

Research Article

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Phase I/II Clinical Trial of Weekly Intraperitoneal Paclitaxel (IP-PTX) with Monthly Intravenous Carboplatin (IV-CBDCA) for Minimal Residual Disease of Ovarian, Tubal, and Peritoneal Carcinoma

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Abstract

We conducted weekly intraperitoneal administration of paclitaxel (IP-PTX) with monthly intravenous administration of carboplatin (IV-CBDCA), as a prospective phase 1/2 setting. The purpose of this study was to assess the pharmacokinetics and to decide the recommended dose (RD) according to modified Fibonacci method. Patients aged 20 -75 years old with histological confirmed mullerian cancers (epithelial ovarian cancer; EOC, fallopian tubal cancer; FTC, and primary peritoneal cancer; PPC) from stage IC to IV or the patients with recurrent disease with small residual disease (including retention of ascetic fluid, para-aortic nodes recurrence after optimal debulked after interval debulking surgery; IDS) were eligible. The protocol regimen consisted of IP-PTX on day1 (D1), 8, and 15, at a starting dose level 1(DL1) of 45 mg/m², with 15 mg/ m² incremental, and IV-CBDCA was fixed dose AUC 5.0 mg/mL.min on D1, monthly. The accrual period was from August 2000 until September 2005. As for result, twelve patients were enrolled. No dose limiting toxicity (DLT) was observed in DL1. In dose level 2 (DL2, 60 mg/m²), one grade 3 (G3) hypersensitive reaction to CBDCA was detected. Further 5 patients had been enrolled but additional DLT was not identified. The RD was decided as DL2, which was the same dose of RD in weekly IP-PTX reported by Francis et al. The serum AUCs of PTX in DL1 and DL2 were 1605 nM.min and 2365 nM.min, respectively. By serum CA125, five complete responses were observed out of 8 evaluable patients by Rustin's criteria. In conclusion, the combination of weekly IP-PTX and monthly IV-CBDCA at AUC 5.0 mg/mL.min was feasible and the recommended dose of IP-PTX was 60 mg/m². The therapy was moderate effective for optimal debulking mullerian carcinomas. From our pharmacokinetic results, as for the patients with extra-pelvic lesions, additional IV-PTX would be necessary like GOG 172 experimental arm.

Keywords: Intraperitoneal paclitaxel, Ovarian cancer, Small residual disease, Carboplatin (CBDCA)

Abbreviations: AE: Adverse Event; AUC: Area Under the Curve; CA125: Cancer Antigen 125, carcinoma antigen 125, or carbohydrate antigen 125, also known as MUC16 which is glycoprotein, and used as biomarker of ovarian

cancer and some of adenocarcinoma; CBDCA: Carboplatin; CC: Cervical Cancer; CDDP: Cis-diamine Dichloroplatinum; cisplatin; CT: Computed Tomography; D: Day; D1, 8, 15: Day one, eight, fifteen; DDS: Drug Delivery System; DIV: Drip Infusion via peripheral Vein; DL: Dose Level; ECOG: Eastern Cooperative Oncology Group in US; EOC: Epithelial Ovarian Carcinoma; 5HT3: 5-hydroxytryptamine; F-Pt: Free platinum (non albumin combined platinum); FTC: Fallopian Tubal Cancer; GOG: Gynecologic Oncology Group (now renamed as NRG) of United States; hr, hrs: Hour, Hours; HPLC: High-Performance Liquid Chromatography; HSR: Hypersensitive Reaction; IDS: Inter Debulking Surgery; IP: Intraperitoneal administration; IP-PTX: Intraperitoneal administration of Paclitaxel; IV: Intravenous administration; IV-CBDCA: Intravenous administration of Carboplatin; IV-PTX: Intravenous administration of Paclitaxel; Log: Logarithm; M: Mol; mOS: median Overall Survival time; mPFS: median Progression Free Survival time; MTD: Maximal Tolerated Dose; ng: nanogram; NSAID: Nonsteroidal Anti-inflammatory Drug; OC: Ovarian Cancer; OS: Overall Survival time; PARP: Poly Adenosine diphosphate ribose polymerase; PC: Paclitaxel-carboplatin; PFS: Progression Free Survival time; PPC: Primary Peritoneal Cancer; PS: Performance Status; PTX: Paclitaxel; RD: Recommended Dose; RECIST: response criteria in solid tumor; t.i.d.: ter in die, three times per day; TTP: Time to Progression

