Cancer Chemotherapy and Pharmacology (2019) 83:145–150
https://doi.org/10.1007/s00280-018-3714-5

ORIGINAL ARTICLE

Safety of intraperitoneal paclitaxel combined with conventional chemotherapy for colorectal cancer with peritoneal carcinomatosis: a phase I trial

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Received: 18 August 2018 / Accepted: 25 October 2018 / Published online: 1 November 2018

Abstract

Purpose Peritoneal carcinomatosis of colorectal cancer origin is associated with poor prognosis. With regard to ovarian, gastric, and pancreatic cancer, the safety and efficacy of intraperitoneal administration of paclitaxel (ip PTX) has been demonstrated. This drug can be administered easily and repeatedly through a catheter into the peritoneal cavity. In this phase I study, we evaluated the safety of ip PTX combined with 5-fluorouracil, folinic acid, oxaliplatin, and bevacizumab (mFOLFOX6-bevacizumab) or capecitabine, oxaliplatin, and bevacizumab (CapeOX-bevacizumab) for colorectal cancer with peritoneal metastasis.

Methods Colorectal cancer patients with histologically confirmed peritoneal carcinomatosis were enrolled. After the implantation of a peritoneal access port, 20 mg/m^2 of ip PTX was administered weekly, in combination with mFOLFOX6-bevacizumab or CapeOX-bevacizumab. Primary endpoint was the safety of the combination chemotherapy.

Results Among the six patients enrolled, three received the mFOLFOX6-bevacizumab plus ip PTX regimen and three received the CapeOX-bevacizumab plus ip PTX regimen. Dose-limiting toxicity was not observed. Overall, grade 3 adverse events, such as leukopenia and neutropenia, were observed in two of three patients (66.7%) for each chemotherapeutic regimen, but no grade 4 adverse events were observed. Moreover, adverse events associated with the peritoneal access port, such as infection or occlusion of the catheter, were not observed.

Conclusions The adverse events of mFOLFOX6-bevacizumab or CapeOX-bevacizumab in combination with ip PTX were considered similar to those described in previous studies of oxaliplatin-based treatment alone. 1 year after the start of chemotherapy, the efficacy of ip PTX will be evaluated as a secondary outcome.

Keywords Phase I trial · Intraperitoneal paclitaxel · Colorectal cancer · Peritoneal carcinomatosis

Introduction

The frequency of peritoneal carcinomatosis of colorectal cancer origin is 4.5–7.9%, which is lower than the rate of liver or lung metastasis [1, 2]. According to a post hoc analysis of results from the N9741 and N9841 studies, which were randomized phase III trials of 5-fluorouracil (5FU) and oxaliplatin or irinotecan for unresectable colorectal cancer, the prognosis of patients with peritoneal carcinomatosis was poor, with a median survival of only 12.7 months [3]. With recent advances in chemotherapy, the median survival was prolonged to up to 16.3 months for patients with peritoneal metastases, as described in a recent study [4]. However, the prognosis for these patients still remains worse than that for patients with lung or liver metastases. Therefore, it is necessary to investigate new chemotherapeutic treatments to improve the outcomes for patients with peritoneal carcinomatosis.

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Intraperitoneal chemotherapy, such as early postoperative intraperitoneal chemotherapy (EPIC) and sequential postoperative intraperitoneal chemotherapy (SPIC), have been performed to achieve a higher drug concentration in the peritoneal cavity [5]. The combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is one of the most common treatment strategies. Macroscopically recognized lesions are surgically resected, and microscopically remaining lesions are targeted using HIPEC. In a review of 76 studies, Huang et al. concluded that the median overall survival for patients with CRS and HIPEC was 12–63 months (mean 29 months), longer than that seen in traditional therapy [6]. However, this treatment was associated with high morbidity and mortality, and 83–90% of the patients had peritoneal recurrence within 5 years [7–10]. Therefore, further progress in treatment targeting microscopically remaining cancer cells is required even in cases of surgical resection.

In ovarian, gastric, and pancreatic cancers, the safety and efficacy of intraperitoneal administration of paclitaxel (ip PTX) has been demonstrated in peritoneal metastases [11–16]. Because of its liposolubility, PTX is slowly absorbable. Therefore, the drug stays in the peritoneal cavity for an extended time, and results in only mild elevation in blood PTX level [12]. Moreover, administration of chemotherapy can be performed easily and repeatedly through a catheter into the peritoneal cavity. This is a significant advantage over HIPEC that can be only performed intraoperatively.

It has been demonstrated that ip PTX decreased peritoneal carcinomatosis in a rat model of colorectal cancer [17]. However, no clinical trials have been performed to evaluate the safety and efficacy of ip PTX in patients with peritoneal carcinomatosis of colorectal cancer origin. Therefore, we started a phase I trial of ip PTX combined with oxaliplatin-based chemotherapy for colorectal cancer with peritoneal metastasis.

