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（分担研究者：鈴木光明）

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II. プロトコル

プロトコル文書

英語版

iPocc Trial

IntraPeritoneal therapy for Ovarian Cancer with Carboplatin

GOTIC-001 / JGOG-3019

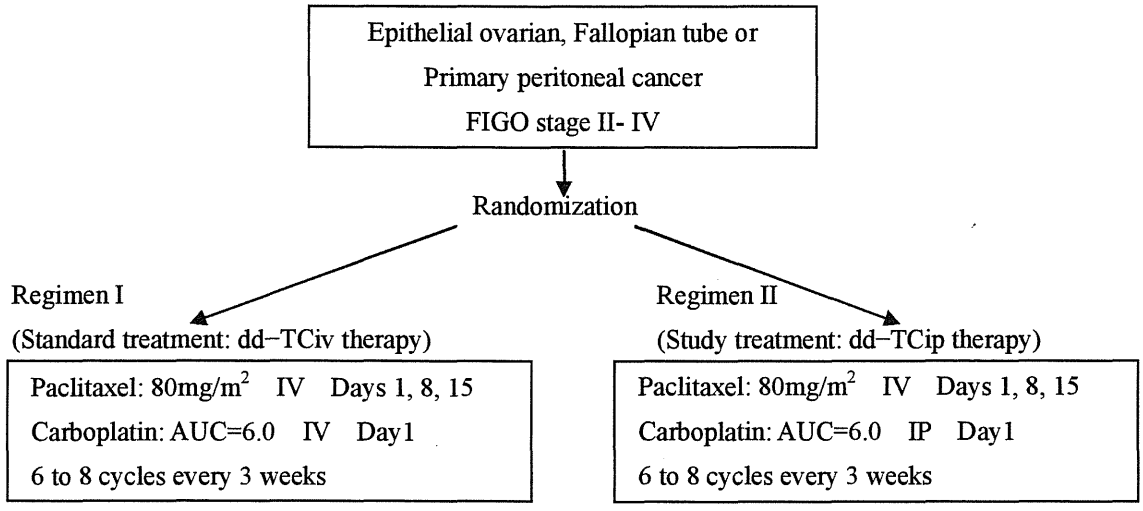
A RANDOMIZED PHASE II/ III TRIAL OF INTRAVENOUS (IV) PACLITAXEL WEEKLY PLUS IV CARBOPLATIN ONCE EVERY 3 WEEKS VERSUS IV PACLITAXEL WEEKLY PLUS INTRAPERITONEAL (IP) CARBOPLATIN ONCE EVERY 3 WEEKS IN WOMEN WITH EPITHELIAL OVARIAN, FALLOPIAN TUBE OR PRIMARY PERITONEAL CANCER

UMIN Unique trial Number: UMIN000003670
Clinical Trials.gov ID: NCT01506856

English version 1.0 (2011/08/25)
English version 1.1 (2011/09/12)
English version 1.2 (2012/04/01)
English version 2.0 (2013/01/20)

0 STUDY OVERVIEW

0.1 Treatment Schema



0.2 Objectives

Phase A: To confirm the feasibility of Paclitaxel administered by intravenous (IV) infusion weekly plus concurrent Carboplatin administered by intraperitoneal (IP) injection once every 3 weeks (dd-TCip therapy).

Phase B: To compare the efficacy and safety of the following two treatment regimens as first-line chemotherapy in women with epithelial ovarian, Fallopian tube or primary peritoneal cancer.

Regimen I (Standard treatment: dd-TCiv therapy)

Paclitaxel administered by IV infusion weekly plus concurrent Carboplatin administered by IV infusion once every 3 weeks

Regimen II (Study treatment: dd-TCip therapy)

Paclitaxel administered by IV infusion weekly plus concurrent Carboplatin administered by IP injection once every 3 weeks

0.3 Phase, Target Sample Size, and Endpoint

0.3.1 Phase A (Phase II Trial) Sample size: 120 (phase A)

A decision to move from phase A to phase B will be made independently and comprehensively by the Independent Data Monitoring Committee (IDMC), based on a review of feasibility, including treatment completion rate, hematologic toxicity, non-hematologic toxicity and response rate (in patients who have measurable disease) in both regimens.