Introduction

Despite the fact that the establishment of standard regimen such as paclitaxel (PTX) plus carboplatin (CBDCA) with/without dose dense setting or bevacizumab or maintenance of PARP inhibitors, cure rate of advanced ovarian cancer (OC), Fallopian Tube Cancer (FTC) and Primary Peritoneal Cancer (PPC) has not been improved satisfyingly. As one of breakthrough strategy from the drug delivery system (DDS) point of view, intraperitoneal administration (IP) of anti-cancer agents had been developed and NCI recommended the IP treatment for the stage 3 patient with minimal residual disease in pelvic cavity in 2004 based on the result of Gynecologic Oncology Group (GOG) randomized study of GOG 172. In spite of the announcement, it has not prevalent even in US. In such advanced patients, the recurrence rate has reached 85% or more during longer observation [1]. The recurrence sites located mainly at peritoneum of pelvis or abdominal cavity. In order to control such peritoneal disease, intraperitoneal administration (IP) was considered as one of modalities. In case of using intraperitoneal administration of some cytotoxic agents, it has been well known that the area under the curve (AUC) of peritoneal fluid becomes much higher than that of peritoneal fluid when the agents were administered via intravenous (IV) way. Markman et al. reported that the relative AUC (IP AUC/ IV AUC ratio) in peritoneal fluid reached about 1,000 folds higher in intraperitoneal administration of paclitaxel (IP-PTX), and it was 12-15 folds in intraperitoneal administration of carboplatin (IP-CBDCA) [2]. The fact suggested a considerable locoregional advantage in IP. PTX in itself is lipophilic agent and considered to be absorbed into adipose tissue of the abdominal visceral organs such as diaphragm, connective tissues, visceral adipose tissue, as well as lymphatic systems when it is administered into peritoneal cavity. Furthermore, due to the lymphatic re-distribution via diaphragm to proximal

lymph nodes (para-aortic nodes), the PTX concentration of the nodes showed 600 folds in IP-PTX in comparison with IV-PTX [3,4]. Therefore, the IP-PTX may be superior to IV-PTX in control the peritoneal disease and para-aortic nodal disease.

So, we hypothesized that weekly intraperitoneal administration would be more effective than dose dense weekly intravenous administration of paclitaxel (IV-PTX) plus tri-weekly intravenous administration of carboplatin (IV-CBDCA), so called dose dense paclitaxel/carboplatin (dd-PC). Before performing a randomized phase 2 or 3 study of dd-PC versus this weekly IP-PTX plus monthly IV-CBDCA (weekly IP-PTX/CBDCA) as experimental arm, it is necessary to elucidate the recommended dose of weekly IP-PTX/CBDCA, at first.

We conducted the phase I study of weekly IP-PTX with monthly IV-CBDCA (AUC 5.0 mg/mL.min) for Japanese women in patients with OC, FTC and PPC with small residual disease (<1.0cm). The primary endpoint was determination of recommended dose (RD). The secondary endpoints were assessment of pharmacokinetics of PTX in this setting and feasibility, overall survival time (OS) and response rate using tumor marker CA125 and response criteria in solid tumor (RECIST) version 1.

Study design

This study was a prospective phase I/II study according to modified Fibonacci method.

Patients and methods

Patients' accrual had been performed from August 2000 until September 2005, after allowance of each institutional review board of cooperative institutions.

Patient eligibility

Patients aged 20 -75 years old with histological confirmed mullerian cancers (epithelial ovarian cancer, fallopian tubal cancer, and primary peritoneal cancer) from stage IC to IV with small residual disease after primary debulking surgery (< 1.0 cm). The patients with recurrent disease with small residual disease (including retention of ascetic fluid, para-aortic nodes recurrence) after interval debulking surgery (IDS) were eligible, as well. Enrollees were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0,1, or 2, and the intervals of prior systemic treatment must be more than 28 days at least before study entry. Prior chemotherapies were allowed less than 3 lines. Patients must have adequate bone marrow, liver and renal functions.

Exclusive criteria

The patient who was not confirmed histological or performance status over 3.

The patient who had severe hypersensitive reaction to paclitaxel or carboplatin. The patient who had severe complications such as diabetes mellitus, heart failure, severe inflammatory disease, life threatening massive pleural effusion or ascites.

The patient who were eager to having baby or pregnant.

The patient who had allergy to polyoxyethylene castor oil containing agent (e.g. cyclosporine) or cremophor-EL, were exclusive.

