kepada keadaan. Juga imunoterapi mungkin boleh digunakan sebagai pilihan rawatan.

Potensi manfaat dan keburukan mengambil bahagian dalam kajian klinikal ini

Ia tidak diketahui sama ada penyertaan anda dalam kajian ini akan memberi manfaat kepada anda secara langsung. Doktor yang merawat anda menjangkakan bahawa rawatan dalam kajian klinikal ini akan menyekat perkembangan dan berulang kanser tanpa menyebabkan kesan sampingan yang kuat; walau bagaimanapun,kami tidak boleh berjanji ini adalah kes tersebut.

Terdapat kedua-dua kebaikan dan keburukan kepada kedua-dua rawatan yang terlibat dalam kajian klinikal ini. Salah satu daripada kebaikan untuk memberi kedua-dua ubat-ubatan secara intravena mungkin adalah bahawa lebih mudah untuk meramalkan apakah kesan sampingan yang akan muncul, kerana rawatan ini telah digunakan lebih lama. Sebaliknya, pemberian peritoneal boleh menyebabkan lebih banyak kesan sampingan; walau bagaimanapun, ini mungkin dapat dikawal dan menghasilkan kesan terapeutik yang lebih baik. Walau bagaimanapun, dengan pemberian peritoneal, pesakit lebih cenderung untuk mengalami kesan sampingan, yang hampir tidak pernah berlaku dalam pemberian intravena (seperti sakit abdomen atau peritonitis) dan yang mungkin merupakan potensi yang merugikan.

Ini adalah hanya anggaran pada tahap "mungkin" , yang kami pertimbangkan daripada hasil kajian klinikal yang kecil dan pengalaman dari masa lalu. Kajian klinikal ini dijalankan untuk menjelaskan keseimbangan kebaikan dan keburukan dalam rawatan ini.

Kami tidak dapat menjamin anda satu manfaat yang jelas pada peringkat ini; walau bagaimanapun, maklumat yang kami boleh diperolehi daripada kajian klinikal ini mengenai kesan dan kesan sampingan yang dikaitkan dengan rawatan ini akan digunakan pada masa hadapan untuk rawatan ramai pesakit yang mempunyai gangguan yang sama seperti anda.

Garis panduan yang kajian ini patuhi

Kajian klinikal ini dilakukan dengan mematuhi Deklarasi Helsinki, yang menggariskan prinsip-prinsip etika perubatan. Kajian ini juga mematuhi garis panduan etika yang berkaitan untuk penyelidikan klinikal di negara ini.

Tidak bersetuju untuk penyertaan tidak mengakibatkan kerugian

Berhubung dengan penyertaan anda dalam kajian ini, kami akan meminta anda untuk membuat keputusan secara sukarela. Anda tidak akan mengalami kerugian dalam rawatan atau penjagaan masa walaupun anda tidak bersetuju. Anda mungkin bimbang pakar perubatan yang merawat akan tersinggung atau anda mungkin tidak dapat menerima rawatan mencukupi jika anda tidak bersetuju untuk mengambil bahagian; walau bagaimanapun, ini tidak benar. Walaupun anda memilih untuk tidak mengambil bahagian dalam kajian ini, doktor yang merawat anda akan menerangkan pilihan rawatan yang lain, sila berbincang dengan teliti dengan pakar perubatan yang merawat anda.

Perjanjian boleh dibatalkan pada bila-bila masa selepas itu

Anda boleh membatalkan penyertaan anda dalam kajian ini pada bila-bila masa. Walaupun selepas rawatan telah bermula, anda boleh membatalkan penyertaan untuk sebarang sebab (seperti tidak mampu untuk menanggung kesan sampingan). Jangan teragak-agak untuk berbincang dengan pakar perubatan yang merawat anda. Walaupun kajian klinikal ini dihentikan, satu lagi rawatan yang sesuai akan disediakan untuk anda.

Walau bagaimanapun, jika anda tidak dapat meneruskan rawatan kajian dan menentukan lawatan ke hospital, data yang dikumpulkan sebelum ini akan digunakan sehingga waktu ini. Juga, jika rawatan dihentikan, anda perlu pergi ke hospital untuk pemerhatian susulan sama ada kanser telah berulang.

Maklumat mengenai kajian

Kedua-dua ubat yang digunakan dalam kajian ini telah dipasarkan. Jika maklumat baru dan penting telah diperolehi semasa penyertaan anda dalam kajian ini, kami akan menyediakan anda dengan maklumat untuk mengesahkan penyertaan anda yang berterusan dalam kajian ini .

Keputusan akhir kajian klinikal ini boleh didapati selepas beberapa tahun. Apabila keputusan dimuktamadkan, pakar perubatan yang merawat anda akan memberikan anda penjelasan mengenai keputusan akhir kajian klinikal ini.