When collection of eCRFs is complete for all patients in phase A, the IDMC will meet to review all data, including feasibility and safety data, and will make recommendations to the study chair regarding whether continuation of the study is acceptable. If a decision is made to continue the study, the efficacy data will be evaluated by, and accessible to, the IDMC, and the results will not be made

public. If a decision is made to discontinue the study, all data including efficacy and safety data will be immediately made public. In the transition from phase A to phase B, patient enrollment should be continued without interruption during the evaluation period.

0.3.2 Phase B (Phase III Trial) Sample size: 565 (Phase B)

Total sample size:	685 (Phase A + Phase B)
Primary Endpoint:	Progression-free survival (PFS)
Secondary Endpoints:	Overall survival (OS)
	Tumor response (only in patients with evaluable disease)
	Incidence of adverse events
	Treatment completion rate
	Quality of Life (QOL) assessments
	Cost-utility analysis

- Data from the 120 patients in phase A will be included in the final analysis.
- 510 events are necessary for the final analysis.

0.4 Patient Selection Criteria

0.4.1 Eligibility criteria

1) Patients assumed to have a stage II–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer as a pre-surgery diagnosis
2) Patients scheduled to undergo laparotomy
   Both optimal and suboptimal patients will be eligible for the study. (Suboptimal patients, as well as those who undergo only exploratory laparotomy, are eligible.)
3) ECOG Performance Status: 0-2
4) Patients who provide consent for placement of the IP port system, if randomized to Regimen II (Study treatment: dd-TCip therapy)
5) Patients expected to receive the first protocol treatment within 8 weeks after the comprehensive staging surgery
6) Lab data and clinical examination
   Data within 28 days before the scheduled date of surgery

Neutrophil count	$\geqq$ 1,500 /mm^3
Platelet count	$\geqq$ 100,000 /mm^3
AST (GOT)	$\leqq$ 100 IU/L
ALT (GPT)	$\leqq$ 100 IU/L
Total bilirubin	< 1.5 mg/dL
Serum Creatinine	< 1.5 mg/dL
Electrocardiogram (ECG)	Patients with normal ECG Asymptomatic patients with abnormal ECGs not requiring medical intervention
Neuropathy(Both motor and sensory)	$\leqq$ Grade1 (CTCAE Version 4.0)

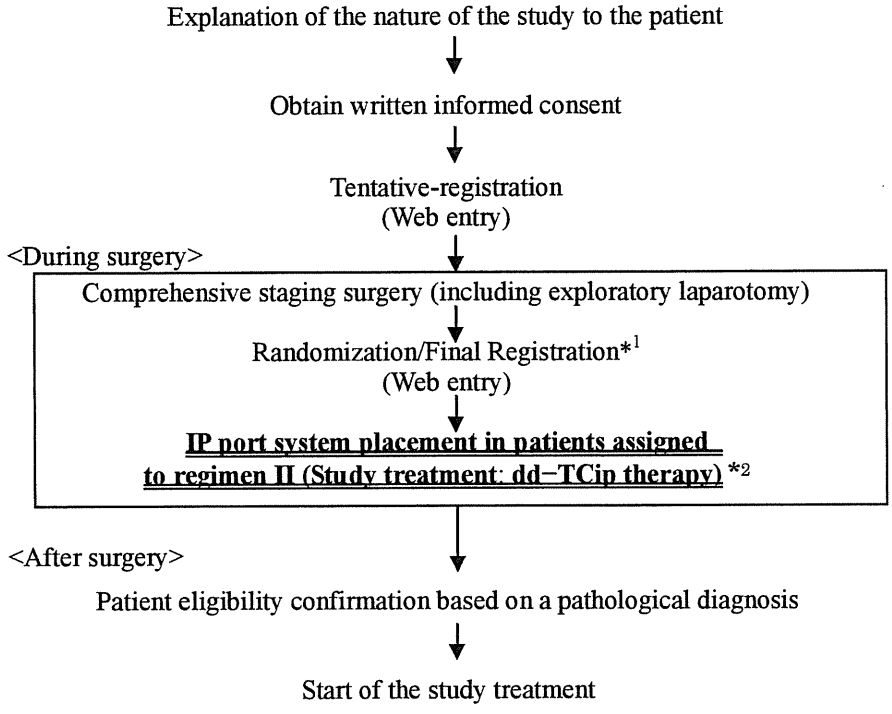
7) Patients expected to survive longer than 3 months from the start date of the protocol treatment
8) Patients aged 20 years and older at the time of tentative registration (with no upper age limit)
9) Patients who provide written informed consent for participation in this trial