This study protocol was approved by the participating institutional review boards and from all patients, written informed consent was obtained. The study followed the current guidelines of the International Conference on Harmonization for good clinical practice and the Declaration of Helsinki.

Treatment methods

Surgery (including placement of IP reservoir port): The surgery must be optimal debulked (small residual foci <1.0 cm) surgery and infuser port (SOPH-A-PORT, SOPHYSA, Paris, French), which was made of polysulfone reservoir port with self-sealing silicone septum and radio-opaque silicone/polyurethane catheters, was set during the surgery. The reservoir port was set under skin over fascia about nearly 8 cm left of umbilicus. The tube was put through 7-8 cm subcutaneous

tunnel and inserted into abdominal cavity at the costal edge and introduced between abdominal wall and liver surface, and the end of catheter was put in the space between the right diaphragm and liver. The catheter has 84 small holes, and the last proximal (reservoir port side) hole must be inside of the abdominal cavity (Figure 1).

Purse-string suture was made around catheter to prevent subcutaneous leakage through not too tight so as not to occlude catheter. Injection was performed using the dedicated rectangle 22 Gauge needle. Silicone septum endures 2,000 times penetration without leakage.

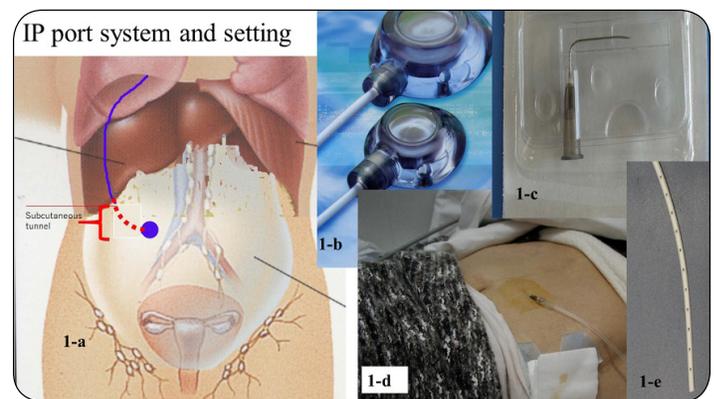


Figure 1: IP port system.

a. Reservoir was put under skin and over fascia. The catheter was introduced after 8 cm of subcutaneous tunnel and inserted to pelvic cavity at lower boundary of liver and leads to cost phrenic angle. All pores must be put intraperitoneally.

b. Reservoir: this port is endurable for 2.000 times puncture.

c. 22 Gauge rectangle needle: It is disposable and only one use was allowed.

d. Administration was performed under aseptic gown technic and sealing.

e. Catheter tip and pores (number is 84).

Chemotherapy/Dose escalation and dose modification: CBDCA: The dose of CBDCA was decided by calculation to reach a target AUC according to the Calvert formula using an estimated glomerular filtration rate from the Jelliffe formula. In this study, AUC was fixed as 5.0mg/mL.min. Intravenous administration of carboplatin (IV-CBDCA) was performed on day1 (D1) via peripheral vein in 15 min (drip infusion: DIV) diluted in 250ml of saline, every 4 weeks (monthly administration).

Paclitaxel (PTX): The doses of PTX were designed 45 mg/m² as dose level (DL) 1 and escalated in 15 mg/m²

increment up to 90 mg/m². DL 0 was set as 30 mg/m² in case DL1 would reach MTD. If the last dose level would be feasible, the RD will be decided as last dose. PTX was lipophilic so that the Cremophor EL (emulsifying agent lipophilic agent PTX to be soluble for saline) was combined. Too much addition of saline promotes re-crystallization of PTX, so that 100ml of saline was appropriate. In order to diffuse overall surface of peritoneum, after IP of PTX administered with 100ml saline, additional 100-1000ml saline was administered intra-peritoneally in natural dropping. It took nearly 30 min in total. After IP, patient must change postures, from supine to left lateral decubitus position, prone position, right lateral decubitus position, Trendelenburg position, sitting position, in turn each for 5 min.

