18 ng/mL and 0.22 ng/mL in plasma, 0.95 ng/mL and 0.82 ng/mL in ascites, and 0.20 ng/mL and 0.17 ng/mL in the product of CART, respectively.

Conclusion: Concentrations of CPT-11 and SN-38 remaining in ascites and the product of CART were low in an advanced gastric cancer patient 9 days after administration of CPT-11.

Keywords: gastric cancer, irinotecan, concentration, CPT-11, SN-38, cell-free and concentrated ascites reinfusion therapy, CART

Introduction

Irinotecan (CPT-11), a camptothecin analog, has been evaluated as monotherapy and combination chemotherapy for various solid malignancies such as gastric, colorectal, lung, breast, and ovarian cancers.[1] CPT-11 is a prodrug that requires bioactivation to its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which acts as a DNA topoisomerase I inhibitor.[2] SN-38 is further glucuronidated by uridine diphosphoglucuronosyltransferase (UGT)1A1, transferred into the bile, and excreted in the feces. Because SN-38 is reabsorbed in patients with impaired luminal passage through the gastrointestinal tract such as ileus, resulting in severe adverse effects such as myelosuppression, CPT-11 is contraindicated to such patients. Furthermore, CPT-11 is also contraindicated to patients with massive ascites because severe myelosuppression is often experienced. The severe myelosuppression by CPT-11 in patients with massive ascites is considered to be attributed to several factors. First, in patients with massive ascites, bowel passage is often impaired to some degree by peritoneal dissemination of cancer cells, and impaired bowel passage leads to reabsorption of SN-38

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excreted in the bile after glucuronidation. Second, third-space distribution can lead to prolonged half-lives of CPT-11 and SN-38, and prolonged reabsorption from the ascites into the bloodstream. Third, reduced hepatic function, often seen in patients with massive ascites, impairs the metabolism and biliary excretion of CPT-11 and SN-38. Fourth, low albumin levels associated with malignant ascites increase the unbound fractions of CPT-11 and SN-38.[3–5]

In unresectable or recurrent gastric cancer, the peritoneum is a common metastatic site, which causes massive ascites, hydronephrosis, bowel obstruction, and deteriorates the quality of life, especially in the later part of the clinical course. The first report of cell-free and concentrated ascites reinfusion therapy (CART) in Japan was published in 1977;[6] CART comprises three processes: (1) filtering ascites to remove cell components, (2) concentrating ascites using a plasma-separating membrane, and (3) intravenous reinfusion of the obtained fluid. In the filtering process, cell components including cancer cells and microbes are removed but plasma proteins such as albumin and γ-globulin are retained due to the maximum pore size of filter with 0.2 μm. CART was initially applied in the treatment of refractory ascites due to liver cirrhosis and peritoneal metastasis.[7–9] CART has been reported to be a safe and effective treatment for large-volume paracentesis with albumin infusion in the management of refractory ascites and is performed under the National Health Insurance by using the approved medical device in Japan.

CART combined with chemotherapy has been reported to be associated with a survival advantage over chemotherapy alone for various malignancies.[10–12] However, because CPT-11 is hardly used for patients with massive ascites, it is not clear whether the product of CART reinfused to a patient after administration of CPT-11 contains not only CPT-11 but also SN-38, and it is concerned that CPT-11 and SN-38 in the product of CART might induce some toxicities. There have been no reports on the concentration of CPT-11 and SN-38 transferred to and remaining in ascites. This is the first report on CPT-11 and SN-38 concentrations in ascites and in CART products during irinotecan treatment of gastric cancer patients with ascites.

Case Presentation

A 66-year-old female patient with gastric cancer underwent a laparoscopic distal gastrectomy with Roux-en-Y reconstruction. During surgery, two nodules suspected of peritoneal metastasis were resected. Postoperative pathological examination of the resected nodule indicated signet ring cell carcinoma, which was diagnosed as pathological stage IV gastric cancer (pT4aN2M1CY0P1) according to the TNM classification, 8th edition. After surgery resulting in R1 resection, oral administration of S-1 (100 mg/day) as adjuvant chemotherapy was initiated, but it was discontinued after only six doses at her own discretion. Six months after surgery, abdominal computed tomography (CT) revealed recurrent peritoneal metastasis. Although systemic chemotherapy was proposed by an attending medical oncologist, the patient refused. One year after surgery, abdominal CT showed the growth of peritoneal nodules and the appearance of ascites when the patient could not consume food. The patient agreed to undergo systemic chemotherapy. Since human epidermal growth factor receptor 2 (HER2) was negative, first-line chemotherapy with 5-fluorouracil (5-FU) (2400 mg/m^2, continuous infusion for 46 hr) + calcium levofolinate hydrate (200 mg/m^2, administered on day 1) + oxaliplatin (85 mg/m^2, on day 1) + nivolumab (240 mg/body, on day 1) per cycle was initiated with intravenous hyperalimentation. After six cycles, she was able to consume food adequately, which was associated with decreased ascites. However, after eight cycles, the disease progressed, and second-line chemotherapy with nanoparticle albumin-bound paclitaxel (nab-PTX, 100 mg/m^2) plus ramucirumab (8 mg/kg) was initiated, which was discontinued after two cycles due to neuropathy.