Patients and methods

Patient selection

This is a single arm, non-randomized, open label, interventional study from a single institution. Colorectal cancer patients with histologically confirmed peritoneal carcinomatosis, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, aged 20–80 years old, and with an expected survival of longer than 3 months were enrolled. The patients were required to have adequate hematologic, hepatic, and renal function (white blood cells > lower limit of standard value and < 12,000/mm^3, neutrophil > 1500/mm^3, hemoglobin > 8.0 g/dl, platelet > 100,000/mm^3; aspartate/alanine transaminase (AST/ALT) < 100 U/L, total bilirubin < 1.5 times as much as the upper limit of normal value; and estimate glomerular filtration rate (eGFR) > 60 mL/min/1.73 m^2). Patients who underwent resection of peritoneal metastases were also included in the present study.

Patients with appendiceal carcinoma, anal canal cancer, or uncontrollable distant metastases were excluded. In addition, patients who had received chemotherapy including oxaliplatin within 1 year of the recruiting date, and cases with a contraindication for the chemotherapeutic agents used in the study design (5FU, levofolinate calcium, capecitabine, oxaliplatin, bevacizumab, or PTX) were excluded. Finally, patients with brain tumor, infectious diseases, or thrombotic diseases within 1 year of the recruiting date, patients requiring anticoagulants, and pregnant patients were also excluded.

Written informed consent was obtained from all patients. This study was approved by the ethics committee of the University of Tokyo (P2015038-11X). The study was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (UNIN000022924).

Treatment plan

Patients underwent implantation of the peritoneal access port. The catheter was laparoscopically inserted into the pouch of Douglas. During the laparoscopic surgery, peritoneal lavage cytology was also performed, and the peritoneal cancer index (PCI) [18] was evaluated for the staging of peritoneal carcinomatosis. The patients could select the chemotherapeutic regimen, 5-fluorouracil, folinic acid, oxaliplatin, and bevacizumab (mFOLFOX6-bevacizumab) or capecitabine, oxaliplatin, and bevacizumab (CapeOX-bevacizumab) until the registry of each regimen reached the prefixed number ($n = 3$).

The protocols of the chemotherapy are shown in Fig. 1. When patients selected the mFOLFOX6-bevacizumab regimen, bevacizumab 5.0 mg/kg followed by 2-h intravenous infusion of oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, and bolus of 5-fluorouracil (5FU) 400 mg/m^2 and 46-h infusion of 5FU 2400 mg/m^2 was administered on day 1 of a 14-day cycle. In addition to mFOLFOX6 and bevacizumab, weekly ip PTX 20 mg/m^2 was administered for 1 h. PTX was diluted in 1 L of normal saline [12].

When patients selected the CapeOX-bevacizumab regimen, bevacizumab 7.5 mg/kg followed by 2-h intravenous infusion of oxaliplatin 130 mg/m^2 was administered on day 1 of a 21-day cycle. Capecitabine 2000 mg/m^2/day was administered orally twice daily from the evening of day 1 to the morning of day 15 [19]. In addition to CapeOX and bevacizumab, weekly ip PTX 20 mg/m^2 was administered for 1 h.

The treatment was interrupted when grade 2 or greater toxicities were observed. The dose of capecitabine, 5FU,

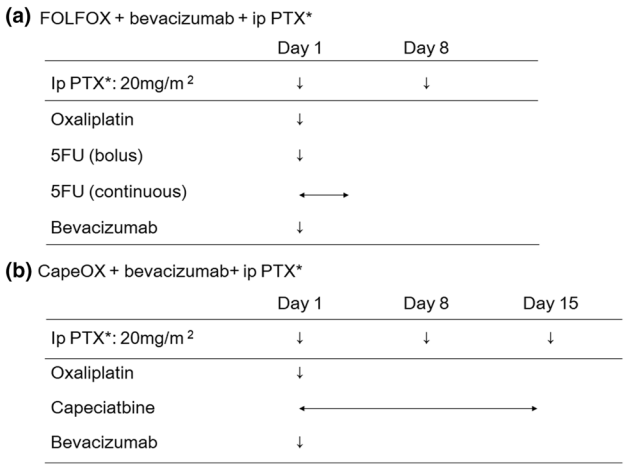

Fig. 1 Protocol of the chemotherapy and the flow chart of the study. Protocol of the chemotherapy of **a** FOLFOX and **b** CapeOX regimen. In addition to the usual mFOLFOX6 or CapeOX and bevacizumab, weekly intraperitoneal paclitaxel was added. **a** Oxaliplatin: 85 mg/m^2, 5FU (bolus): 400 mg/m^2, 5FU (continuous): 2400 mg/m^2, bevacizumab: 5 mg/kg. **b** Capecitabine: 2000 mg/m^2/day, oxaliplatin: 130 mg/m^2, bevacizumab: 7.5 mg/kg

and oxaliplatin were reduced according to the worst adverse effects during the previous cycle [20, 21]. These chemotherapeutic agents were also reduced when the interruption periods were more than 14 days. PTX was reduced by 50% when adverse effects associated with ip PTX were observed. PTX was stopped when grade 2 or greater allergic reaction was observed.