The premedication of this IP-PTX with IV-CBDCA was performed as the same way in usual IV-PTX with IV-CBDCA in short protocols, which were histamine 1 and 2 blocker, diphenhydramine hydrochloride, 50mg per os and 19.8 mg of dexamethasone together were administered bolus intravenously and drip infusion via peripheral vein then DIV of saline in 30 min before IP-PTX and IV-CBDCA was performed. In case of use the premedication in DIV, further 30min.intervals was needed before administration of PTX. Anti-emetics such as 5HT₃ receptor selective inhibitors were used in case of expression of G1 emesis later than second course of the protocol treatment. The prophylactic use of anti-emetics was not performed in first course in this study because of phase 1 study.

The dose limiting toxicities (DLTs) were defined as follows (adverse events, AEs, were graded according to the NCI-CTCAE ver.2):

Hematologic toxicities: Grade 4 (G4) any except neutropenia and G4 neutropenia lasting more than 7 days with GCSF administration, or neutropenic fever over 38.3 degrees Celsius lasting more than one hour (hr).

Non-hematologic toxicities: Grade over 3, any, without nausea, vomiting.

As for abdominal pain, prophylactic NSAID administration was allowed.

Disease assessment

The progression or response of the disease was estimated by Rustin's Criteria [5]. CT (helical CT with slice <=5 mm) evaluation was performed in order to detect

new lesions as progression of the disease on every two courses and evaluated according to the response evaluation criteria in solid tumor (RECIST) version 1.

Protocol discontinuation

Progressive disease (PD) according to RECIST or Rustin's criteria using serum CA125, and delay of administration more than fourteen days due to AEs were regarded as discontinuation of the protocol treatment.

Pharmacological study

Plasma samples and samples of peritoneal fluid aspirated from the reservoir for the pharmacokinetic evaluation of PTX were collected from 3 patients in each dose levels (DL1 and DL2) at the time of first and second cycles. Heparinized blood samples were obtained before infusion, at, 1, 2, 4, 8, 12, 24, 48, 72, 96, hours (hrs) after infusion. Samples were stored at below -80 °C until analysis. Concentrations of PTX in plasma and abdominal fluid samples were determined by high-performance liquid chromatography (HPLC) according to the modified Grem's method [6] at Sumikin bioscience KK (Sagamihara, Kanagawa, Japan). The AUCs were determined by the linear trapezoidal rule, extrapolated to infinity [7].

Statistical analyses and data accumulation

We used Stat View J 5.0 (SAS, NC, US) for fundamental statistics such as median, average, standard errors. Kaplan-Meier Curve was not significant because of small case number. Every data was collected and accumulated in file by data manager in accessible anonymization and dealt with new numbers like DL1-1, DL2-1, and so on.

Results

Patient's characteristics

Twelve patients were enrolled in total. The characteristics of the 12 patients were shown in table 1.

Five patients out of 12 patients were performed interval debulking surgery (IDS), and the rests had been received the protocol treatment as primary chemotherapy. The fundamental statistical data were shown in table 2.

Dose escalation and toxicity

First accrual of 3 patients for dose level 1 (DL1) had completed without DLTs. At dose level 2 (DL2), one patient had shown the G3 hypersensitive reaction (HSR) to CBDCA, and then additional three patients had

been enrolled. No further DLTs had been identified in the additional three patients. Only one DLT had been identified out of 9 patients at DL2 (Table 2,3). The MTD had not been reached but the dose of PTX had reached 60 mg/m² already, which was the recommended dose of weekly PTX single agent- IP therapy by Markman et al., the further escalation was stopped in ethical reason [8]. The RD was decided in this study as DL2; IP-PTX 60 mg/m², on D1, 8,15, with monthly IV-CBDCA AUC 5.0 mg/mL.min., on D1, q=4weeks.

The phase I study was completed in 9 patients. In order to confirm the feasibility of this study, further three patients were enrolled. No severe or unknown AEs were identified in the additional three patients.

As for abdominal pain, which had been thought to be the irritation induced by alcohols combined with PTX, the first patient of DL2 complained G1 abdominal pain at the first IP-PTX. Thus, the prophylactic NSAID, loxoprofen sodium hydrate 60 mg ter in die (t.i.d.), had been started on next D8 administration for 4 days. Under prophylactic NSAID administration, abdominal pain was controlled within G1.

All the adverse events were listed on table 3.

As for hematological toxicity, G3 leukopenia and neutropenia had been seen at a DL2. As for non-hematologic adverse events, abdominal pain, which was one of DLTs, but by the prophylactic NSAID abdominal pain was controlled within G1. HSR to CBDCA had been seen in two case, both of the patients had received the prior chemotherapy including CBDCA. No allergic and HSR to PTX had not been detected.