0.4.2 Exclusion criteria

1) Patients assumed to have a borderline malignancy of the ovary, fallopian tube, or primary peritoneal cancer
2) Patients who have received previous chemotherapy or radiation therapy to treat the current disease
3) Patients who have a synchronous malignancy or who have been progression-free less than 5 years for a metachronous malignancy (Patients with basal and squamous cell carcinoma of the skin, as well as carcinoma in situ, and intramucosal carcinoma cured by local treatment, are eligible for the study)
4) Patients with serious medical complications, such as serious heart disease, cerebrovascular accidents, uncontrolled diabetes mellitus, uncontrolled hypertension, pulmonary fibrosis, interstitial pneumonitis, active bleeding, an active gastrointestinal ulcer, or a serious neurological disorder
5) Patients who have had a hypersensitivity reaction to polyoxyethylated or hydrogenated castor oil
6) Patients with a pleural effusion requiring continuous drainage
7) Patients with an active infection requiring antibiotics
8) Patients who are pregnant, nursing or of child-bearing potential
9) Patients with evidence upon physical examination of brain tumor and any brain metastases
10) Patients for whom completion of this study and/or follow-up is deemed inappropriate for any reason
11) Patients with any signs/symptoms of interstitial pneumonia

0.5 Registration and Randomization

<Before surgery>



*1 If the patient is not proceeding to the final registration or does not receive protocol treatment, please enter the patient data and reasons for not proceeding/not receiving protocol treatment into the Rave system.

*2 For institutions other than those in Japan where IP port placement is performed after comprehensive staging surgery as a regular practice, IP port placement can be done after the patient's randomization to regimenII. IP port can be placed during the surgery for all study patients, and then IP port can be removed, when the patient is assigned to regimenII. 【See 6.3.3】

0.6 Study Duration

Target sample size and Accrual period

Target sample size: Phase A (120 patients)
Phase B (565 patients)
Total sample size: 685 (Phase A + Phase B)

- Data from the 120 patients in phase A will be included in the final analysis.

Accrual period: May 2010 to May 2015

Follow-up period: Follow-up is until 510 events are observed or until 3 years from the last patient is randomized to the study, whichever comes first.
Consequently, follow-up is estimated to be completed in May 2018.

- Patients are able to refuse protocol treatment at any time for any reason.
- Follow-up observation will be continued unless the consent is withdrawn.

0.7 Contact Information

【Queries which require a medical opinion】

Study chair

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【All other queries】

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Kitasato University Research Center for Clinical Pharmacology,

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Appendix

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1. Study-specific manuals

A. Manuals for IPS insertion procedures and intraperitoneal injection

B. Flow of serious adverse event reporting

C-①. STUDY WEB-PAGE Procedure Manual

C-②. EDC System Procedure Manual

C-③. iPocc Trial Patient Registration Procedure Manual

D. Drug ordering, distribution and management system

E. Request for cooperation for QOL survey

2. Form (as samples)

①. Informed consent documents

②. Form A / Form C (REQUEST FORM for Rave USER ADMINISTRATION)