Two months after the last dose of second-line chemotherapy, the patient developed abdominal distension and decreased oral intake. Because she refused re-administration of nab-PTX for fear of worsening of neuropathy and could not take food, the available active anti-tumor agents recommended in the treatment guidelines were CPT-11 and ramucirumab. Although the tolerability and efficacy of CPT-11 plus ramucirumab as salvage chemotherapy have been previously reported,[13] it was concerned that CPT-11 would cause severe myelosuppression in patients with massive ascites. After these risks were explained in detail, and the patient gave her consent, she was hospitalized for third-line chemotherapy. Physical examination revealed abdominal distention due to ascites. Abdominal contrast-enhanced CT showed ascites throughout the abdominal cavity and thickening of the peritoneum (Figure 1a). Laboratory data showed hemoglobin of 9.8 g/dL, leukocyte count of 10,980/μL, neutrophil of 10,300/μL, albumin of 3.0 mg/dL, direct bilirubin of 0.5 mg/dL, total protein of 6.2 g/dL (Table 1). The patient received CPT-11 (150 mg/m^2) and ramucirumab (8 mg/kg). After chemotherapy, the patient experienced diarrhea

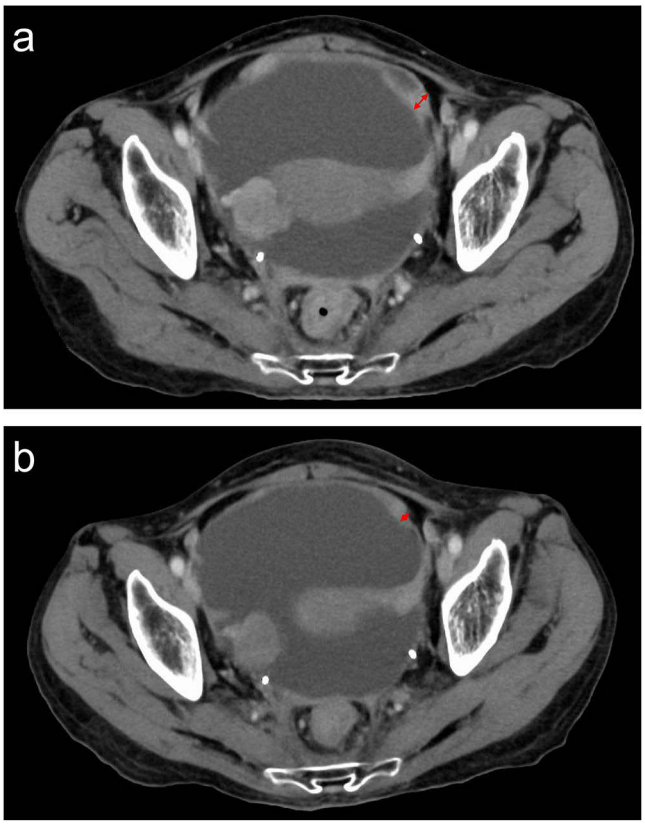

Figure 1 Abdominal contrast-enhanced computed tomography showing ascites and peritoneal metastasis (↔ thickness of peritoneal metastasis) (**a**) on admission (12.8mm) and (**b**) 20 days after administration of CPT-11 and ramucirumab (7.9mm).

