On-Going IP Chemotherapy Trials

- iPocc Trial (GOTIC-001/JGOG3019)
- GOG-0252 Trial
- NCIC OV21/GCIG Trial

On-Going IP Chemotherapy Trials

- iPocc Trial (GOTIC-001/JGOG3019)
- GOG-0252 Trial
- NCIC OV21/GCIG Trial

Cannot answer the questions by themselves, but may be able to answer when these trials are combined

iPocc Trial (JGOG3019)

GOTIC JGOG

Stage II to IV Ovarian, primary peritoneal, or fallopian tube cancer Including Suboptimal

RANDOMIZE

Paclitaxel 80 mg/m²/1h IV, Weekly
Carboplatin AUC 6 IV

Paclitaxel 80 mg/m²/1h IV, Weekly
Carboplatin AUC 6 IP

- **Accrual goal: 746 pts**
- **Primary end point: PFS**

GOG0252 Trial

Stage II or III (≤1cm residual after GOG262 opened), Ovarian, primary peritoneal, or fallopian tube cancer

RANDOMIZE

Paclitaxel 80 mg/m²/1h IV, Weekly Cycles 1-6
Carboplatin AUC 6 IV, Day 1, Cycles 1-6
Bevacizumab 15 mg/kg IV, Cycles 2-22

Paclitaxel 80 mg/m²/1h IV, Weekly, Cycles 1-6
Carboplatin AUC 6 IP, Day 1, Cycles 1-6
Bevacizumab 15 mg/kg IV, Cycles 2-22

Paclitaxel 135 mg/m²/3h IV, Day 1, Cycles 1-6
Cisplatin 75 mg/m² IP, Day 2, Cycles 1-6
Paclitaxel 60 mg/m² IP, Day 8, Cycles 1-6
Bevacizumab 15 mg/kg IV, Cycles 2-22

- **Accrual goal: 1100 pts**
- **Primary end point: PFS**

NCIC OC21/GCIG

Pick the winner strategy

Neoadjuvant Chemotherapy
for Stage III
Epithelial Ovarian Cancer
Followed by
Interval Debulking Surgery
Resulting
Residual Disease < 1 cm

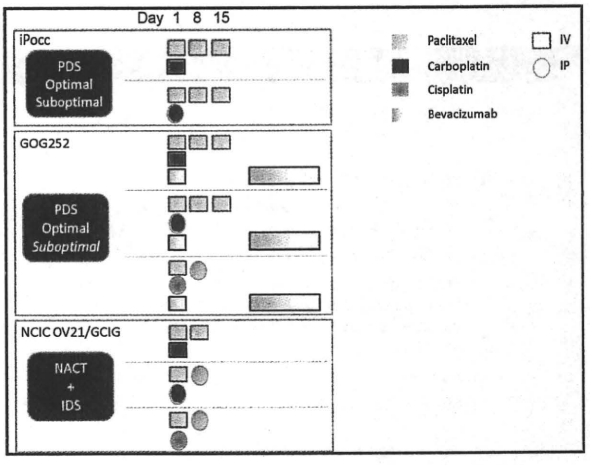
RANDOMZE

Paclitaxel 135 mg/m2 IV
Carboplatin AUC 6 IV
Paclitaxel 60 mg/m2 IV D8
Q21, 6-8 Cycles

Paclitaxel 135 mg/m2 IV
Carboplatin AUC 6 IP
Paclitaxel 60 mg/m2 IP D8
Q21, 6-8 Cycles

Paclitaxel 135 mg/m2 IV
Cisplatin 75 mg/m2 6 IP
Paclitaxel 60 mg/m2 IP D8
Q21, 6-8 Cycles

Total Sample Size 830

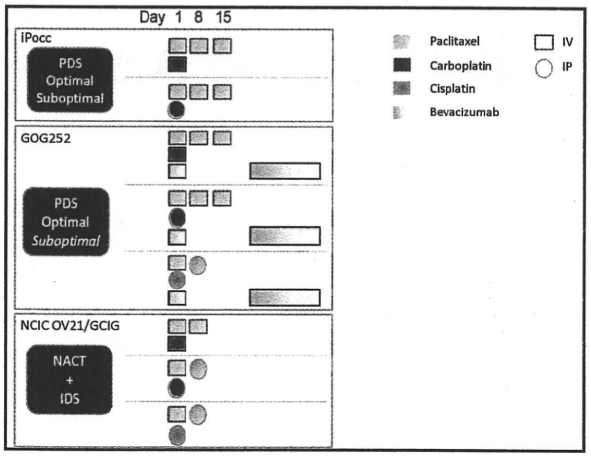


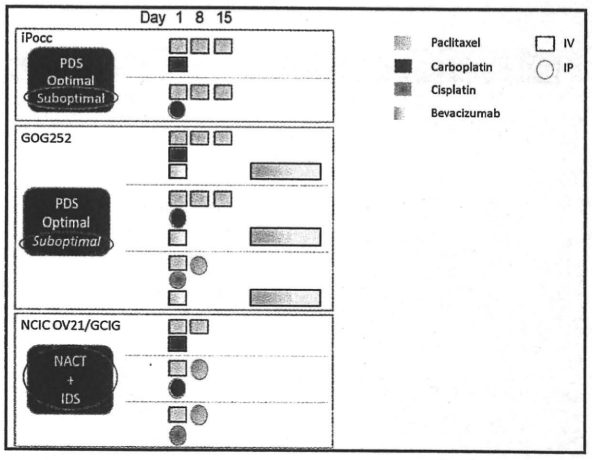
Based on the EORTC55791 trial

- There will be a trend of more NACT + IDS approach
  - Does this mean that there will be less room for IP chemotherapy?
  - Under the current concept of IP chemotherapy being effective only for small residual disease?
- Questions for the Future
  - What will be the
    - Role of IP chemotherapy upfront?
    - Role of IP chemotherapy after NACT + IDS?