③. Patient Registration Form: Emergency Use Only

④. eCRFs, iPocc Trial eCRF Completion Manual

⑤. SAE REPORT、iPocc SAE REPORT Completion Manual

⑥. QOL questionnaire

⑦. Survey form for costs associated with treatment for patients

3. Guidelines

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II. ECOG PS

III. CTCAE version 4.0

IV. RECIST Guidelines version 1.1

V. Drug Package Insert

VI. Procedures for hypersensitivity reactions

VII. ASCO guidelines for the use of G-CSF

1 OBJECTIVES AND ENDPOINTS

1.1 Objectives

Phase A: To confirm the feasibility of Paclitaxel administered by intravenous (IV) infusion weekly plus concurrent Carboplatin administered by intraperitoneal (IP) injection once every 3 weeks (dd-TCip therapy).

Phase B: To compare the efficacy and safety of the following two treatment regimens as first-line chemotherapy in women with epithelial ovarian, fallopian tube or primary peritoneal cancer.

Regimen I (Standard treatment: dd-TCiv therapy)

Paclitaxel:	80 mg/m^2	1 hour IV infusion	Days 1, 8, and 15
Carboplatin:	AUC = 6.0	1 hour IV infusion	Day 1

The 3-week period (21 days) is 1 cycle. A total of 6 to 8 cycles will be repeated.

Regimen II (Study treatment: dd-TCip therapy)

Paclitaxel:	80 mg/m^2	1 hour IV infusion	Days 1, 8, and 15
Carboplatin:	AUC = 6.0	IP injection	Day 1

The 3-week period (21 days) is 1 cycle. A total of 6 to 8 cycles will be repeated.

1.2 Endpoints

1.2.1 Phase A (Phase II trial)

In phase A, feasibility, including treatment completion rate (in patients who have measurable disease), hematologic toxicity, non-hematologic toxicity and response rate in the two arms, will be determined independently by an Independent Data Monitoring Committee (IDMC).

When the collection of eCRFs is complete for all patients in phase A, the IDMC will meet to review all data including feasibility and safety data, and will make recommendations to the study chair regarding whether continuation of the study is acceptable.

For transition from the phase A trial to the phase B trial, the committee will make a decision based on the following criteria.

1) An unexpectedly high incidence of Grade 3 or greater hematologic and/or non-hematologic toxicities observed in dd-TCip therapy compared to dd−TCiv therapy.
2) An unexpectedly low response rate observed in dd-TCip therapy compared to dd−TCiv therapy.
3) An unexpectedly low treatment completion rate observed in dd-TCip therapy compared to dd−TCiv therapy.

Each criterion is evaluated on the basis of both statistical considerations, based on the odds ratio with a 95% confidence interval, and clinical considerations on whether or not to move to phase B. If all of the criteria (1), (2), and (3) are met, the transition to phase B will be abandoned after review by the IDMC. If any of the criteria are met, the IDMC will have a comprehensive discussion, and may refer to additional criteria, to determine whether or not to move to phase B. If none of the criteria is met, the transition to phase B will be decided after a review by the IDMC.

If a decision is made to continue the study, the efficacy data will be evaluated by and accessible to

the IDMC, and the results will not be made public. If a decision is made to discontinue the study, all data, including efficacy and safety data, will be immediately made public.

In the transition from phase A to phase B, patient enrollment should be continued without interruption during the evaluation period.

1.2.2 Phase B (Phase III trial)

Primary Endpoint:	Progression-free survival (PFS)
Secondary Endpoints:	Overall survival (OS)
	Tumor response (only patients with evaluable disease)
	Incidence of adverse events
	Treatment completion rate
	Quality of Life (QOL) assessments
	Cost-utility analysis

2 BACKGROUND AND RATIONALE

2.1 Background and rationale for this study

2.1.1 Background

Approximately 8,000 women are estimated to receive a diagnosis of epithelial ovarian cancer each year in Japan. This disease has a very poor prognosis: 4,006 women died in 1996 and 4,467 women in 2005 [1]. To date, no effective screening regimen has been identified for ovarian cancer, so by the time patients see a doctor, 70% are diagnosed with stage III or IV cancer. The number of affected patients is currently on the increase. While the age-adjusted mortality rate in patients with ovarian cancer was 2.5 per 100,000 women in 1970, it was 4.7 in 1994, which is 1.9-fold increase in a period of 25 years. The rate is estimated to reach 7.4 in 2015, and the disease is likely to be the second leading cause of death due to gynecologic malignancies, after breast cancer [2].