Perlindungan maklumat peribadi

Sebahagian daripada rekod perubatan anda akan dihantar kepada Pusat Penyelarasan Percubaan iPocc (Pusat Penyelidikan Universiti Kitasato untuk Farmakologi Klinikal, Pusat Penyelarasan Percubaan Klinikal: 5-9-1 Shirokane, Minato-ku, Tokyo Japan). Kakitangan kajian Pusat Penyelarasan boleh melihat rekod yang mengandungi maklumat perubatan anda; walau bagaimanapun, laporan tersebut tidak mengandungi maklumat peribadi anda.

Untuk memeriksa yang kajian klinikal ini telah dijalankan dengan sewajarnya, kakitangan yang dilantik, seperti juruaudit dan monitor, boleh melihat rekod tersebut. Selain itu, mungkin ada siasatan mengenai kajian oleh para wakil pihak berkuasa kerajaan, seperti Menteri Kesihatan, Buruh dan Kebajikan (MHLW) di Jepun. Dalam semua kes-kes ini, kami akan mengambil penjagaan sepenuhnya dalam melindungi maklumat peribadi dan privasi anda.

Keputusan yang diperolehi dalam kajian ini akan digunakan untuk mengesahkan keselamatan dan keberkesanan rawatan yang digunakan. Kami merancang untuk menerbitkan hasil kajian yang akan dibentangkan pada mesyuarat perubatan dan jurnal akademik. Walau bagaimanapun, anda diberi jaminan yang maklumat peribadi anda (seperti nama anda) tidak akan diterbitkan, kerana hasil kajian akan dilaporkan sebagai agregat kira-kira 746 pesakit.

Dalam kes-kes kesan sampingan

Kami akan menjalankan rawatan dengan teliti; walau bagaimanapun, ada kemungkinan bahawa bahaya kesihatan mungkin berlaku semasa kajian atau selepas selesainya kajian berhubung dengan rawatan yang telah anda terima. Anda tidak akan diberi pampasan kewangan pada dasarnya, sama dengan mana-mana kajian klinikal yang menyelidik kesan ubat-ubatan anti-kanser. Walau bagaimanapun, jika sebarang kesan sampingan berlaku, kami akan memberikan rawatan yang sesuai. Fi yang terhasil untuk situasi tersebut akan dilindungi oleh insurans kesihatan dengan sebahagian bayaran daripada pesakit sendiri.

Kajian klinikal ini dilindungi oleh insurans percubaan klinikal di Jepun. Dalam sesetengah kes, jika anda tercedera akibat kesalahan dalam protokol kajian itu, yang menyatakan prosedur untuk kajian, pampasan mungkin dilindungi dengan insurans ini. Ia adalah penting bahawa anda memberitahu pakar perubatan anda, jika anda merasa bahawa anda telah cedera kerana mengambil bahagian dalam kajian ini bukan sahaja semasa

kajian tetapi juga selepas tamat pengajian.

Permintaan bagi pesakit yang menyertai kajian

Semasa tempoh kajian, kami meminta anda untuk bekerjasama dalam pemeriksaan yang diperlukan bagi penilaian yang sesuai bagi kesemua rawatan, di samping untuk keselamatan anda. Juga, jika anda mengalami sebarang keadaan fizikal yang tidak normal, sila dapatkan rawatan daripada pakar perubatan yang merawat anda secepat mungkin. Jika anda perlu pergi ke hospital lain, anda perlu memberitahu mereka bahawa anda sedang mengambil bahagian dalam kajian klinikal, dan beritahu pakar perubatan yang merawat anda di institusi ini bahawa anda telah berjumpa seorang doktor di luar. Sila pastikan untuk memberitahu pakar perubatan yang merawat anda sekiranya anda mengambil sebarang ubat-ubatan lain (termasuk ubat-ubatan dan makanan tambahan yang dibeli di kaunter). Jika anda mempunyai sebarang soalan mengenai kajian klinikal ini, jangan teragak-agak untuk bertanya pakar perubatan yang merawat anda pada bila-bila masa.

Permintaan untuk pesakit dengan liang reservoir peritoneal yang diimplan

Dalam contoh yang sangat jarang berlaku, anda mungkin diminta berhenti di pengesan logam di lokasi seperti pintu lapangan terbang . Kami mengesyorkan supaya anda membawa dokumen diagnosis, di samping kad yang menunjukkan anda mempunyai liang reservoir peritoneal yang diimplan. Anda akan selamat untuk menjalani pemeriksaan seperti X-ray/MRI/CT semasa liang itu diimplan.

Penilaian etika kajian klinikal ini

Kajian klinikal ini telah diselidik dengan teliti oleh ramai golongan profesional perubatan. Selain itu, kajian ini diluluskan oleh lembaga institusi kajian (IRB) sebagai mempertimbangkan perlindungan hak-hak dan keselamatan pesakit. Kakitangan hospital yang terlibat dalam kajian klinikal juga akan bertindak untuk melindungi mereka. Jika anda mempunyai pertanyaan mengenai hak-hak pesakit, sila hubungi butiran di bawah ini.