Based on the EORTC55791 trial

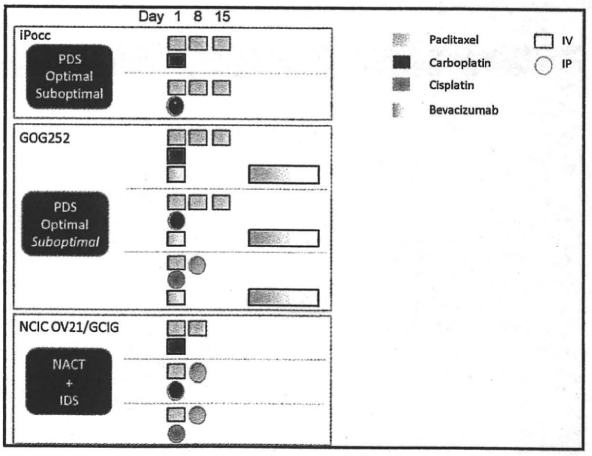
- There will be a trend with more the NACT + IDS approach
  - Does this mean less room for IP chemotherapy, based on the current concept that IP chemotherapy is effective only for small residual disease?
- Questions for the Future
  - What about
    - Role of IP chemotherapy upfront?
      - JGOG3019 and GOG252
    - Role of IP chemotherapy after NACT + IDS?
      - OV21

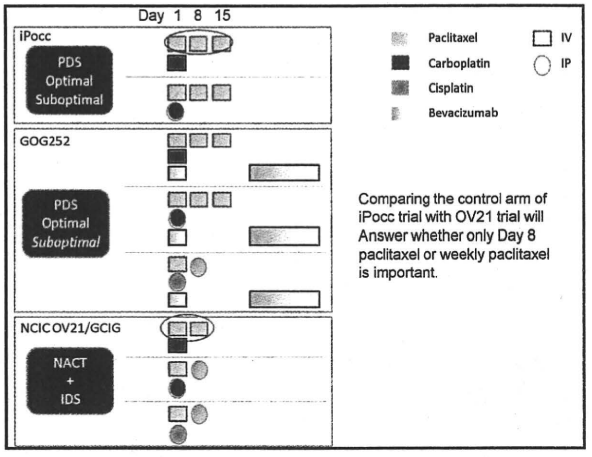


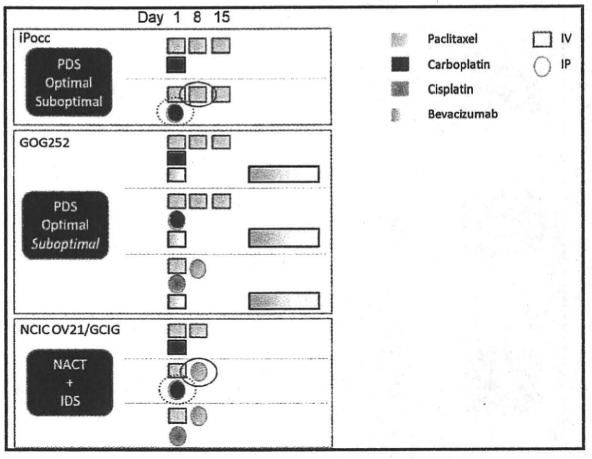


Result of JGOG3016

- Questions for Day 8 IP Paclitaxel in GOG172 Trial
  - Does Day 8 paclitaxel matter?
    - All of the trial incorporated weekly paclitaxel either IV or IP, but OV21 does not include the Day 15 Pac.
  - Does Day 8 IP paclitaxel matter?
    - OV21 may give some answer with some confusion because Day 8 paclitaxel is given IP, as well as cisplatin or carboplatin is given IP (Day 1): Two variables.
  - GOG252
    - More confusions.

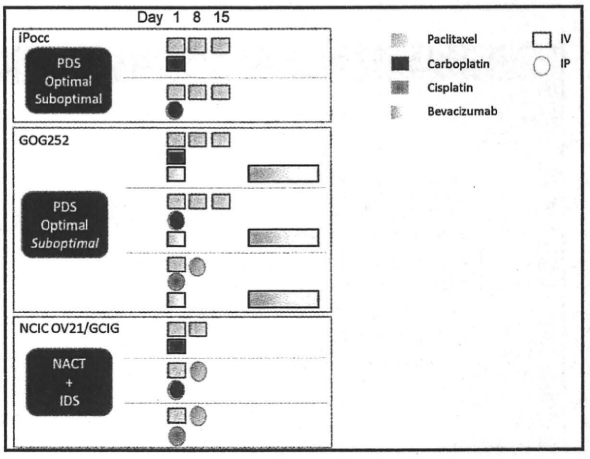


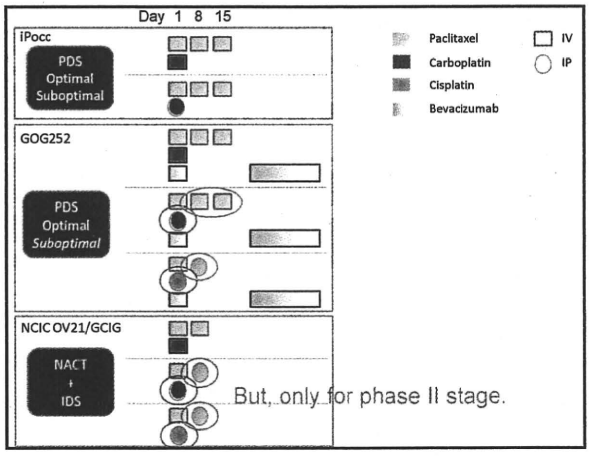




IP Cisplatin vs Carboplatin

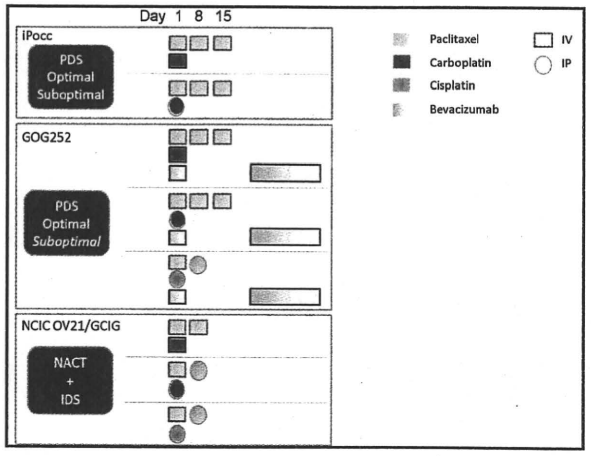
- GOG252 will give some answer with some confusion because paclitaxel is given IP on day 8 for IP cisplatin arm, but paclitaxel is given every week on IP carboplatin arm
- OV21 will give some answer but only for phase II fashion.