Unlike many other solid tumors, it is well known that appropriate cytoreduction is associated with improved survival among women with epithelial ovarian cancer. The recommended treatment includes initial surgery, with the aim of removing as much tumor as possible, followed by chemotherapy [3), 4)]. Previously, platinum-based CAP therapy or CP therapy was the standard chemotherapy for epithelial ovarian cancer. Then, following the development of Paclitaxel, a taxane drug, large scale comparative studies of a regimen that included Paclitaxel were conducted (GOG-111 and OV-10) [5), 6)]. In a comparison between the combination of cisplatin and Paclitaxel and cisplatin and cyclophosphamide in 410 stage III or IV ovarian cancer patients with residual tumor, it was found that combination therapy with Paclitaxel was associated with significantly better results for both response rate (73% vs. 60%) and overall survival (38 months vs. 24 months). Based on these results, Paclitaxel and cisplatin combination was considered a new standard chemotherapy for epithelial ovarian cancer. Subsequently, in order to reduce renal toxicity and gastrointestinal toxicity associated with cisplatin, clinical trials of combination therapy were conducted in which Carboplatin was substituted for cisplatin (AGO and GOG-158). The results showed a reduction in toxicity even though the effectiveness of the Paclitaxel and Carboplatin was equivalent to that of the Paclitaxel and cisplatin. Thus, partly because of the simplicity of its dosing regimen, the combination of Paclitaxel and Carboplatin has become recognized as a new standard therapy [7), 8)]. Consequently, in

Japan, intravenous Paclitaxel 175 to 180 mg/m^2 over 3 hours and intravenous Carboplatin AUC=5 to 6 over 1 hour (TC therapy) has been commonly used as standard chemotherapy for epithelial ovarian cancer [1].

2.1.2 Validity of using weekly administration of Paclitaxel as standard treatment

In patients with different types of solid tumors, an attempt has been made to increase the antitumor effect by decreasing the dosing interval of Paclitaxel from 3 weeks to 1 week based on the concept of dose-dense therapy. Recently, researchers have reported that in a phase III trial of postoperative adjuvant therapy in patients with breast cancer, patients who received weekly Paclitaxel have a significantly better prognosis than those with once-every-3-week administration [9]. In patients with epithelial ovarian cancer, the findings of a phase III randomized controlled trial of dose-dense therapy with Paclitaxel (JGOG-3016) conducted by the Japan Gynecologic Oncology Group (JGOG) were presented at the 2008 annual meeting of the American Society of Clinical Oncology [10]. In the trial, the standard TC therapy with once-every-3-week administration was compared with the combination therapy, that is, once-every-3-week administration of Carboplatin and weekly administration of 80 mg/m^2 of Paclitaxel (dd–TC therapy). The results showed the progression-free survival was significantly longer in patients with the dd–TC therapy, 17.2 months vs. 28.0 months, and 3-year overall survival rate was significantly higher in those with the dose-dense therapy, 65.1% vs. 72.1%, (HR 0·75, 0·57–0·98; p=0·03). The study showed no difference in peripheral neurotoxicity; however, patients who received the dd–TC therapy had a significantly higher frequency of hematologic toxicity, and a lower treatment completion rate (63% vs. 48%). These findings provided by Japanese researchers have strongly impacted other researchers all over the world, and in the future, it is likely that weekly administration of Paclitaxel will be substituted for the conventional dosing regimen in TC therapy. Therefore, the idea of using the dd–TC therapy as a standard treatment in a future of phase III trial is considered sufficiently valid.