Adverse events concerning IP port

The complication of IP port was seen in one case of leakage of agents at the reservoir and tube at third cycles of DL2 case, and further therapy was declined by the patient. After removal of the reservoir, the screw connection between reservoir and catheter cuff had been loosen. No severe complications (infection, perforation of intestine, ileus, sub-ileus) nor occlusion had not been identified.

Pharmacokinetics

Pharmacokinetics was examined in three patients for both DL1 and DL2. The plasma concentrations of PTX at DL1, and DL2 were shown in figure 2.

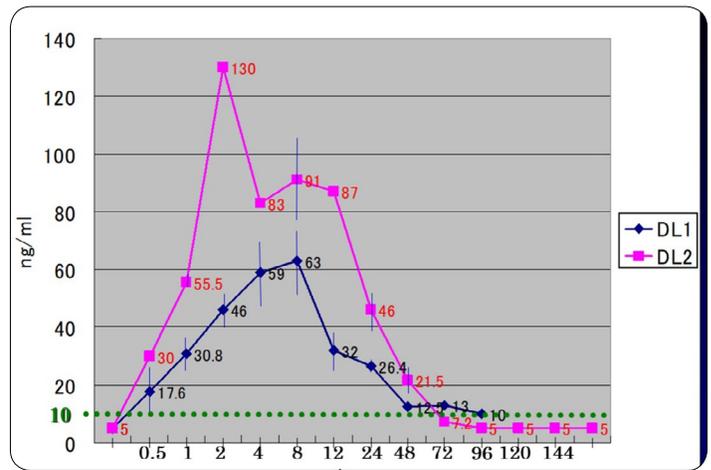


Figure 2: Serum Concentration of Paclitaxel. The mean peak value of the concentration was gotten at 8 hrs after initiation of administration and lasted for 96 hrs over 10ng/mL. Serum Concentration of PTX at DL2 was overlain on the graph of DL1. The area under the curve (AUC) of DL1 and DL2 were 1371ng/mL.min and 2020ng/mL.min, respectively. The AUC of DL2 amounted 1.47 folds in case of DL1.

IP-PTX usually was performed in 1hr intraperitoneal drip infusion. The mean peak value of the concentration had been obtained at 8 hrs after initiation of administration, and the effective concentrations lasted for 48 hrs at a level of over 10 ng/mL. The AUC of IP-PTX at DL1 and DL2 were 1371 ng/mL.hr and 2020 ng/mL.hr, respectively. The AUC of DL2 amounted 1.47 folds of DL1.

Responses, PFS, OS

The response was assessed by the fluctuation of plasma CA125 levels in 11 patients out of 12. In one patient, the plasma CA125 level had not detected before and during treatment. Only ascites was a non-target lesion in RECIST criteria, and the ascites had disappeared at the end of the treatment. Prognosis was evaluated at median observation time as 116.3 months. The median progression free survival time (mPFS) was 25.0 months and the median overall survival time (mOS) was 49.2 months (Table 3).

Discussion

To date, although the optimal surgery followed by the chemotherapy of taxane-platinum regimen was the standard treatment in patients with OC, FTC and PPC, the cure rate in advanced disease such as stage III/IV has not been improved. Most of the patients recur in abdominal cavity, para-aortic lymph nodes, parenchyma of liver or lung. In order to improve the cure rate, various methods

such as dose-intensification, additional third agent, maintenance chemotherapy, changing of DDS and some new molecular targeted agents and immune checkpoint inhibitors have been used. Unfortunately, the efficacy of the high-dose chemotherapy [9] and the triplets regimens had failed [10]. As for changing of an administration schedule, the dose dense chemotherapy alone could be achieved better median progression free survival time (mPFS) and median overall survival time (mOS) in such patients than usual tri-weekly PC therapy [11]. The new agent of anti-angiogenic agent, bevacizumab, showed PFS improvement but not in OS, unfortunately [12, 13]. Furthermore, new agents of Poly Adenosine diphosphate-Ribose Polymerase (PARP) inhibitors or immune-checkpoint inhibitors will improve both PFS and OS in near future, however, as for PARP inhibitor; the phase III trials showed elongation of OS but not confirmed the plateau in Kaplan-Meier curve in OS [14, 15]. The results of phase III trial using immune checkpoints inhibitor of PD-1 inhibitor, nivolumab, have not been matured.