(grade 3 according to the Common Terminology Criteria for Adverse Events), nausea (grade 2), and vomiting (grade 2). On day 7, laboratory data showed leukocyte count of 1,290/μL, and neutrophil of 480/μL. Although she was afebrile, she received filgrastim (150 μg, single dose) and meropenem (1.5 g/day for six days) prophylactically because ascites drainage of 1000 mL was performed due to abdominal distension. On day 9, CART was performed by using ascites filtrating device AHF-MO and the concentrating device AHF-UF (Asahi Kasei Medical Co., Ltd., Tokyo, Japan) because the patient complained of abdominal distension. Owing to the shallow echo-free space and difficulty of puncture, the volume of ascites drainage was 640 mL, and the final CART product was 80 mL, which was reinfused. No additional adverse events were observed after the CART. On day 12, leukocyte and neutrophil counts increased. On day 20, CT revealed shrinkage of peritoneal metastasis (Figure 1b). Despite achieving some efficacy, the patient refused to continue the chemotherapy due to her general condition. While she was treated with the best supportive care, the frequency of CART decreased. She died 6 months after starting tertiary chemotherapy.

After obtaining her consent to assay the concentrations of CPT-11 and SN-38 in the plasma, ascites and the product of CART for research purpose, 5 mL of each was collected. The concentrations of CPT-11 and SN-38 were determined with an ultra-performance liquid chromatography-tandem mass spectrometry method validated in accordance with the US Food and Drug Administration Guidance for Industry Bioanalytical Method Validation.[14] The concentration range of the standard curves of CPT-11 and SN-38 were 0.08–2.0 ng/mL and 0.04–2.0 ng/mL, respectively. The concentrations of CPT-11 and SN-38 were 1.18 ng/mL and 0.22 ng/mL in plasma, 0.95 ng/mL and 0.82 ng/mL in ascites, and 0.20 ng/mL and 0.17 ng/mL in the product of CART, respectively, as shown in Table 2. The amounts of CPT-11 and SN-38 in ascites of 640 mL and in the CART product of 80 mL were calculated by multiplying the concentrations by the volume of fluids. The concentrations of total protein and albumin in the collected samples were also assayed (Table 2).

Table 1 Laboratory findings on day 9 of admission

Blood cell count			**Genetic Analysis**		
WBC (/uL)	**10,980**		***UGT1A1***	***1/*1**	
Neu (%)	93.8	**Biochemical test**			
RBC (/uL)	303 x10^4	TP (g/dL)	6.2	LDH (U/L)	166
Hb (g/dL)	9.8	Alb (g/dL)	3	ALP (U/L)	95
MCV (fL)	100.7	BUN (g/dL)	25.1	γ-GTP (U/L)	66
MCH (pg)	32.3	Cre (mg/dL)	1.1	Amylase (U/L)	127
Plt (/uL)	33.5 x10^4	eGFR (mL/min/1.73m^2)	39	T-Bil (mg/dL)	0.3
Coagulation		UA (mg/dL)	6	Na (mEq/L)	139
PT-INR	0.92	AST (U/L)	19	K (mEq/L)	3.1
APTT (s)	23.9	ALT (U/L)	13	Cl (mEq/L)	97
Fib (mg/dL)	406			CRP (mg/dL)	0.23

Abbreviations: WBC, White Blood Cell count; Neu, Neutrophils; RBC, Red Blood Cell count; UGT1A1, UDP-glucuronosyltransferase 1A1; TP, Total Protein; LDH, Lactate Dehydrogenase; Hb, Hemoglobin; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Hemoglobin; Plt, Platelet count; Alb, Albumin; BUN, Blood Urea Nitrogen; Cre, Creatinine; Egfr, Estimated Glomerular Filtration Rate; UA, Uric Acid; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; ALP, Alkaline Phosphatase; γ-GTP, Gamma-Glutamyl Transpeptidase; T-bil, Total Bilirubin; Na, Sodium; K, Potassium; Cl, Chloride; CRP, C-Reactive Protein.

Table 2 Concentrations and/or Amounts of CPT-11, SN-38, Total Protein and Albumin in Each Fluid

	Plasma	**Ascites**		**Product of CART**	
	Concentration	**Concentration**	**Amount in 640 mL**	**Concentration**	**Amount in 80 mL**
CPT-11	1.18 ng/mL	0.95 ng/mL	608.0 ng	0.20 ng/mL	16.0 ng
SN-38	0.22 ng/mL	0.82 ng/mL	524.8 ng	0.17 ng/mL	13.6 ng
Total protein	5.3 g/dL	2.9 g/dL	18.6 g	4.4 g/dL	3.5 g
Albumin	2.4 g/dL	1.6 g/dL	10.2 g	2.8 g/dL	2.2 g

Discussion

In this report, we determined the concentrations of CPT-11 and its active metabolite SN-38 in plasma, ascites, and the product of CART in gastric cancer patients with massive malignant ascites 9 days after the administration of CPT-11 and ramucirumab. To date, reports on the concentration of drugs in bodily fluids including ascites are limited, and there are no reports on the concentration of drugs in the final CART product.