2.1.3 History and current status of intraperitoneal chemotherapy in patients with ovarian cancer

Ovarian cancer often spreads to different sites within the peritoneal cavity via direct shedding or dissemination at an early stage. Because of this, several decades ago, intraperitoneal (IP) administration of anticancer drugs was proposed for patients with residual tumor after initial surgery or recurrent lesions confined to the peritoneal cavity [11]. When administered by intraperitoneal injection, certain drugs, including cisplatin and Paclitaxel, have distinct pharmacokinetic advantages [12–14]. That is, these drugs remain longer in the peritoneal cavity at a higher concentration than with intravenous (IV) administration [16]. With IP administration of cisplatin, for example, a 10- to 20-fold greater exposure was reported in the peritoneal cavity compared with IV administration. Due to the fact that such highly concentrated drugs remain in the peritoneal cavity over a long period of time, IP administration of anticancer drugs theoretically shows greater promise for disease in the peritoneal cavity than IV administration. Conducting a randomized controlled study of IP cisplatin plus cyclophosphamide versus IV cisplatin plus cyclophosphamide for stage III ovarian cancer (GOG-104), Alberts et al. reported that patients in the IP group had a significantly better prognosis (median survival of 49 months vs. 41 months) and a reduction in adverse effects, compared with those in the IV group [14]. In subsequently-conducted GOG-114, a randomized controlled study of IP

cisplatin plus IV Paclitaxel versus IV cisplatin plus IV Paclitaxel, survival was not significantly different (median of 63.2 months vs. 52.2 months), but patients in the IP group had a significantly better recurrence-free survival (median of 27.9 months vs. 22.2 months) [17]. In the latest of the three American trials (GOG-172), patients receiving a regimen consisting of IV Paclitaxel, IP cisplatin, and IP Paclitaxel on Day 8 had a significantly better prognosis (median overall survival of 65.6 months vs. 49.7 months)[18].

Based on the results of these three randomized controlled studies, the National Cancer Institute (NCI) and Gynecologic Oncology Group (GOG) conducted a meta-analysis including other randomized controlled studies. The results showed that the IP therapy reduced the risk of death by 21.6%, compared with IV therapy. On January 5, 2006, NCI issued a clinical announcement stating, "For patients with ovarian cancer (FIGO stage III) who have undergone optimal surgical cytoreduction, consideration should be given to a regimen containing IP cisplatin and a taxane, whether given IV only or IV plus IP." [19] Following these results, much attention was focused on IP therapy for patients with epithelial ovarian cancer; however, because of toxicity concerns, including dosing regimen and catheter-related problems, this therapeutic approach has not been widely accepted. Furthermore, in GOG-172, the number of patients completing the planned 6 cycles of IP chemotherapy was only 42% due to toxicity; therefore, development of a regimen with lower toxicity is essential.

2.1.4 Rationale for substituting IP administration of Carboplatin for that of cisplatin

It is well known that with IV administration, substitution of Carboplatin for cisplatin achieves similar efficacy with less toxicity. With IP administration, on the other hand, based on animal studies and small scale, retrospective clinical reports showing that Carboplatin is inferior to cisplatin in efficacy, cisplatin has primarily been used. Since these studies did not take into account effective doses of cisplatin and Carboplatin, the necessity of reviewing the effectiveness of IP Carboplatin with adequate dosing has been controversial. In recent years, researchers have been accumulating data demonstrating the superiority of IP administration of Carboplatin over that of cisplatin. By retrospectively studying many cases, Fujiwara et al. reported that patients had a better prognosis when they received an adequate dose of IP Carboplatin, $\geq$400 mg/m^2.[20] Miyagi et al. conducted a pharmacological analysis using a mathematical model. According to their report, there was no difference in platinum AUC in the serum between IP and IV administrations of Carboplatin, but platinum AUC in the peritoneal cavity was approximately 17 times higher when IP Carboplatin was administered. They also pointed out that IP administration of Carboplatin is likely to be pharmacologically more effective than IV administration [21]. In light of these findings, Carboplatin may achieve similar efficacy with reduced toxicity. Therefore, it is suggested that determining the efficacy of IP administration of Carboplatin in phase III trials would provide a strong rationale for improving the QOL of patients receiving chemotherapy.