Kajian klinikal ini disemak oleh:

Nama:

Pengasas:

Alamat:

URL web:

Butir-butir hubungan penyelidik untuk kajian ini adalah seperti berikut:

Penyelidik

Nama:

Hubungi (affiliasi): (panggilan)

No tel.:

Jika anda mempunyai sebarang aduan berkaitan dengan kajian ini, anda boleh bercakap kepada orang yang tidak terlibat secara langsung dalam kajian ini. Sila hubungi orang di bawah:

Wakil pesakit

Nama wakil pekerja

Affiliasi (panggilan)

No. tel

Dana penyelidikan dan konflik kepentingan

Kajian klinikal ini diasaskan terutamanya oleh Geran Penyelidikan Sains Kesihatan Buruh dari MLW, dengan perbelanjaan penyelidikan, sebahagiannya dibayar oleh GOTIC (Percubaan Onkologi Gynecologic dan Konsortium Penyiasatan) dan JGOG (Kumpulan Onkologi Gynecologic Jepun).

Di Nama hospital:_____, kami pastikan supaya semua kakitangan yang terlibat secara langsung dalam kajian ini tidak dalam keadaan di mana mereka boleh mendapat keuntungan secara peribadi daripada kajian ini (ini dikenali sebagai percanggahan kepentingan). Juga, ahli-ahli pasukan kajian yang lain di institusi yang lain serta yang ada di Pusat Penyelarasan Percubaan iPocc telah menjalani penilaian terhadap konflik kepentingan yang berkaitan kajian oleh pihak berkenaan.

Maklumat kajian secara terbuka

Kajian ini didaftarkan dalam daftar UMIN percubaan klinikal (Rangkaian Maklumat Universiti Hospital Universiti) dalam Bahasa Jepun http://www.umin.ac.jp/ctr/index-j.htm, serta clinical.gov dalam Bahasa Inggeris http:// clinicaltrials.gov / untuk tujuan menjadikan maklumat kajian tersedia kepada orang ramai. Maklumat seperti kaedah, kemajuan, dan hasil kajian boleh diperolehi oleh sesiapa sahaja melalui internet.

Nota akhir

Mengambil bahagian dalam kajian ini adalah pilihan anda. Anda boleh memilih sama untuk mengambil bahagian atau tidak mengambil dalam kajian ini. Jika ada apa-apa yang tidak jelas, jangan teragak-agak untuk bertanya pakar perubatan yang merawat anda pada bila-bila masa.

Jika selepas pertimbangan teliti anda membuat keputusan untuk mengambil bahagian dalam kajian klinikal ini, sila tangan dan tarikhkan borang persetujuan pada halaman seterusnya dan serahkan kepada pakar perubatan yang merawat. Kami akan membuat satu salinan borang persetujuan untuk anda simpan.

Borang Persetujuan Pesakit

Kepada pengarah (nama hospital)_____

Tarikh penerangan (HH / BB / TTTT)

Pakar perubatan yang menyediakan maklumat

Nama Jabatan

Nama pakar perubatan (tandatangan)

Saya telah diberi semua salinan XX (masukkan jumlah muka surat) muka surat borang ini. Saya telah membaca maklumat kajian termasuk QOL dan kos penyelidikan atau ia telah dibacakan kepada saya. Saya faham maklumat tersebut dan soalan saya telah dijawab. Saya bersetuju untuk mengambil bahagian dalam kajian ini, "**Fasa rawak II / III percubaan intravena (IV) Paclitaxel seminggu sekali ditambah dengan IV Carboplatin setiap 3 minggu sekali berbanding IV Paclitaxel seminggu sekali ditambah dengan intraperitoneum (IP) Carboplatin sekali setiap 3 minggu di kalangan wanita dengan kanser ovari epitelium , tiub fallopio atau peritoneal primer** "

- □ **Saya akan mengambil bahagian dalam kajian termasuk QOL dan kos penyelidikan**
- □ **Saya akan mengambil bahagian dalam kajian ini kecuali kos penyelidikan**

Nama pesakit (tandatangan) Tarikh

Nama wakil yang sah [jika perlu] Tarikh
Hubungan dengan pesakit
* Isi hanya apabila diperlukan (tandatangan)

Saya mengesahkan bahawa saya telah diberikan penerangan yang mencukupi mengenai kajian di atas, bahawa persetujuan telah diperolehi dari pesakit, dan bahawa saya telah menyerahkan satu salinan maklumat dan borang persetujuan pesakit.

Pakar perubatan yang merawat (tandatangan) Tarikh

V. 文 献

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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

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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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A phase I study with an expanded cohort to assess the feasibility of intraperitoneal carboplatin and intravenous paclitaxel in untreated ovarian, fallopian tube, and primary peritoneal carcinoma: A Gynecologic Oncology Group study

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ABSTRACT

Objective. This study aimed to determine the first-cycle maximum tolerated dose (MTD) of intraperitoneal carboplatin in combination with intravenous paclitaxel and then assess the feasibility of this dose over multiple cycles.