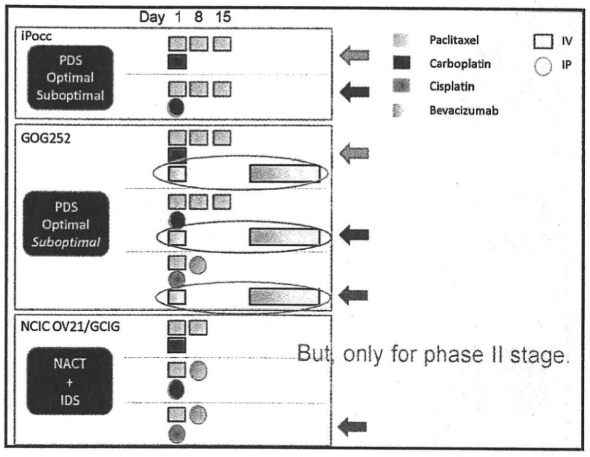




GOG218 Results

- What is the role of bevacizumab in combination with IP chemotherapy





Summary

- After the 3 large scale randomized trials for IP chemotherapy on-going worldwide,
  - Some of the important unanswered questions can be answered
  - Not perfectly, but reasonably for the role of IP chemotherapy
    - in neoadjuvant chemotherapy area
    - in weekly schedule area
    - in bevacizumab area

Thank You !

IRB承認施設

	施設名
1	埼玉医科大学国際医療センター
2	自治医科大学付属病院
3	独立行政法人国立病院機構四国がんセンター
4	東北大学病院
5	新潟県立がんセンター　新潟病院
6	鳥取市立病院
7	栃木県立がんセンター
8	群馬大学医学部附属病院
9	JA広島総合病院
10	市立三次中央病院
11	埼玉社会保険病院
12	筑波大学・大学院　人間総合科学研究科　婦人周産期医学
13	新潟大学医歯学総合病院
14	市立貝塚病院
15	神戸市立医療センター中央市民病院
16	沖縄県立中部病院
17	聖隷浜松病院
18	大木記念女性のための　菊池がんクリニック
19	三沢市立三沢病院
20	東邦大学医療センター　大橋病院
21	済生会長崎病院　産婦人科
22	癌研有明病院
23	埼玉医科大学総合医療センター
24	久留米大学病院
25	大阪府立成人病センター
26	国立病院機構　千葉医療センター
27	中国労災病院
28	山口赤十字病院
29	独立行政法人国立病院機構呉医療センター・中国がんセンター
30	獨協医科大学病院
31	三重県立総合医療センター

V. 文　献

特定非営利活動法人 婦人科悪性腫瘍化学療法研究機構

化療ニュース

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喜多恒和、杉山裕子、津田浩史、深澤一雄、
三上幹男、矢島正純

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（会員の声）

iPocc試験開始に当たって

埼玉医科大学国際医療センター婦人科腫瘍科

藤原 恵一　　長尾 昌二

この度、JGOG3019試験としてカルボプラチンを用いた腹腔内化学療法の有用性を検証する大規模比較試験を開始させていただくことになりました。本試験の趣旨を理解いただき、ご協力くださいますようお願い申し上げます。

本試験のタイトルは「上皮性卵巣癌・卵管癌・腹膜原発癌に対する Paclitaxel毎週点滴静注+Carboplatin 3週毎点滴静注投与 対 Paclitaxel毎週点滴静注+Carboplatin 3週毎腹腔内投与 のランタム化第II/III相試験」で、ニックネームはiPocc（アイポック）試験と名付けました。Intra Peritoneal therapy for Ovarian Cancer

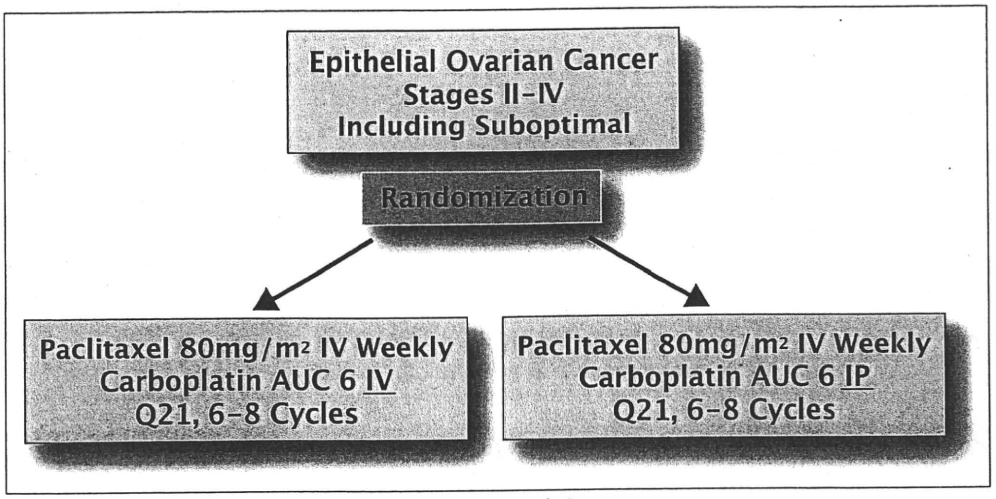

図1 iPocc試験デザイン

with Carboplatinの略です。

本試験の構想は10年間余り暖め続けておりましたが、平成21年度厚生労働省科学研究費助成が獲得できたことから、本格的な準備に入ることが可能となりました。まず、厚労科研グループと北関東婦人科がん臨床試験コンソーシアム(GOTIC)プロトコル委員会、JGOG卵巣癌委員会委員有志でプロトコルの骨子を作成しました。同時に、平成20年度から開始された厚労省の新しい研究システムである高度医療評価制度適応の準備を勧め、準備万端整った段階でJGOGの試験として採用いただきました。

本試験は、図1に示しますように、TC療法においてCarboplatinを腹腔内投与(IP)することによって、点滴静注（標準治療）と比較して予後改善可能かどうかを検証する、単純明快な試験です。本試験に至る背景および意義の詳細に関してはプロトコルをお読みいただくとして、本稿ではiPocc試験の重要な特徴についてご紹介いたします。