The treatment was continued until disease progression or 1 year from the start of chemotherapy. When the peritoneal carcinomatosis became resectable, patients were given the option to undergo curative resection. After resection, patients could continue treatment until the appearance of new metastatic lesions or 1 year from the start of chemotherapy.

Assessment

The primary endpoint of this study was the safety of the chemotherapy combined with ip PTX. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events version 4.0. Dose-limiting toxicity (DLT) was defined as grade 4 neutropenia or thrombocytopenia, febrile neutropenia, or grade 3 non-hematological toxicity lasting more than 5 days.

Initially, three patients in each regimen, a total of six patients, received one course of chemotherapy. If DLT was not observed, the treatment course was continued. If DLT was observed in any of the three patients, additional three patients would be enrolled for that chemotherapeutic regimen. If two or more DLTs were observed, the chemotherapeutic regimen would be stopped. The safety of ip PTX was also evaluated 3 months after the start of chemotherapy.

Results

Patient characteristics

A total of six patients were enrolled in the present study. Among them, three patients received mFOLFOX6 and bevacizumab plus ip PTX and three patients received CapeOX and bevacizumab plus ip PTX. Additional patient enrollment was not necessary since no DLT was observed. The characteristics of the six patients are shown in Table 1. Five patients (83.3%) had unresectable synchronous metastases, and one patient received curative resection of peritoneal metastasis. No patients had distant metastasis except for peritoneal carcinomatosis. The mean PCI was 16 (range 0–25) at the time of staging laparoscopy. Five patients (83.3%) had positive peritoneal lavage cytology.

Safety of ip PTX

All patients were able to continue this treatment regimen for at least 3 months, and the adverse events 3 months after the start of chemotherapy were evaluated (Table 2). Grade 3 leukopenia or neutropenia was observed in two of six (33.3%) patients, and grade 3 ALT elevation and nausea in one patient (16.7%). Although peripheral neuropathy was observed in all patients, grade 3 or 4 neuropathy did not occur. The other grade 3 adverse event was fracture of the femoral neck that was not associated with the chemotherapy or implantation of the peritoneal access port. No grade 4 or 5 adverse events were observed. Adverse events associated with the peritoneal access port, such as infection or occlusion of the catheter, were not observed.

The adverse events are summarized according to chemotherapeutic regimen in Table 3. Adverse events of any grades were observed in all patients. Grade 3 adverse events were observed in two of three patients (66.7%) for each chemotherapeutic regimen.

Discussion

This is the first trial of ip PTX for patients with peritoneal metastases from colorectal cancer. Due to the lack of studies investigating combination therapy of ip PTX and mFOLFOX6 or CapeOX with bevacizumab, we evaluated the safety of this chemotherapeutic regimen. With regard to patients with gastric cancer, a previous study showed that 20 mg/m^2 of ip PTX could achieve much higher drug

Table 1 Patient characteristics ($n=6$)

	Number (%)
Gender	
Male	2 (33.3%)
Female	4 (66.7%)
Age (year)	
Median (range)	64 (33–76)
ECOG performance status	
0	6 (100%)
1	0 (0%)
Location of primary tumor	
Cecum	1 (16.7%)
Ascending colon	1 (16.7%)
Sigmoid colon	2 (33.3%)
Rectum	2 (33.3%)
Peritoneal metastases	
Synchronous	5 (83.3%)
Metachronous	1 (16.7%)
Prior surgery for primary lesion	
No	2 (33.3%)
Yes	4 (66.7%)
Resection of peritoneal metastases	
No	5 (83.3%)
Yes	1 (16.7%)
Multiple organ metastases	
Absent	6 (100%)
Present	0 (0%)
CEA (ng/ml)	
> 5	5 (83.3%)
< 5	1 (16.7%)
PCI score	
Median (range)	16 (0–25)
Peritoneal lavage cytology	
Negative	1 (16.7%)
Positive	5 (83.3%)

ECOG Eastern cooperative oncology group, *CEA* carcinoembryonic antigen, *PCI* peritoneal cancer index

Table 2 Adverse events ($n=6$)