Methods. Beginning at an intraperitoneal (IP) carboplatin dose area under the curve (AUC) of 5 and a fixed intravenous dose of 175 mg/m^2 paclitaxel, patients were entered on a dose-escalating phase evaluating first-cycle dose-limiting toxicity (DLT). After estimating the MTD, cohorts of 20 patients were then entered in an expanded phase to evaluate DLT over four cycles.

Results. Twenty-one patients were entered on the dose-escalating phase. A first-cycle MTD of carboplatin at AUC 8 was tolerated although thrombocytopenia was dose-limiting over multiple cycles. An additional 69 patients were treated in expanded cohorts. Only 5/90 (5.6%) patients discontinued treatment because of a port problem. Four-cycle DLT required de-escalation to a carboplatin AUC of 6, and even at that dose, there were 14 dose-limiting toxic effects in 40 patients (35%). Seven dose-limiting toxicities were due to neutropenia, and 6 were due to grade 3/4 thrombocytopenia. Six cycles of therapy were completed in 75% of eligible patients, but dose adjustments were required.

Conclusions. The first-cycle MTD did not predict the tolerability of this regimen over multiple cycles. Using an IP carboplatin dose of AUC 6 in combination with paclitaxel, the regimen can be administered with a high completion rate over multiple cycles. Because neutropenia is a frequent DLT, the addition of hematopoietic growth factors may permit a high completion rate while maintaining this dose.

Introduction

Cytoreductive surgery followed by combined platinum and taxane chemotherapy is the accepted standard treatment for patients with advanced epithelial ovarian cancer [1]. In patients with small volume residual disease, three large randomized Phase III studies comparing intraperitoneal (IP) to intravenous (IV) cisplatin-based chemotherapy have reported favorable survival results for the IP arms [2–4]. Despite this, IP cisplatin-based chemotherapy has not been widely utilized as a standard treatment because of issues regarding toxicity and difficulties with administration. Although IV administration of carboplatin is as efficacious as cisplatin but less toxic, early studies have suggested inferiority of IP carboplatin [5,6]. However, pharmacological data now show that more than 2/3 of free platinum enters into the systemic

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circulation after IP carboplatin administration, and Miyagi et al. demonstrated that the 24-hour free platinum area under the curve (AUC) in the serum was identical with IP or IV administration [7,8]. Concentrations may be even higher in retroperitoneal lymph nodes [9]. A Japanese study found that patients treated with greater than 400 mg/m^2 of IP carboplatin had a significantly longer survival than patients treated with lesser doses [10]. A Greek Phase III trial of IP or IV carboplatin at 350 mg/m^2 with intravenous cyclophosphamide showed excellent response rates (75%) and equivalent survival [11].

In an effort to find a less toxic intraperitoneal chemotherapy regimen, the Gynecologic Oncology Group (GOG) initiated a series of Phase I trials evaluating regimens utilizing IP carboplatin. We report the results of an international, multi-institutional Phase I trial of intraperitoneal carboplatin combined with intravenous paclitaxel in women with chemotherapy-naive ovarian, primary peritoneal, or fallopian tube cancer. This study evaluates the combination of intraperitoneal carboplatin with intravenous paclitaxel, with the goal of determining the optimal dose of IP carboplatin to be used with IV paclitaxel in a randomized Phase III trial. Recognizing that a Phase I maximum tolerated dose (MTD) based on first-cycle dose-limiting toxicity (DLT) may not determine a dose that is acceptable over many cycles in a Phase III trial, we used an expanded cohort methodology to explore the effect of the regimen given at first-cycle MTD over multiple cycles.

Patients and methods

Eligibility criteria

Eligible patients had to be ≥18 years of age and have previously untreated stage II, III or IV, epithelial ovarian, primary peritoneal or fallopian tube carcinoma regardless of residual disease following surgery. A GOG Performance Status of ≤2 was required, and patients were entered within 12 weeks of surgery. Patients had to have adequate bone marrow function (absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L, platelets $\geq 100\times10^9$/L), renal function (creatinine ≤1.5× institutional upper limit normal (ULN)), hepatic function (bilirubin ≤1.5×ULN, ALT, AST, and alkaline phosphatase ≤2.5×ULN) and neurologic function (sensory or motor neuropathy ≤grade 1). After Institutional Review Board approval, written informed consent consistent with all federal, state and local requirements was obtained from all patients before study entry.