まず、本試験は前述したように「高度医療評価制度」に基づいて行います。高度医療評価制度は、製薬メーカーなどが「開発治験」を行うメリットのない薬剤の適応拡大試験を医師が行おうとする場合や、新しい医療技術開発研究を行う場合、通常の保険診療と新規治療法を自費請求する混合診療を認める制度です。我が国の保険制度では原則的に、自費診療が一部でも含まれた場合、診療全体が自費となってしまいますが、高度医療評価制度で認定されたものに関しては、混合診療が可能となったのです。すなわち、保険適応のないCarboplatinのIP投与を混合診療として合法的に試行することが可能となったわけです。

しかし本試験のデザインでは、点滴静注は保険診療で行えるがIP投与は自費なってしまい、これではIP群に割り付けられた患者の負担が大きく比較試験は成り立ちません。そこで、IP投与するカルボプラチンを無償提供していただく交渉を行い、ブリストル・マイヤーズ、サンド製薬の協力を得ることが出来ました。さらに、Paclitaxelの毎週投与も保険償還されないことを厚労省保険局から指摘されましたので、この件に関しても交渉の末、日本化薬、沢井製薬から提供していただくことになりました。各社にはこの場を借りて厚く御礼申し上げます。

高度医療評価制度に基づいて試験を行うためには、厚労省の認定を受ける他、無償提供試験薬の管理を薬剤部に依頼する、混合診療の請求を医務課が行うなど種々の院内手続きが必要となります。この点につきましては、北里大学臨床薬理

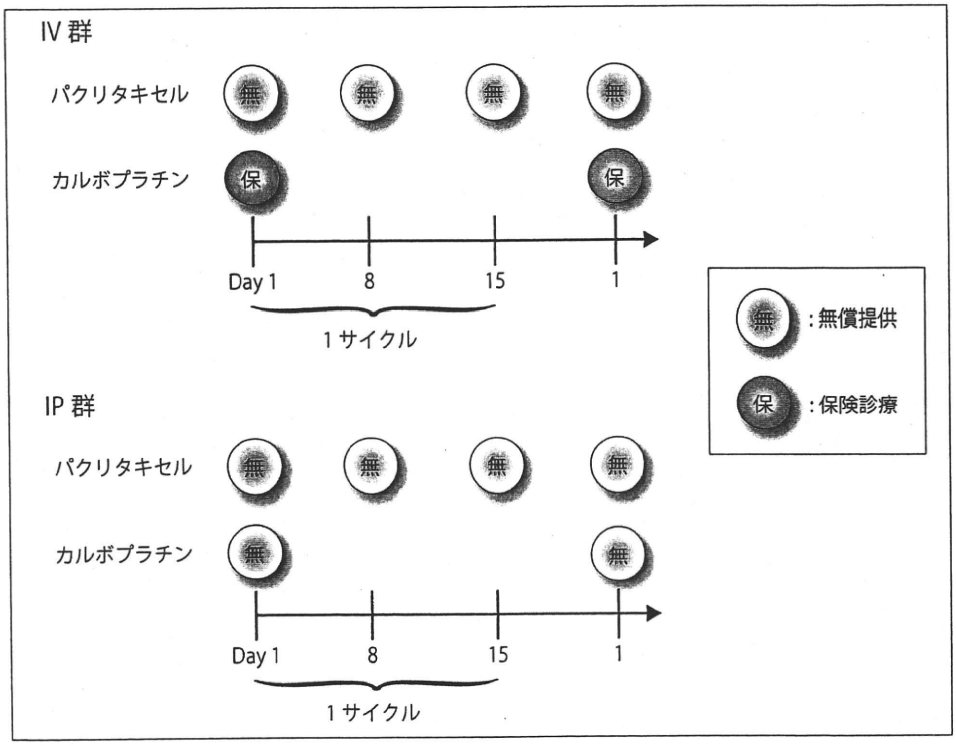

図2 薬剤負担

研究所、臨床試験コーディネーティング(CTCC)部門の全面的協力により、参加希望施設の支援を行っていただけるようになりました。このように、本試験は研究グループやデータセンターの尽力のみならず、厚労省担当官、製薬メーカー、北里CTCCの格別な支援、そして参加施設関係者の協力があって始めて成り立つことが出来ることを強調させていただきたいと思います。

iPoccの科学性に注目しますと、CarboplatinのIP療法の意義を問うだけではなく、suboptimal residual diseaseに対するIP療法の有用性を検証するという、これまでの常識に挑戦する全く新しい研究目標も掲げております。また、婦人科癌領域で始めて本格的にQOLと医療経済効果を評価する意欲的なものでもあります。現在、米国GOG、カナダGCIG関係グループで2つのIP第Ⅲ相臨床試験が行われていますが、試験デザインの複雑さが問題視されています。一方、iPocc試験ではその試験デザインのシンプルさが海外でも高く評価されており、SWOG、KGOG、ANGOGなどが参加する可能性が見えてきてきたため、プロトコルの英訳も開始いたしました。JGOG3016, 3017に続くJGOGの卵巣癌first line試験として全力を挙げて遂行していく所存です。重ねまして先生方のご協力をよろしくお願い申し上げます。

Japanese GOG and Korean GOG Meeting for iPocc Trial
Minutes

Minutes taker: Eriko Aotani

Date: January 27th, 2011

Time: 15:25-16:15

Venue: Gallery Room
Manchester Grand Hyatt Hotel San Diego

Participants: KGOG: Joo-Hyun Nam, Soon Beom Kang, Jae Hoon Kim, Sang Young Ryu, Jae Weon Kim, Hyun Hoon Chung, Seon Hee Kim, and Jong Soon Kim
JGOG: Keiichi Fujiwara, Eriko Aotani, Shoji Nagao, Kosei Hasegawa, and Min Miyata

Minutes

Dr. Fujiwara welcomed all the participants, and Dr. Fujiwara presented the outline of the iPocc trial. Following points were emphasized

1. The iPocc trial has been funded by Japanese government, but so far, no institution in Japan has been financially supported for the operations.
2. Both weekly paclitaxel and IP carboplatin have not been approved for the health insurance coverage in Japan, so that the investigational drugs were donated by pharmaceutical companies including generic makers.
3. These agents can be shipped from Japan to Korea as investigational agents. However, JGOG does not know what will be the issues to be encountered when we export the study agents to Korea. Therefore, we would like to know the actions we have to take, at this moment.
4. Weekly paclitaxel will be covered by the national health insurance in 2-3 month in Japan.