In GOG-172, both hematologic and non-hematologic toxicity were significantly higher in the IP arm than in the IV arm, and among patients in the IP arm, only 42 % completed 6 cycles of IP therapy. Because of the complex design of GOG-172, it is not clear whether this is due to IP administration of cisplatin, Paclitaxel on Day 8, total dose of Paclitaxel, or IP administration of Paclitaxel. In addition, 34% of the patients who were unable to complete treatment had catheter-related problems.

In a phase II trial of IP Carboplatin and IV Paclitaxel, less than 10% of patients discontinued treatment due to IP catheter-related issues, suggesting better tolerance. However, it is necessary to perform the study with careful attention to potential adverse events associated with silicon catheters (e.g. port infection, obstruction, bowel adhesion, and bowel perforation).[24)]

2.1.5 Rationale for including patients with suboptimal residual disease

When administered into the peritoneal cavity, anticancer drugs are thought to penetrate only several millimeters directly into the tumor. This has excluded IP administration in patients with large volume residual disease after initial surgery [22)]. A recent report on a retrospective study of TC therapy showed that a high response rate, 79%, was observed in patients with suboptimal residual disease after initial cytoreduction who were given IP Carboplatin [23)]. In a phase II trial conducted by Miyagi of the Sankai Gynecology Study Group, an IV Paclitaxel plus IP Carboplatin combination yielded a superior response rate in patients with residual tumor [24)]. Furthermore, no difference was found in serum platinum AUC in the IP and IV groups. IP administration of Carboplatin is considered to be a route of systemic administration that can be theoretically expected to be equally or even more effective in patients with suboptimal residual disease than IV administration. Thus, including patients with suboptimal residual disease is valid and very likely to increase the number of patients who could derive a benefit from IP administration.

2.1.6 Rationale for conducting a phase II/III trial

The efficacy and safety of dd-TCiv therapy has already been validated in JGOG-3016. In a preliminary toxicity analysis study [25)] and the above phase II trial by the Sankai Gynecology Study Group, the efficacy and safety of IP Carboplatin plus IV Paclitaxel once every 3 weeks has been tested. As a result, the recommended dose of IP Carboplatin when IV Paclitaxel 175 mg/m^2 was given concurrently was AUC 6 to 7 [25)], with a response rate when Paclitaxel 175 mg/m^2 IV was given concurrently with Carboplatin AUC 6 of 83%. Moreover, the completion rate for the planned 6 courses of treatment was very high at 85%, and toxicity was the same as that for IV administration [24)]. Toxicity associated with the IP port was observed in only 1 patient (4%) who had a port obstruction. These findings suggest that dd-TCip therapy is not inferior to dd-TCiv therapy in efficacy and may be a safe method of administration. However, efficacy and safety data are insufficient, and it is considered necessary to conduct a phase II trial prior to a phase III trial. In diseases such as ovarian cancer, however, the number of patients is limited, and now that chemotherapy is rapidly being developed, starting a phase III trial anew after completion of phase II trial creates a problem in terms of effective use of resources. Evaluating dd-TCip therapy using a phase II/III trial design, where patients for a phase II trial can also be candidates for phase III, allows the prompt implementation of a study, providing a strong rationale for conducting a phase II/III trial.

The purpose of this study is to verify the hypothesis that IP is superior to IV for Carboplatin administration. At this time, prior to conducting the study, there is no evidence to indicate the superiority of IP administration of Carboplatin. In addition, it is very unlikely that patients assigned to an IP arm will be exposed to any unacceptable risks associated with the IP administration of Carboplatin. Therefore, the social benefits provided by this study are not considered not to undermine the well-being of the subjects.

Based on scientific evidence discussed above, we have planned a dd-TC therapy, that is, a