Treatment plan

On day 1 of each 21-day treatment cycle, paclitaxel was administered as a 3-hour IV infusion. The paclitaxel dose was kept constant at 175 mg/m^2. One liter of saline or 5% dextrose in water was infused IP during or after the IV paclitaxel. This was followed by the IP administration of carboplatin at the assigned dose in 100 cm^3 to 1000 cm^3 of normal saline as rapidly as possible (usually 15 minutes). The IP carboplatin dose was started at an AUC 5 and was calculated by the Calvert formula with the creatinine clearance being estimated by the method of Jelliffe [12]. The volume used for the IP carboplatin was left to the investigator's discretion based on body size (1000 cm^3 recommended). No attempt was made to drain the infusate, although ascites could be drained prior to infusion if a large amount was present. Routine premedication to prevent hypersensitivity, nausea, or vomiting was used and included dexamethasone, diphenhydramine and cimetidine. Ondansetron or granisetron were suggested as antiemetics given prior to the IP carboplatin. Patients could receive up to eight cycles of therapy during the dose-seeking phase, but the protocol was amended to only allow a maximum of six cycles for the expanded phase. Commercially available carboplatin (Paraplatin®, Bristol-Myers Squibb Oncology) and paclitaxel (Taxol®, Bristol-Myers Squibb Oncology) were used.

Evaluation during study

Pretreatment evaluation consisted of a history and physical examination, chest X-ray, complete blood count, prothrombin time, activated partial thromboplastin time, CA-125 testing, serum electrolytes, creatinine, liver function tests, electrocardiogram. A baseline imaging study (computed tomography scan or magnetic resonance imaging of the abdomen and pelvis) was performed in patients with greater than 1 cm residual nodules after surgery. Complete blood function tests were obtained prior to each cycle. The FACT/GOG-NTX questionnaire was administered after each cycle to evaluate neurotoxicity. Patients were also examined prior to every cycle. Measurable lesions noted at baseline were reevaluated after cycles 4 and 8 during the dose escalation phase and after cycles 3 and 6 in the expanded phase. Response Evaluation Criteria in Solid Tumors (RECIST) were used to assess response [13]. Patients were followed for 1 year after treatment.

Dose-limiting toxicity

In accordance with the NCI Common Terminology Criteria for Adverse Events, Version 3 (NCI CTCAE v3), DLT was defined as either hematologic or non-hematologic toxicity that occurred in the first cycle during the dose-seeking phase (or in the first 4 cycles in the expanded phase). Hematologic DLT included a dose delay of >2 weeks due to failure to recover counts adequately (see Dose Adjustments), study-treatment-related febrile neutropenia (fever ≥38.5 °C) when the absolute neutrophil count (ANC) is $<1.0\times10^9$/L, grade 4 neutropenia lasting ≥7 days and grade 3 or 4 thrombocytopenia. Non-hematologic DLT included study-treatment-related grade 3 or 4 toxicities (excluding fatigue, hypersensitivity reaction, nausea and vomiting) or any drug-related death.

Dose adjustments

Initial treatment modifications consisted of cycle delay and dose reduction. Subsequent cycles of therapy could not begin until the ANC was $\geq 1.5\times10^9$/L (NCI-CTC grade 1) and the platelet count was $\geq 75\times10^9$/L. Therapy could be delayed for a maximum of 2 weeks until these values were achieved; otherwise, the patient was removed from study. Two dose reductions of IP carboplatin were allowed for grade 3 or 4 thrombocytopenia, or thrombocytopenia-associated bleeding that required a platelet transfusion. One dose reduction of IV paclitaxel was allowed for febrile neutropenia and/or grade 4 neutropenia lasting ≥7 days. Dose modifications were not made for anemia. Patients could receive red blood cell transfusions and/or erythropoietin using standard supportive care guidelines. Other hematologic growth factors were allowed after the above dose adjustments at the discretion of the treating physician.

Dose delay up to 2 weeks was allowed and modification was required for any drug-related grade 3 or 4 non-hematologic toxicity. Treatment was discontinued in patients with persistent peripheral neuropathy ≥grade 3. Persistent grade 2 neuropathy required a one-time dose reduction of paclitaxel. Otherwise, patients with non-hematologic toxicity had to return to ≤grade 1 before continuing therapy.

Statistical considerations

The study was carried out in two phases. The dose-seeking phase was designed to find the MTD of the study regimen and utilized a standard 3+3 phase I design. Doses were escalated to next planned dose if 0/3 or 1/6 patients experienced DLTs. Once an estimate of the MTD was established, the second "expanded" phase was initiated.

A two-stage sequential design was used in the expanded phase to assess the feasibility of delivering multiple cycles of the study regimen.

The decision rules for whether or not to advance to the next stage of the study are summarized in Table 1. Based on the estimated frequency of dose modification and/or delay with the two-drug combination of carboplatin and paclitaxel in Protocol GOG-158 [14], the regimen in this study would be considered *not* feasible for a Phase III study if the true event (DLT) probability within the first 4 cycles of therapy was ≥40%. If the true event rate for this regimen was 40%, this design provided a 91% chance of classifying the regimen as not feasible, with a 58% chance reaching this conclusion before beginning the second stage. If the event rate was as low as 20%, the design provided a 91% chance of classifying the regimen as feasible and a 63% chance of reaching this conclusion before beginning the second stage.