After Dr. Fujiwara's presentation, discussions were made mainly for logistics and operational issues for KGOG.

1. Funding.
   (a) Currently Japanese institutions are not funded at all, but we are currently working hard to allocate the government research fund as per capita to the Japanese institutions.

(b) However, we are not sure whether Japanese government would allow us to send the governmental research fund to a foreign country.

(c) It is expected that we get feed-back from Japanese government in a couple of weeks.

2. Supply of IP port.

(a) In Japan, IP port is covered by insurance, so that it is not provided by the study PI, but we will negotiate with the company whether they can provide the IP port for Korean institutions.

3. Supply of paclitaxel exceeding to the three weekly doses (65mg of paclitaxel per cycle).

(a) Currently, weekly paclitaxel is supplied with free of charge to the participating institutions in Japan from the study PI.

(b) Those drugs are provided by the pharmaceutical companies specifically for this study.

(c) However, paclitaxel will become being covered by the national health insurance in a few months, and there is a possibility those company will stop supplying further, but Dr. Fujiwara will request the companies to continue to provide for the international collaborators.

4. Randomization during surgery.

(a) It will not be an issue for Korean institutions. Either calling in or accessing the web for randomization during surgery is possible.

5. Import/export of the investigational agents from Japan to Korea.

(a) In order to figure out the regulatory requirements in both countries for the importation/exportation of the study agents, the coordinators of KGOG and JGOG will further communicate.

To further precede this project with KGOG, the following investigator was nominated for the study.

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Department of Obstetrics and Gynecology
University of Ulsan College of Medicine
Asan Medical Center
ymkim@amc.seoul.kr
+82-2-3010-3640

It was confirmed that Dr. Fujiwara of JGOG will contact him and discuss further.

The meeting was adjourned.

2nd Japanese GOG and Korean GOG Meeting for iPocc Trial

Minutes

Minutes taker: Keiichi Fujiwara

Date: March 7th, 2011

Time: 11:25-12:00

Venue: Floridian Room Foyer

Astoria Wardolf Hotel Convention Center, Orlando, Fl

Participants: KGOG: Joo-Hyun Nam, Sang-Wun Kim, Jae-Hoon Kim.

JGOG: Keiichi Fujiwara

Minutes

Based on the minutes of January 27th meeting, the following discussion was made.

1. The Korean institution will be funded 100,000 Japanese Yen per patient for iPocc trial. This was approved by Ministry of Welfare Health and Labor.
2. The drug information confirming biological equivalency of the generic drugs for weekly paclitaxel and IP carboplatin should be submitted to Korean FDA. Dr. Fujiwara will ask Sandz, Nippon Kayaku, and Sawai Seiyaku, to supply the information as soon as possible.
3. Labeling of investigational drug will be done in Korea.
4. Supply of IP port was not confirmed, but it has been under the negotiation with port supply company (Japanese vendor).
5. Experience of IP therapy is low (10%) among Korean Gynecologic Oncologist. The most experienced physician, Dr. Young-Tae Kim of Yonsei University Severance Hospital, will help Dr. Fujiwara.
6. Dr. Fujiwara will attend the KGOG Annual Meeting that will be held in Kyung Ju on April 28th, 2011 and present about iPocc Trial.

The meeting was adjourned.

Japanese Journal of Clinical Oncology Advance Access published October 11, 2010

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010
doi:10.1093/jjco/hyq182

Clinical Trial Note

A Randomized Phase II/III Trial of 3 Weekly Intraperitoneal versus Intravenous Carboplatin in Combination with Intravenous Weekly Dose-Dense Paclitaxel for Newly Diagnosed Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Keiichi Fujiwara[1,*], Eriko Aotani[2], Tetsutaro Hamano[2], Shoji Nagao[1], Hiroyuki Yoshikawa[3], Toru Sugiyama[4], Junzo Kigawa[5], Daisuke Aoki[6], Noriyuki Katsumata[7], Masahiro Takeuchi[2] and Mitsuaki Suzuki[8]

[1]Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka-City, Saitama, [2]Clinical Trial Coordinating Center, Kitasato University Research Center for Clinical Pharmacology, Tokyo, [3]Department of Obstetrics and Gynecology, Tsukuba University, Tsukuba, Ibaraki, [4]Department of Obstetrics and Gynecology, Iwate Medical University, Iwate, [5]Department of Gynecologic Oncology, Tottori University Cancer Center, Yonago, Tottori, [6]Department of Obstetrics and Gynecology, Keio University, Shinjuku-ku, [7]Division of Medical Oncology, National Cancer Center Hospital, Tokyo and [8]Department of Obstetrics and Gynecology, Jichi Medical University, Shimono, Tochigi, Japan

*For reprints and all correspondence: Keiichi Fujiwara, Department of Gynecologic Oncology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka-City, Saitama 350-1298, Japan. E-mail: fujiwara@saitama-med.ac.jp

Received July 21, 2010; accepted August 29, 2010

Retrospective studies and a Phase II trial demonstrated the promising efficacy and safety of intraperitoneal administration of carboplatin in ovarian, fallopian tube and primary peritoneal cancer. A Japanese Gynecologic Oncology Group 3016 randomized Phase III trial for these cancers showed dose-dense weekly administration of paclitaxel significant improvement of progression-free survival and overall survival over every 3-week administration. From June 2010, we have been conducting a randomized Phase II/III trial of intravenous versus intraperitoneal administration of carboplatin every 3 week in combination with dose-dense weekly administration of paclitaxel. The purpose of this trial is to prove the superiority of intraperitoneal administration of carboplatin over intravenous administration. Primary endpoint is progression-free survival and secondary endpoints include overall survival, quality of life assessment and cost–benefit. The first 120 patients will be evaluated for the feasibility of intraperitoneal arm and a total of 746 patients will be enrolled in a Phase III study.

Key words: ovarian cancer – intraperitoneal chemotherapy – carboplatin – paclitaxel – dose-dense chemotherapy

INTRODUCTION

In Japan, it is estimated that incidence of epithelial ovarian cancer is approximately 8000 per year and almost half of the patients died of this disease. There is no established screening method; therefore, 60–70% of the patients are at Stages III or IV when newly diagnosed. A standard treatment strategy for the advanced ovarian cancer is a maximum debulking surgery followed by chemotherapy. The standard chemotherapy regimen has been a combination of carboplatin at AUC of 5–6 and paclitaxel at 175 mg/m^2 given intravenously every 3 weeks (1). This regimen has been utilized as standard since 1999, yet the prognosis of advanced ovarian cancer is poor. Numerous efforts have been made to improve the survival, and two distinct innovations on the chemotherapy were achieved recently, which are intraperitoneal chemotherapy and weekly dose-dense administration of paclitaxel.