Grade	1	2	3	4
Leukopenia (%)	–	1 (16.7%)	1 (16.7%)	–
Neutropenia (%)	1 (16.7%)	–	1 (16.7%)	–
Anemia (%)	2 (33.3%)	2 (33.3%)	–	–
Thrombocytopenia (%)	2 (33.3%)	–	–	–
Elevated AST/ALT[a] (%)	4 (66.7%)	–	1 (16.7%)	–
Nausea/vomiting (%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	–
Diarrhea (%)	–	1 (16.7%)	–	–
Abdominal pain (%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	–
Hand-foot syndrome (%)	2 (33.3%)	1 (16.7%)	–	–
Neuropathy (%)	4 (66.7%)	2 (33.3%)	–	–
Oral mucositis (%)	1 (16.7%)	2 (33.3%)	–	–
Others (%)	3 (50.0%)	–	1 (16.7%)	–

[a]*AST/ALT* aspartate/alanine transaminase

Table 3 Adverse events according to the chemotherapeutic regimen

	FOLFOX ($n=3$)		CapeOX ($n=3$)	
	All grades	Grade 3/4	All grades	Grade 3/4
All (%)	3 (100%)	2 (66.7%)	3 (100%)	2 (66.7%)
Leukopenia (%)	1 (33.3%)	–	1 (33.3%)	1 (33.3%)
Neutropenia (%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	–
Anemia (%)	2 (66.7%)	–	2 (66.7%)	–
Thrombocytopenia (%)	–	–	2 (66.7%)	–
Elevated AST/ALT[a] (%)	2 (66.7%)	1 (33.3%)	3 (100%)	–
Nausea/vomiting (%)	–	–	3 (100%)	1 (33.3%)
Diarrhea (%)	–	–	1 (33.3%)	–
Abdominal pain (%)	2 (66.7%)	–	2 (66.7%)	1 (33.3%)
Hand-foot syndrome (%)	2 (66.7%)	–	1 (33.3%)	–
Neuropathy (%)	3 (100%)	–	3 (100%)	–
Oral mucositis (%)	2 (66.7%)	–	1 (33.3%)	–
Others (%)	2 (66.7%)	–	2 (66.7%)	1 (33.3%)

[a]AST/ALT: aspartate/alanine transaminase

concentration at the tumor site compared with intravenous administration of 80 mg/m^2 of PTX [12]. Moreover, 40 mg/m^2 of weekly ip PTX has potential to increase the occurrence of adverse events. Therefore, in the present study, we evaluated the safety of weekly 20 mg/m^2 of ip PTX.

In the present study, neither DLT nor grade 4 adverse events were observed. Grade 3 adverse events were observed in 66.7% of patients for each chemotherapeutic regimen. In previous prospective studies, any grade of adverse events were observed in 99%, and grade 3 or 4 adverse events were observed in 76–87% of the patients treated with mFOLFOX6 and bevacizumab [22–24]. Similarly, any grade of adverse events were observed in 99–100%, and grade 3 or 4 adverse events were observed in 60–75% of the patients treated with CapeOX and bevacizumab [20, 23, 24]. Grade 3 or 4 neutropenia was observed in 34–40% treated with mFOLFOX6 and bevacizumab [23–25], and 6–16% treated with CapeOX and bevacizumab [20, 23, 24]. Grade 3 or 4 sensory neuropathy was observed in 14–18% in mFOLFOX6 and bevacizumab [22–25], and 12–18% in CapeOX and bevacizumab [20, 23, 24]. Although we cannot compare the frequency of adverse events directly between the current study and the previous trials due to different doses and durations of chemotherapeutic drugs, the rate of adverse events in the present study appeared comparable to that in the previous studies.

Conclusion

The adverse events in patients treated with chemotherapy in combination with ip PTX were considered similar to that without ip PTX. 1-year survival rate, progression-free survival, response rate, the rate of improvement of peritoneal cancer index, and the rate of negative conversion of the cytology of peritoneal lavage will be evaluated as secondary outcomes.

Acknowledgements This research is supported by Grants-in-Aid for Scientific Research (C: Grant number; 16K07143, C: Grant number; 16K07161, C: Grant number; 17K10620, C: Grant number; 17K10621, C: Grant number; 17K10623 and C: Grant number; 18K07194) from Japan Society for the promotion of Science. This research is supported by the Project for Cancer Research and Therapeutic Evolution (P-CREATE, grant number: 18 cm0106502h0003 from the Japan Agency for Medical Research and Development (AMED).

Compliance with ethical standards

Conflict of interest K. Muro is on the advisory board meeting for Bristol-Myers Squibb and Nippon Kayaku Co, Ltd. All remaining authors have declared no conflicts of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee of the University of Tokyo (P2015038-11X) and with the 1964 Helsinki declaration and its later amendments. The study was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (UNIN000022924).

Informed consent Written informed consent was obtained from all individual participants included in the study.

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