On the other hand, the concept of IP was based on both dose-intensification and changing DDS and it originated in 1950's [16]. Several fundamental studies revealed the superiority of drug-AUC in the peritoneum and abdominal organs [1, 3, 17, 18]. The AUC differences in the abdominal cavity between IP-PTX and IV-PTX have taken a great role, and it was the key factor of this strategy. The AUC of peritoneal cavity of IP-PTX reached to 3 log-levels higher than that of IV-PTX. A phase I study was performed by the same group to investigate the feasibility of weekly IP-PTX. Doses were escalated from 20 mg/m² to 75 mg/m². Doses less than 65 mg/m² were well-tolerated, without G3 or G4 leukopenia or thrombocytopenia. They reported that the abdominal pain had been the most frequent toxicity, but it was G1 or 2 at worst and unrelated to dose in the dosage ranges. Although our study had not reached MTD, because of no further escalation of IP-PTX would not be performed in ethical reason that the dose had reached the recommended dose reported by Francis et al. in weekly IP-PTX in single regimen, of which MTD was 65mg/m² and RD was 60mg/m², already [8]. If we had performed the further level of DL 4 75 mg/m² it would have been harmful without much efficacy. We would like to know RD for next randomized P II/III study, so that there was not necessary to decide the MTD over Francis' recommended dose, 60mg/m² in our study.

From the bio-availability point of view, relevant concentrations were achieved and maintained in the peritoneal cavity for at least 7 days after administration

(5ng/ml in serum which equaled to 5mg/ml in peritoneal concentration), which with weekly dosing may provide continuous IP drug exposure (Figure 2). The limitation of IP was the problem of depth of penetration of agent into tumor tissue or peritoneum. It was reported that the penetration depth of cis-diamine dichloroplatinum; cisplatin (CDDP) had been limited in less than 4 mm from the surface. However, CDDP is hydrophilic and its active form of free platinum (F-Pt) binds instantly to protein (albumin) which is rich in ascites usually and CDDP is inactivated very soon. In contrast, PTX is lipophilic and deposited in adipose tissue around the peritoneal adipose tissue long time. Thus, the intraperitoneal administered PTX is preferably absorbed in adipose tissue of small intestine, large intestine, peritoneum, mesenterium and adipose tissue of diaphragm, and then PTX was taken from the lymphatic vessels system of diaphragm and omentum and accumulated in distal para aortic lymph node. Furthermore, from the mesenterium of intestines, PTX is absorbed and transferred via lymphatic stream to liver mesenchymal tissue. The transition stream was the same of lymphatic metastases of ovarian, fallopian tube and primary peritoneal cancers. Thus, high dose of PTX goes to metastatic lesions, but if the vessels are occluded by tumor or resected completely, the extension of PTX would be restricted. Because the reason stated above, minimal disease would be appropriate for this treatment. In the present study, the peripheral concentration of paclitaxel had been maintained for at least 48 hrs above 0.1 micromol/L (85.4 microgram/L, 0.0854 microgram/mL), which seemed to be the least tumor-cidal concentration of paclitaxel [19-22].

As for the kinds of IP-agent, cisplatin was the first candidate in 1980's, and paclitaxel has been thought to be the second agents. IP-CBDCA was tested by Fujiwara et al. and its pharmacokinetics and efficacy were reported [23-25] and JGOG3019 has been performed as a phase III study of IP-CBDCA (on D1) followed by IV-PTX (on D1, 8, 15) versus IV-CBDCA (on D1) with IV-PTX (weekly PTX in 80mg/m² on D1, 8, 15) has just finished but the survival data have not been matured.

We conducted the phase I study of weekly IP-PTX (on D1, D8, D15) with monthly IV-CBDCA (on D1). The IV-CBDCA was fixed as AUC 5.0 mg/mL.min. The recommended dose (RD) of IP-PTX was determined 60 mg/m² according to modified Fibonacci method. The pharmacokinetics of serum PTX had been examined as follows:

C_{max} of IP-PTX in serum had reached as about 0.10

microgram/mL at 8hrs after initiation of administration, which was 4-log lower compared with that of IV-PTX, 2000-4000 microgram /mL in 80 mg/m² weekly IV-PTX. The serum concentration of PTX had been obtained in DL2 for nearly 4 hrs only, on the other hand, the effective concentration of intraperitoneal lesion had been 1,000 folds of serum concentration, so that 0.0854 ng/mL (0.1micromol/mL) was the limited line in serum by calculation [19], then the effective exposure time of IP-PTX above 0.1 ng/mL($T_{>0.1}$) in serum lasted 48 -96 hrs (Figure 2). Thus, IP-PTX alone could not attack the extra-pelvic mass of tumor systematically, so that additional concomitant administration via peripheral venous infusion must be necessary like GOG 172 experimental arm.