Three large randomized trials have been conducted in the USA and all of them showed improvement of overall survival (OS) and/or progression-free survival (PFS) (2–4). US

National Cancer Institute and Gynecology Oncology Group (GOG) conducted a metanalysis and found that intraperitoneal (IP) chemotherapy improved OS at the hazard ratio of 0.78 (5). In response to this result, US NCI has issued a clinical announcement in 2006 to recommend IP cisplatin-based chemotherapy for optimally debulked Stage III ovarian cancer patients. In spite of these efforts, IP chemotherapy has not been accepted in the gynecologic cancer community, mainly because of the toxicity. It is expected that replacement of cisplatin to carboplatin may reduce the toxicity without sacrificing the efficacy (6).

Another innovation was the application of dose-dense weekly paclitaxel. Japanese Gynecologic Oncology Group (JGOG) has conducted a large-scale randomized trial and demonstrated significant improvement in PFS and OS (7).

Therefore, it is of great expectation that the combination of dose-dense weekly administration of paclitaxel with IP administration of carboplatin will improve the prognosis further.

This protocol was designed by the Protocol Committee of Gynecologic Oncology Trial and Investigation Consortium (GOTIC) and Ovarian Committee member of JGOG. The protocol was approved by Clinical Trial Review Committee of GOTIC as GOTIC-001 on 9 September 2009, and that of JGOG as JGOG-3019 on 26 April 2010. The protocol was submitted for the Evaluation System of Investigational Medical Care of Ministry of Health, Labor and Welfare, Japan, and was approved to conduct under the Japanese governmental health insurance system on 16 April 2010. This trial was registered at the UMIN Clinical Trials Registry as UMIN000003670 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF GOTIC-001/JGOG-3019

Purpose

This study was designed to prove superiority of IP administration of carboplatin over IV administration in newly diagnosed carcinoma of the ovary, fallopian tube and primary peritoneum. The combination of paclitaxel is the dose-dense weekly fashion based on the JGOG-3016 trial result.

Study Setting

This is a multi-institutional randomized Phase II/III trial.

Resource

Grants-in Aid for Cancer Research (H21–014), from the Ministry of Health, Labor and Welfare, Japan. Gynecologic Oncology Trial and Investigation Consortium and JGOG support this trial.

Endpoints

The primary endpoint of this study is PFS. Secondary endpoints are OS, response rate in patients with measurable disease, quality of life assessment and cost–benefit.

Eligibility Criteria

(i) The patient must be planned to undergo laparotomy surgery for formal registration. Since this trial includes patents with both optimal and suboptimal residual disease, the patients with exploratory laparotomy are also eligible.
(ii) Patient who is preoperatively anticipated to be FIGO II to IV epithelial ovarian, fallopian tube or primary peritoneal cancer is eligible for pre-registration. And the patient must be clinically at Stages II–IV at the time of formal registration.
(iii) Patient who signed the consent for the placement of IP port system when she is assigned to the IP arm.
(iv) The patients who are planned to receive chemotherapy within 8 weeks after initial surgery.
(v) ECOG performance status must be 0–2.
(vi) Patient must have adequate organ functions.
(vii) Survival can be expected 3 month or more.
(viii) Age 20 or older.

Written informed consent must be obtained from the patient or legal guardian.

Exclusion Criteria

(i) Patients with borderline malignancies.
(ii) Patients who have received chemotherapy or radiation therapy for the current disease before enrolment.
(iii) Patients with any of the active concurrent malignancies or past history of malignancies of which the follow-up is within 5 years.
(iv) Patients with severe complications: patients with severe heart disease or cerebrovascular disease, or uncontrolled diabetes or hypertension, pulmonary fibrosis, interstitial pneumonitis, active bleeding, active gastrointestinal ulcer or sever neuropathy.
(v) Patients with history of hypersensitivity polyoxyethylene castor oil.
(vi) Patients with pleural effusion that need continuous drainage.
(vii) Patients with active infectious disease.
(viii) Patients with possibility of pregnancy or under breast-feeding.
(ix) Patients with symptomatic brain metastasis.
(x) Patients whose circumstances at the time of entry onto the study would not permit completion of study or required follow-up.

Study Flow

The patient who is anticipated to have Stage II, III or IV carcinoma of the ovary, fallopian tube or primary peritoneum will be pre-registered through Web Registration System of Kitasato University Clinical Trial Coordinating Center (CTCC), after written informed consent was obtained. At the time of surgery, the physician will call to the Kitasato CTCC

before closure of the abdominal wall. The coordinator will ask the stratification factors, clinical stages and the size of residual disease, then randomization result will be informed. This is considered as a formal registration. When the patient is randomized to IP arm, the Bard IP Port (#14 Fr) will be placed according to the surgical manual. For patient who randomized to the IV arm, IP port will not be placed. The protocol chemotherapy will be started within 8 weeks after confirmation of histology as epithelial cancer.

Control Arm Treatment

For patients randomized to IV arm will receive paclitaxel at 80 mg/m^2 as 1 h intravenous (IV) infusion followed by carboplatin at AUC 6 as a 30–120 min IV infusion on Day 1. IV administration of paclitaxel will be repeated at 80 mg/m^2 on days 8 and 15. This regimen is considered as one cycle.

Experimental Arm Treatment

For patients randomized to IP arm will receive paclitaxel at 80 mg/m^2 as 1 h IV infusion. During the paclitaxel infusion, 1000–1500 ml physiological saline or 5% glucose will be administered through IP port. This will allow the confirmation that IP port is not obstructed and dense adhesion does not occur surrounding the catheter. After completion of the hydroperitoneum, carboplatin at AUC 6 will be infused. To confirm that the hypersensitivity of carboplatin does not occur, 10 ml will be administered and after waiting for 10 min, the rest of the amount will be infused. These procedures will be done on day 1. IV administration of paclitaxel will be repeated at 80 mg/m^2 on days 8 and 15. This regimen is considered as one cycle.