Results

Patient characteristics

A total of 90 patients were entered on the trial from June 2004 until June 2008. Twenty-one patients were entered on the dose-seeking phase (evaluating cycle 1 toxicity). One patient was ineligible for toxicity evaluation due to a wrong starting dose, and another did not receive protocol therapy due to an IP catheter malfunction. Sixty-nine patients were entered on the expanded phase (evaluating 4-cycle toxicity). Nine patients were not evaluable for four-cycle toxicity (4 had hypersensitivity reactions to paclitaxel before cycle #4, three had progression of disease before cycle #4, and two were treated at the wrong dose). Demographics for all 90 patients entered on study are listed in Tables 2 and 3. Toxicity is only reported for 19 evaluable patients in the dose-seeking phase and 60 evaluable patients in the expanded phase (20 at AUC 7 and 40 at AUC 6).

Dose escalation phase: toxicity

IP carboplatin AUC 5. Of the three patients treated, there were no first-cycle DLTs and all received eight cycles. One had a dose reduction after cycle #5 for grade 3 thrombocytopenia.

IP carboplatin AUC 6. Of the four eligible patients treated, there were no first-cycle DLTs and three patients completed eight cycles. One of these three patients had a dose reduction of paclitaxel for febrile neutropenia after cycle #7, and the fourth patient had a port malfunction after the first cycle and was removed from study.

IP carboplatin AUC 7. Of the six eligible patients treated, there was 1 first-cycle DLT (grade 4 thrombocytopenia). However, only one patient completed eight cycles. Three were removed from study for a >2-week delay in recovering blood counts (after cycle #2, 5, 6), one was removed after cycle #1 due to persistent grade 2 neuropathy and another was removed for a hypersensitivity reaction to paclitaxel after cycle #3.

IP carboplatin AUC 8. Of the six patients treated, there was one first-cycle DLT (grade 3 thrombocytopenia). That patient was removed from study after cycle #2 due to grade 4 thrombocytopenia despite dose reduction. Only one patient completed 8 cycles and she had a dose reduction of IP carboplatin after cycle #2 due to grade 3 thrombocytopenia (Table 4). Three patients were removed for a >2-week delay in recovering blood counts, and one other patient was removed after cycle #4 due to an IP port infection.

Table 1
Expanded phase[a] = DLT.

Stage	Cumulative accrual	Maximum no. of events[a] to stop the study and consider the regimen feasible for phase III	Minimum no. of events[a] to stop the study and consider the regimen not feasible for phase III
1	20	4	8
2	40	11	12

[a] Events = dose-limiting toxicity.

Table 2
Demographics. Dose escalation phase ($n=21$).

Characteristic	Category	Number	Percentage of cases
Age (years)	17–49 years	2	10
	50–59 years	7	33
	60–69 years	8	38
	70–79 years	4	19
	80–89 years		
Ethnicity	Hispanic	1	5
	White	18	85
	Asian	2	10
	Black	0	
Performance status	0	14	66
	1	4	19
	2	3	15
Site of disease	Ovary	18	85
	Fallopian tube	0	
	Primary peritoneal	3	15
Stage	IIb	0	
	IIc	0	
	IIIa	4	19
	IIIb	1	5
	IIIc	15	71
	IV	1	5
Debulking	Optimal	14	67
	Suboptimal >1 cm	7	33
Measurable disease	No	14	67
	Yes	7	33

Expanded phase: rationale for dose selection

Since there was only one first-cycle DLT in six patients treated at an IP carboplatin dose AUC 8, dose escalation to AUC 9 was considered. However, on reviewing the results of patients treated at an AUC of 7 and 8, only two of twelve patients were able to complete the planned regimen of 8 cycles and both patients required a dose reduction by cycle #4 (grade 3, 4 thrombocytopenia). Also, nine of twelve patients had a DLT by cycle #4, and six patients were removed from study due to a >2-week delay in recovering blood counts. Since

Table 3
Demographics. Expanded cohorts AUC 6 and 7 ($n=69$).

Characteristic	Category	Number	Percentage of cases
Age (years)	17–49 years	13	19
	50–59 years	18	26
	60–69 years	26	38
	70–79 years	11	16
	80–89 years	1	1
Ethnicity	Hispanic	3	4
	White	58	84
	Asian	7	10
	Black	1	1
Performance status	0	35	51
	1	29	42
	2	5	7
Site of Disease	Ovary	52	75
	Fallopian tube	4	6
	Primary peritoneal	13	19
Stage	IIb	2	3
	IIc	6	9
	IIIa	2	3
	IIIb	6	9
	IIIc	46	67
	IV	7	10
Debulking	Optimal	57	83
	Suboptimal >	12	17
Measurable disease	No	60	87
	Yes	9	13

Table 4
Toxicity at AUC 8 in dose-escalating phase ($N=6$).