In cases of ascites without ileus, it is logically expected that CPT-11 can be safely administered after reducing the amount of ascites using CART. Indeed, the present case demonstrated that CPT-11 treatment after concomitant CART was safe and effective in a gastric cancer patient with massive ascites accumulation but without ileus confirmed by defecation.

Upon administration of irinotecan at 100 mg/m^2 and 350 mg/m^2, the mean plasma concentrations of CPT-11 and SN-38 at 24 hours after administration of CPT-11 were 100–1000 ng/mL and almost 10 ng/mL, respectively.[15] Compared with these concentrations, the plasma concentrations of CPT-11 and SN-38 on day 9 in this patient seem to be negligible clinically.[16,17] The reinfused amounts of CPT-11 and SN-38 into the patient were 16.0 ng and 13.6 ng, respectively, which were also negligible clinically.

The concentration of SN-38 was found to be much higher in ascites than in plasma after 9 days of administrating CPT-11, whereas those of CPT-11 in plasma and ascites were comparable (Table 2). A drug in ascites, which distributes from blood according to the concentration gradient, cannot be eliminated without returning into blood. Small molecule drug binds to plasma proteins such as albumin and α_1-acid glycoprotein depending on their specific affinity. An unbound drug is more likely to traverse cell membranes than a bound drug, because plasma proteins usually have a molecular size that restricts their passage across cell membranes and capillary walls. The protein-binding fractions of CPT-11 and SN-38 are reported to be 30–40% and 92–96%, respectively.[18] Therefore, it is speculated that the amount of SN-38 traversing the peritoneal membrane from ascites into blood at the elimination phase might be smaller than that of CPT-11, resulting in a higher concentration of SN-38 than that of CPT-11.

The concentrations and amounts of CPT-11 and SN-38 in the product of CART were lower than those in ascites (Table 2). Unbound drug is removed through the filtering process for concentrating ascites. Furthermore, because the protein binding is reversible, and an equilibrium exists between the bound and unbound forms, it is speculated that most of CPT-11 and SN-38 might be removed regardless of their protein-binding affinities in the filtering process as unbound forms which appeared sequentially after dissociation from plasma proteins along with removal of preexisting unbound forms. Notably, more than 97% of CPT-11 and SN-38 are removed during this process.

This case report has some limitations. The concentrations of CPT-11 and SN-38 in plasma and ascites were not monitored on consecutive days, and serial changes were not known. The patient underwent 1,000 mL ascites drainage on day 7 of admission, which limited the drainage volume (640 mL) of ascites for CART on day 9. While the standard CART for massive ascites typically yields over 3000 mL of effluent and around 500 mL of product, the volumes of CART on day 9 were so small as 640 mL and 80 mL, respectively, after drainage of ascites which contained some amounts of CPT-11 and SN-38 on day 7. The drainage on day 7 might affect the concentrations of CPT-11 and SN-38 especially in ascites on day 9 and adverse reactions by infusion of the CART product. However, because the volume of ascites drainage on day 7 was not so large, it is considered that the impacts of ascites drainage on day 7 was not clinically relevant. The negligible amounts of CPT-11 and SN-38 in the product of CART on 9 days after CPT-11 administration in this patient provide important information for considering more concrete treatment strategy of combining CPT-11-based chemotherapy and CART for gastric cancer patients with massive ascites.

Conclusion

Concentrations of CPT-11 and its active metabolite SN-38 of the product of CART on day 9 are so low as to be clinically negligible. Based on these concentrations of CPT-11 and its active metabolite SN-38 in the CART formulation, this report showed specific data which support that the product of CART could be safely administered at least on day 9 during the CPT-11 irinotecan-based chemotherapy.

Ethical Considerations

In our institution, case reports do not require approval from the ethics committee for publication. Therefore, institutional approval was not necessary for publishing the details of this case. At the time of writing the case report, the patient had already passed away. Written consent for the publication of the case details was provided from the patient's husband, who provided permission on behalf of the deceased after the patient's husband was fully informed of the nature of the case report and the intention to publish the findings.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Prof. Dr. Narikazu Boku reports personal fees from Daiichi-Sankyo, personal fees from Eli Lilly, personal fees from Ono pharmaceutical, personal fees from Bristol Myers Squibb, personal fees from Taiho pharmaceutical, during the conduct of the study. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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