Number of Cycles

The protocol treatment will be repeated for six cycles for patients with chemotherapy only after primary surgery. However, in patient, who will undergo interval debulking surgery after response to the suboptimal residual disease, they may receive up to eight cycles. Interval debulking surgery can be performed after three to five cycles of protocol chemotherapy, and then patient can receive three more cycles of chemotherapy.

Study Design and Statistical Considerations

This study was designed as a randomized Phase II/III trial.

Target sample sizes and event were as follows.

Phase A: 60 patients/arm
Phase B: 510 events (target sample size: 746 patients, including Phase A patients)

Planned patient accrual duration is 3 year and planned follow-up duration will be either 3 year or until the time when the 510 events are observed, whichever it comes first.

Sample sizes were determined based on the following considerations.

Phase II Part (Phase A)

In the previous JGOG-3016 study, treatment completion rate for dose-dense pacliaxel plus carboplatin (dd-TC) was 47.0%, and hematologic adverse event (more than or equal to grade 3) rate for dd-TC was the following, neutropenia: 91.7%, leukocytes: 80.4%, hemoglobin: 68.6%, platelets: 43.6%. Furthermore, the response rate for dd-TC was 55.8%. According to above evidence, we performed statistical simulations for these factors to find a sample size which would be necessary to obtain 95% confidence intervals of these estimates with 15% precisions in the IV arm, and we calculated that 46 patients is needed. We also assumed that treatment completion rate in the IP arm is expected to be lower than the IV arm and hematologic adverse event rates defined above are expected to be higher, thereby the required sample size in the IP arm would be larger than those of the IV arm. Furthermore, we also assumed that some patients would not have a measurable site. Thus, we plan the sample size of 120 patients (60 patients for each arm) to be targeted. Phase II patients will be included in the Phase III analysis.

Phase III Part (Phase A + Phase B)

The primary endpoint of this study is PFS. In the previous JGOG3016 study, the median PFS was approximately 28 months for dd-TC. Furthermore, in a meta-analysis conducted by the National Cancer Institute (NCI) and the Gynecologic Oncology Group, the hazard ratio for PFS in the IP as compared with the IV was 0.784, indicating the 21.6% hazard reduction in the IP treatment).

According to above evidence, we assumed that the median PFS was 28 months for the IV arm and the hazard ratio for PFS in the IP arm as compared with the IV arm was 0.78. The 22% hazard reduction would be acceptable as a new standard treatment regimen. With an accrual period of 3 years and a minimum follow-up period of 3 years, 746 patients (373 patients for each arm) and 510 events (239 in IP arm) are required in order to detect this hazard ratio using the log-rank test with an overall two-sided type I error of 0.05 and a power of 80%. The final analysis will be performed either after the required events will be observed or after the minimum follow-up period will be completed, whichever comes first. If the required events will not be observed after the minimum follow-up period will be completed, extension of the follow-up duration will be considered.

Randomization and Stratifications

Patients will be centrally randomized. A minimization technique will be used for random treatment allocation stratifying by the enrolling institutions, initial FIGO stage of disease (II, III or IV) and the size of residual disease (complete, less than 1 cm, between 1 and 2 cm and more than 2 cm).

Analysis Method

Phase III part: analysis set. Efficacy analyses will be performed on all randomly assigned patients based on the intent-to-treat principle. Patients receiving at least one partial infusion of the study drug will be qualified for safety analysis.

Primary efficacy analysis. The PFS curves will be estimated using Kaplan–Meier method. Non-parametric 95% confidence intervals will be calculated for the median PFS, and the curves will be compared in the two treatment groups based on the two-sided log-rank test with an overall significance level of 5%. Multiplicity adjustments in regard to interim analysis will be noted in the section of the interim analysis.

Secondary efficacy analysis. The OS curves will be also estimated using Kaplan–Meier technique and compared using log-rank test. The response rates in the case with measurable site, and the treatment completion rates will be estimated by arms. We define the treatment completion case as the patient who receives treatment to the sixth cycle. Exact 95% confidence intervals will be calculated for each response rate and treatment completion rate. The rates for the two treatment groups will be compared using Fisher's exact test and a normally approximated 95% confidence interval for the odds ratio.

Interim analysis. Under the proportional hazard assumption, alternative hypothesis and uniformly patients' enrollment, the half of the required events (255 events) would be observed when approximately 3.2 years go by from a starting point of this trial. One interim analysis will be carried out either when 3.5 years go by from a starting point of this trial or when the required events will be observed, whichever comes first. In order to maintain an overall significance level of 5%, the PFS curves would be compared with Type I error of 0.3% in the interim analysis and of 4.7% in the final analysis calculated by the O'Brien and Fleming-type alpha spending function.

Subgroup analysis. In order to support analyses of primary and secondary endpoints, all comparisons and estimates will be stratified by randomization factors and other demographic data.

Exploratory analysis. Statistical models (e.g. Cox's proportional hazard model and logistic regression model) will be used for further explorations.

Safety analysis. The number of patients for each adverse event will be summarized for each treatment group. The rates of adverse events will be estimated for each group and compared using an approximate 95% confidence interval for the odds ratio.

Quality of life and Cost-effectiveness analyses. Quality of life (QOL) and cost-effectiveness (CE) of IP arm and IV arm will be analyzed when 2 years go by from a starting point of this trial, assuming that 300 qualified patients would be observed at that time. CE data are also analyzed at the same time of QOL analysis. These endpoints will also be analyzed after the study completion (or study termination) with efficacy endpoints. Baseline QOL score will be analyzed using linear model adjusting for age and baseline ECOG performance status (PS). Other QOL scores will be analyzed using linear mixed model with age, PS and baseline QOL scores. Further details of QOL and CE analysis will be specified in the statistical analysis plan.

Analysis results of QOL evaluation will be published after 2 years go by from a starting point of this trial, assuming that 300 qualified patients would be observed at that time. For CE analysis, we define the analysis set of all patients who will be registered and agreed with informed consents of CE analysis. Analysis and report of cost-effectiveness with primary endpoints will be reviewed.

Feasibility Analysis. In the Phase II period, the feasibility of combination of IV dose-dense paclitaxel and IP carboplatin will be evaluated. The number of patients for treatment completion, hematologic and non-hematologic toxic effects will be summarized for each treatment group. The rates of toxic effects will be estimated for each group. Furthermore, the rates at the end of the treatment will be estimated for each treatment group. Exact 95% confidence intervals will be calculated for each rate. These rates for the two treatment groups will be compared using Fisher's exact test and an approximate 95% confidence interval for the odds ratio to aid the IDMC in reaching decisions about study continuation.