Adverse effect	Grade					
	0	1	2	3	4	Total
Leukopenia	0	0	0	6	0	6
Thrombocytopenia	0	0	1	4	1	6
Neutropenia	0	0	0	0	6	6
Anemia	0	0	4	2	0	6
Cardiovascular	5	0	1	0	0	6
Constitutional	1	2	3	0	0	6
Dermatologic (not alopecia)	4	0	2	0	0	6
Gastrointestinal	0	1	4	1	0	6
Genitourinary/Renal	4	1	0	1	0	6
Hepatic	5	1	0	0	0	6
Infection/Neutropenic	5	0	0	1	0	6
Infection/Not neutropenic	4	0	0	2	0	6
Metabolic	2	3	1	0	0	6
Neuropathy—sensory	0	6	0	0	0	6
Neuropathy—other	5	0	1	0	0	6
Pain (abdominal)	1	3	1	1	0	6

Table 5
Toxicity in expanded phase cohort AUC 7 ($N=20$).

Adverse effect	Grade					
	0	1	2	3	4	Total
Leukopenia	0	1	3	11	5	20
Thrombocytopenia	2	9	2	4	3	20
Neutropenia	0	1	1	2	16	20
Anemia	0	2	13	5	0	20
Cardiovascular	13	4	2	1	0	20
Constitutional	2	3	13	1	1	20
Dermatologic (not alopecia)	12	8	0	0	0	20
Gastrointestinal	0	6	11	2	1	20
Genitourinary/Renal	15	1	2	1	1	20
Hepatic	13	5	2	0	0	20
Infection/Neutropenic	15	0	1	3	1	20
Infection/Not neutropenic	14	1	2	3	0	20
Metabolic	7	5	4	4	0	20
Neuropathy—sensory	8	10	2	0	0	20
Neuropathy—other	7	5	7	1	0	20
Pain (abdominal)	10	6	4	0	0	20

the goal of the study was to determine the tolerability of treatment over multiple cycles, escalation to an AUC of 9 was not felt prudent. The expanded phase was therefore opened at an IP carboplatin AUC of 7 with plans to escalate or de-escalate based on the results. The total number of planned cycles was also reduced to six to be consistent with the standard recommended cycle number for intravenous carboplatin and paclitaxel on other GOG trials.

Expanded phase: toxicity

IP carboplatin AUC 7. Twenty-two patients were entered and two were not eligible for 4-cycle toxicity evaluation due to hypersensitivity reactions to paclitaxel in the first cycle. Of the 20 eligible patients treated, there were nine DLTs within four cycles (Table 5). There was one death due to neutropenic sepsis associated with a *c. difficile* infection after cycle #1. There were four DLTs due to a delay of >2 weeks to recover neutrophil counts, two due to neutropenic fever (including the death), two due to grade 3 or 4 thrombocytopenia, and one due to grade 4 metabolic toxicity. Given that there were greater than eight DLTs, this regimen was not considered feasible for a Phase III trial. In addition, there was only 1 IP port problem (port abscess requiring removal) and 11 patients (55%) completed six cycles.

IP carboplatin AUC 6. Forty-seven patients were entered and seven were not eligible for four-cycle toxicity evaluation (two treated at wrong dose, two hypersensitivity reactions to paclitaxel in first cycle, two progression of disease by cycle 3, and one patient refused IP therapy after the first cycle). Of the 40 eligible patients treated, there were 14 DLTs. There were six DLTs due to grade 3 or 4 thrombocytopenia, four DLTs due to a delay of >2 weeks to recover neutrophil counts, two DLTs due to neutropenic fever, one grade 4 neutropenia >7 days, and one DLT due to grade 3 mental status changes requiring hospitalization. Thirty (75%) patients completed six cycles of IP therapy with dose adjustments after cycle #4 when required by protocol. There were two IP port malfunctions. Both were replaced and both patients completed six cycles. The highest grade of toxicity for each of the 40 evaluable patients is listed in Table 6.

Response rates and progression

Response rates and data regarding progression were evaluated for patients treated at an AUC 6 in the expanded phase. An intent-to-treat analysis revealed that of all 47 patients entered at an AUC 6, 14 (30%, 95% CI 17–45%) had disease progression within 1 year of initiating protocol treatment. Two patients had progression of disease before cycle #4. Of the 35 patients treated at an AUC 6 who completed at least four cycles of protocol therapy, nine (26%, 95% CI, 12–43%) had evidence of disease progression within 1 year of initiating therapy. Four of 35 patients (11%) had suboptimal disease. However, only two of those patients had measurable disease on radiologic imaging and both had a complete clinical response after treatment.

Discussion

The GOG has sought to develop regimens using IP carboplatin for use in a Phase III trial comparing systemic carboplatin and paclitaxel to intraperitoneal chemotherapy. Retrospective evaluation of the experience with IP carboplatin and IV paclitaxel (175 mg/m^2) as primary treatment of ovarian, peritoneal or fallopian tube cancer in Japan confirms that myelotoxicity, especially thrombocytopenia, appears to be dose limiting [15]. In the study reported here, grade 4 neutropenia was seen in 63% of patients treated at an IP carboplatin AUC of 6. Grade 3 or 4 thrombocytopenia was only seen in 15% of patients at this dose but was always considered dose limiting. In GOG-158, 72% grade 4 neutropenia and 39% grade 3 and 4 thrombocytopenia were observed in patients treated with IV paclitaxel (175 mg/m^2) and IV carboplatin (AUC=7.5) [14].