In summary, we had re-considered that the lipophilic agent of paclitaxel was very suitable agent for intraperitoneal chemotherapy from Markman's studies. As for AEs, there were no severe adverse events in both hematologic and non-hematologic AEs in present study (Table 2). Two patients had been detected hypersensitivity reaction to CBDCA, because of the numbers of administration of carboplatin had exceeded to 8 courses. Neutropenia increased dependently in a concentration manner of C_{max} , especially over 85 ng/mL [22,26]. On the other hand, the neurotoxicity depends on the AUC of PTX, sensory neuropathy increased over 20 microgram/mL.hr[26,27]). The C_{max} of tri-weekly IV-PTX (175mg/m², 3hrs IV) and weekly IV-PTX (80mg/m², 1hr IV) were 4800 ng/mL and 3280 (2124-4436) ng/mL, respectively. The AUC were 16.5 microgram/mL.hr and 3.3 (2.8-3.8) microgram/mL.hr, respectively [27,28].

From the results of the present study showed that the C_{max} of DL1 (45 mg/m²) and DL2 (60 mg/m²) were 63±21 ng/mL and 91±17 ng/mL, respectively. The serum AUC of PTX were very low as 1.37 microgram/mL.hr and 2.02 microgram/mL.hr, respectively.

The AEs of the present study had been mild, and it was explained well by the comparison of pharmacodynamic study in relationship PTX dose and method of DDS and IP-PTX affected milder bone marrow suppression than IV-PTX and no neurotoxicity from the concentrations of peripheral AUC level of PTX.

As for pain, no pain of joint and skeletal muscles was seen. Although abdominal pain of irritation of peritoneum was seen at DL2 (60 mg/m²), prophylactic non-steroidal anti-inflammatory drug (NSAID, loxoprofen sodium,

Loxionin, Daiichi-Sankyo, pharm., Tokyo, Japan) use at a dose of 60 mg per os t.i.d. for 4days after administration prevented the patients from the abdominal pain and uncomfortable feelings due to distension.

We used only 200mL saline with Taxol. Japanese women usually are lower body-surface-area (BSA), and body weight, 200mL of saline would be sufficient for the peritoneal infusion. Adding that, PTX is hydro-phobic agents in itself, more than one-liter titration by saline causes precipitation of PTX in the bottle.

Speaking of the port derived complications, it is well known that an occlusion of catheter, infection, sub-ileus, perforation of intestines, tube penetration to vagina or adjacent tissues occur sometimes in IP-Device. We used a fully implantable reservoir port attached to a single lumen silicone catheter of fenestration without Dacron cuffs, SOPH-A-PORT. It has softer tube than otherwise with 84-pores, and as for setting, the direction and location of tip of tube had been put into the costophrenic space. This location of setting would prevent adhesion or pressing to intestines, and the occlusion had reduced dramatically. The most important point of peritoneal flow was absorption via diaphragmatic lymph system and re-circulation, and the high dose intensity of PTX by IP would attack the metastases of diaphragm and mesenterium. Normally, it takes one and half day that IP agents are brought by the lymph fluid circulation of abdominal cavity via main lymph vessels (diaphragm lymph vessels-thoracic duct) to blood circulation and brought again toward abdominal cavity. In this trial, there had not been identified severe adverse event except one leakage from connector of reservoir and tube.

In future, CBDCA AUC5-6mg/mL.min IP on D1, and PTX 80mg/m² div onD1, then PTX 60mg/m² on D8 and D15, q=3 weeks would be best pharmacokinetics. Further randomized phase II study in comparison with usual 3-weeks PC with Bevacizumab versus dose dense PC would be warranted.

Conclusion

The combination of weekly IP-PTX and monthly IV-CBDCA AUC 5.0 mg/mL.min was feasible and the recommended dose of IP-PTX was 60 mg/m². The therapy was moderate effective for optimal debulking mullerian tumors with small residual disease.