Study Monitoring

Study monitoring will be performed by the Kitasato University Clinical Trial Coordinating Center, to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. On-site monitoring on the selective institution will be performed once a year. The monitoring reports will be submitted to the Independent Data and Safety Monitoring Committee every 6 months.

Participating Institutions

Leading institution as the study under the Evaluation System of Investigational Medical Care (ESIMeC) is Saitama Medical University International Medical Center. Other institutions waiting for the governmental approval for the ESIMeC as of 15 July 2010 are as follows. Iwate University, Jichi Medical University, Keio University, National Cancer Center Hospital, Tottori University, Tsukuba University, Gunma University and Saitama Medical University Medical Center. Other institutions are under the process of ESIMeC submission.

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Conflict of interest statement

None declared.

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高度医療評価制度を用いた大規模第Ⅲ相がん臨床試験への取り組み

■

First Attempt of Large Phase Ⅲ Oncology Trial Using Japanese New Trial Evaluation System, the Evaluation System of Investigational Medical Care

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ABSTRACT

Background This is the first attempt to conduct a large-scale phaseⅢ oncology trial using the Evaluation System of Investigational Medical Care (ESIMeC).

Methods The study design is a randomized phaseⅡ/Ⅲ trial comparing administration routes of carboplatin either intravenously (IV) or intraperitoneally (IP) in combination with weekly administration of paclitaxel for ovarian cancer patients. Target accrual is 746. Both IP carboplatin and weekly paclitaxel have not been approved for national insurance coverage in Japan.

Results Because of the expensive drug cost, it was first assumed impossible to conduct the trial if the study chair is responsible for purchasing the investigational drugs from the limited research grant or the patients have to pay for the investigational drugs without insurance coverage. Therefore, we negotiated with the pharmaceutical companies including generic makers to supply the investigational drugs with free of charge. The duration from initial consultation to the Ministry of Health, Labor, and Welfare to the finial approval to conduct the trial using ESIMeC was 8 months.

Conclusion The ESIMeC appears to be an efficient system as the official evaluation process of investigator-initiated, non-indication directed clinical trials, which manifestly require quality control of the trials. However, cost coverage for the investigational medicine or technique remains as an important issue to be resolved in the future, especially in large phaseⅢ oncology trials.

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KEY WORDS Evaluation System of Investigational Medical Care, Cancer, Weekly paclitaxel, Intraperitoneal carboplatin, PhaseⅢ oncology trial

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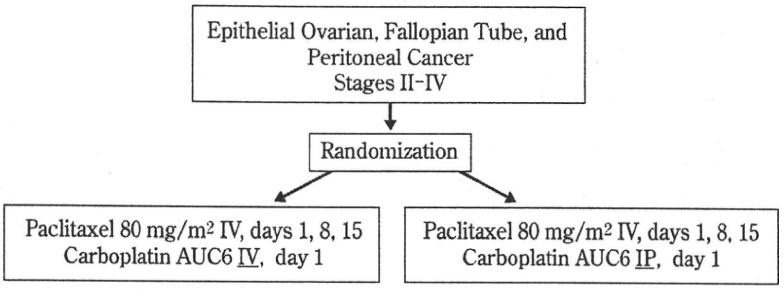

図 1　iPocc 試験デザイン

はじめに

がん治療においては，すでに厚生労働省による製造販売承認を得た抗がん剤を用いて，多剤併用化学療法や手術・放射線治療との集学的治療を行うことが多い。したがって，がん治療法開発の一端は，研究者が実臨床で実施する臨床試験の成果が担っていると言える。

わが国において未承認または適応外の抗がん剤（用法・用量の変更を含む）を用いた臨床試験を行う際，最も障害となるのは，試験対象となる新規治療技術や薬剤が保険償還されず，さらに保険診療と自費のいわゆる混合診療が禁じられていることである。この点を是正するため，2008 年 3 月 31 日に厚生労働省より「高度医療評価制度に関する通知」が発出され，この制度を用いた臨床試験が 4 月より実施可能となった。本制度では，試験実施計画書を高度医療評価会議で審査し，科学的・倫理的妥当性が評価される。その後，先進医療専門家会議に送られ，同時に保険局の指示で自費診療部分と保険診療部分が切り分けされたうえで，厚生労働大臣名で承認された後に地方厚生局に伝達され，申請施設での試験開始が可能となる。

本制度に基づく医療は「第 3 項先進医療技術」として公示される[1]。2010 年 6 月 1 日現在 23 の医療が承認されているが，このほとんどが新規医療技術に対するものであり，抗がん剤を用いた臨床試験としては，東京大学医学部附属病院が申請した paclitaxel 腹腔内投与の有用性を検証する第 II 相試験のみであった。

われわれは今回，高度医療評価制度を用いて多施設共同第III相比較試験を行うことを目的に準備を進め，先進医療としての実施承認にこぎつけた。わが国初となるこの経験を報告するとともに，本制度の意義および問題点について考察したい。

I　対象と方法

1　試験内容

本試験は，平成 21 年度厚生労働科学研究費補助金（がん臨床研究事業），進行卵巣：腹膜癌に対する腹腔内化学療法確立のための研究（H21-がん臨床一般-014）として平成 21 年 4 月から準備を開始した。試験目的は，癌性腹膜炎を伴う卵巣癌・腹膜原発癌・卵管癌に対して，現在の標準治療法である静注（IV）paclitaxel＋IV carboplatin の併用療法と比べて，carboplatin を腹腔内（IP）投与することによって予後を改善できるかどうかを検討するものである（iPocc 試験）。具体的な試験デザインは以下の通りである（**図 1**）。

IV 群（標準治療群）：

paclitaxel：80 mg/m^2　1 時間点滴静注　days 1，8，15

carboplatin：AUC＝6.0　1 時間点滴静注　day 1

3 週（21 日）を 1 サイクルとして 6〜8 サイクル繰り返す。

IP 群（試験治療群）：

paclitaxel：80 mg/m^2　1 時間点滴静注　days 1，8，15

carboplatin：AUC＝6.0 one shot 腹腔内投与　day 1

3 週（21 日）を 1 サイクルとして 6〜8 サイクル繰り返す。