The most recently reported GOG randomized trial of intraperitoneal chemotherapy (GOG-172) demonstrated a relative risk of recurrence of 0.73 and a 15.9-month improvement in overall survival with the IP regimen. This was despite the fact that only 42% of patients completed the planned six cycles IP and 49% in the IP arm received three or fewer IP treatments [3]. IP catheter problems occurred in 34% of patients and were a major reason for discontinuing IP therapy [16]. In the study reported here, only 7/90 (8%) of patients entered had problems related to the IP catheter and five were responsible for discontinuing IP therapy. This low rate may be due to the use of IP carboplatin alone, more common placement of catheters at the time of initial surgery or more experienced surgeons and staff participating in Phase I trials with the GOG. The progression rate at 1 year (30%) for the expanded cohort treated at a carboplatin dose of AUC 6 is comparable to GOG-172 where 25% of patients had disease progression in 1 year [3].

This Phase I trial established that the first-cycle MTD of IP carboplatin was at least an AUC of 8 when given every 3 weeks with paclitaxel at 175 mg/m^2. However, follow-up of patients on the dose-seeking phase treated beyond the first cycle revealed that it was unlikely that multiple cycles would be tolerated at the MTD. In the expanded phase, evaluating four-cycle toxicity, even an AUC 7 was not considered feasible in a Phase III trial. At a carboplatin AUC 6, 13/14 DLTs were due to myelosuppression: six due to thrombocytopenia and seven due to leukopenia or neutropenia.

Table 6
Toxicity in expanded phase cohort AUC 6 ($N=40$).

Adverse effect	Grade					
	0	1	2	3	4	Total
Leukopenia	0	5	16	18	1	40
Thrombocytopenia	13	13	8	2	4	40
Neutropenia	0	0	4	11	25	40
Anemia	1	14	17	7	1	40
Cardiovascular	28	7	5	0	0	40
Constitutional	4	21	14	1	0	40
Dermatologic (not alopecia)	28	11	1	0	0	40
Gastrointestinal	4	20	10	6	0	40
Genitourinary/Renal	39	0	1	0	0	40
Hepatic	16	12	0	2	0	40
Infection/Neutropenic	36	0	0	3	1	40
Infection/Not neutropenic	29	0	8	3	0	40
Metabolic	19	17	1	3	0	40
Neuropathy—sensory	6	21	9	4	0	40
Neuropathy—other	26	7	3	4	0	40
Pain (abdominal)	18	12	5	5	0	40

Although not feasible for incorporation into a Phase III trial based on the criteria of this study, the regimen of IP carboplatin at an AUC 6 with IV paclitaxel at 175 mg/m^2 is well tolerated over multiple cycles with a high six cycle completion rate (75%). Serious outcomes associated with myelosuppression, such as febrile neutropenia or bleeding, were infrequent. The pattern of DLTs suggests that with broadened criteria for dose delay or incorporation of granulocyte colony-stimulating factors, this dose could be feasible in a Phase III trial.

The GOG has recently opened a randomized trial comparing IV and IP chemotherapy (Fig. 1, online only). All regimens will also contain bevacizumab during treatment and for 11 months after chemotherapy. The IP carboplatin dose chosen is an AUC of 6, combined with IV paclitaxel (80 mg/m^2) on days 1, 8, and 15 based on recent trial suggesting improved survival and comparable toxicity with the dose-dense regimen versus the standard 3-week IV regimen [17]. Given the survival advantage of IP therapy in the treatment of women with ovarian, fallopian tube, and primary peritoneal carcinoma, it is hoped that findings from this study which have been incorporated into the ongoing GOG trial will make this therapy equally efficacious and more tolerable.

Supplementary materials related to this article can be found online at doi:10.1016/j.ygyno.2010.12.358.

Conflict of interest statement
The authors wish to report that they have no conflicts of interest.

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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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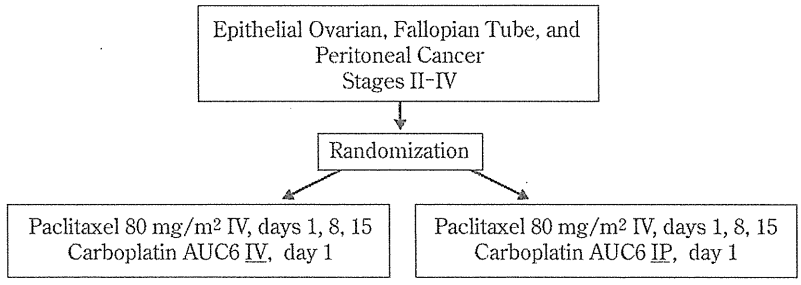

図 1 iPocc 試験デザイン

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。