Table 1: Patient's Characteristics.

case	Diagnosis & original stage or recurrence	age	Residual tumor volume and site, (pc: number of prior regimen)
1	Tubal IIIc	53	Cytology (+). Para Aortic nodes<1.0cm, prior chemo (PL=0)
2	Ovarian IV	63	Post IDS, mesenterium <0.5cm, (PL=2)
3	Ovarian Ic/R	53	Post IDS, Cytology (+), optimal, pelvic<0.5cm, (PL=1)
4	Ovarian Iic/R	47	Optimal,recurrent in liver parenchyma, (PL=1)
5	Ovarian Ic/R	54	Stage 1c(a), cytology (+), (PL=0)
6	Ovarian Iv/R	64	Post IDS, pelvis, Micro, pleural effusion, (PL=3)
7	Ovarian IIc	74	peritoneum<0.5cm, cytology (+), (PL=0)
8	Ovarian IIIc	62	mesenterium<1.0cm, Recurrence, (PL=1)
9	Ovarian Ic/R	47	Post IDs, Stage Ic (a), cytology (+), (PL=1)
10	Ovarian IIIc	59	peritoneum<1.0cm, liver surface-abdominal wall, (PL=0)
11	Ovarian IIIc	63	mesenterium(military dissemination), colon peritoneum, bladders peritoneum, optimal surgery<1.0cm, (PL=0)
12	Ovarian IV	31	Post IDs(splenectomy),resident(.), (PL=1)

PL: Number of prior line of chemotherapy, IDS: Interval Debulking Surgery, R=recurrence, Stage was determined at the first treatment of the disease

Table 2: Adverse events.

Hematologic AEs	Leukopenia					Neutropenia					Anemia					thrombocytopenia				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Dose level 1 PTX 45 mg/m ²	3	0	0	0	0	3	0	0	0	0	2	0	1	0	0	1	1	1	0	0
Dose level 2 PTX 60 mg/m ²	2	3	1	3	0	2	2	2	3	0	1	4	4	0	0	7	2	0	0	0
Non-Hematologic AEs	Abdomina Pain					Nausea/ Vomiting/Diarrhea					Asthenia					Myalgia/ Neurological sensory disorder				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Dose level 1 PTX 45 mg/m ²	1	2	0	0	0	2	1	0	0	0	3	0	0	0	0	3	0	0	0	0
Dose level 2 PTX 60 mg/m ²	2	6	1	0	0	9	0	0	0	0	7	2	0	0	0	9	0	0	0	0
	Alopecia					Liver/Renal					Cardiac/ Pneumonol					Hypersensitivity				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Dose level 1 PTX 45 mg/m ²	3	0	0	0	0	3	0	0	0	0	3	0	0	0	0	3	1**	0	0	0
Dose level 2 PTX 60 mg/m ²	9	0	0	0	0	9	0	0	0	0	9	0	0	0	0	8	0	0	1**	0

**Hypersensitivity to carboplatin

Table 3: Response and outcome.

Case (course numbers performed)	Overall survival time (days)	Progression free survival time (days)	CA125 response	outcome	Recurrence sites
DL1-1 (6)	1722	697	CR	DOD	Lung
DL1-2 (6)	361	301	CR	DOD	Lung
DL1-3 (3)	2337+	2337	CR	NED	-
DL2-1 (3)	1248	619	PR	DOD	Liver mesenchymal metastases
DL2-2 (2)	2433+	2274	CR	Rec PAN	PAN
DL2-3 (2)	317	0	SD	DOD	Lung
DL2-4 (5)	2080+	701	PR	AWD	PEN
DL2-5 (3)	731	731	NE	Died of other disease	-
DL2-6 (3)	382	382	CR	DOD	PEN, ileus
DL2-7 (6)	811	450	CR	DOD	Lung, and PAN
DL2-8 (6)	1509	780	CR	DOD	Lung, peritonitis carcinomatosa
DL2-9 (3)	1545+	1157	CR	AWD	Rectal mucosa
Median	1722	701	-	-	-

Abbreviations: CR: complete response, PR: partial response, SD: stable disease, NE: not evaluable, AWD: alive with disease, DOD: dead of diseases, NED: no evidence of disease, PAN: para aortic nodes, PEN: pelvic nodes

Declarations

Ethics approval and consent to participate

The documents of protocol, informed consent and case report forms were approved by IRB of each institution.

Informed consent was obtained from every patient accrued.

Consent for publication

All authors' consent for publication was obtained.

Availability of data and material

If necessary, every data was available for further study after additional approval for new studies.

Competing interests

I have no conflict of interest concerning this study to declare.

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