卵巣癌に比べ再発率とリンパ節転移が低い傾向がみられたが生存率に関しては有意な差を認めなかった。

E. 結論

現在取り扱っているすべての卵管癌がType II 卵巣癌と同一ではないので、現在の診断区分でのそれぞれの疾患における臨床的な特徴は、実臨床では有用な治療情報となり得る可能性がある。

F. 健康危険情報

特記すべき事項なし(総括研究報告書にまとめて記入しますので記入しません)

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H. 知的財産権の出願・登録状況（予定含）

１．特許取得

なし

２．実用新案登録

なし

３．その他

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書

卵巣癌に対する抗癌剤感受性試験 Collagen Gel Droplet Embedded Culture Drug Sensitivity Test (CD-DST)の検討

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研究要旨

抗癌剤感受性試験 Collagen Gel Droplet Embedded Culture Drug Sensitivity Test（ CD-DST ）を卵巣癌 22 例に施行し，抗癌剤感受性について検討した。中等度感受性以上は CDDP ： 5%， epirubicin ： 16%，etoposide ： 10%，paclitaxel ： 19%，irinotecan(SN38)： 22%，paclitaxel/CDDP を用いた同時添加による感受性検索では 25%に相乗効果が認められた。漿液性腺癌，類内膜腺癌では中等度感受性以上は epirubicin：20%，etoposide：13%， paclitaxel：18%，irinotecan：30%，paclitaxel/ CDDP の同時添加では 27%であった。CDDP 低感受性症例における同時添加の相乗効果は主に漿液性腺癌，類内膜腺癌でみられた。明細胞腺癌では 1 例（25%）に paclitaxel，epirubicin に中等度感受性が認められたが，paclitaxel/ CDDP の同時添加での相乗効果は全くみられなかった。以上の成績より，明細胞腺癌に対する化学療法は白金製剤を除く新規レジメンを考慮する必要があると推察された。

A. 研究目的

卵巣癌に対する化学療法は，paclitaxel/ platinum (TC)療法が標準的治療とされている。しかしながら，組織型によっては化学療法が奏効しない症例も存在し，有効な抗癌剤を選択できない盲目的な側面もある。今回，卵巣癌における有効な抗癌剤を予測できる抗癌剤感受性試験 Collagen Gel Droplet Embedded Culture Drug Sensitivity Test (CD-DST)を施行し，その感受性分布を組織学的に検討することを目的とした。

B. 研究方法

2001～2003 年の間に同意を得て CD-DST を施行した卵巣癌 22 例（漿液性腺癌 14 例，類内膜腺癌 3 例，明細胞腺癌 4 例，粘液性線癌 1 例）を対象とした。 卵巣材料 0.5g を採取し，CD-DST を施行した(三菱化学 BCL に依頼提出)。使用した薬剤は cisplatinum (CDDP)，epirubicin hydrochloride (EPI)，etoposide (ETP)，paclitaxel (TXL)，irinotecan (SN38)である。 抗腫瘍効果の評価は薬剤処理群(T)と薬剤未処理群(C)の比 T/C(%)≦50%:高感受性，50＜T/C≦60%:中等度感受性，T/C＞60%：低感受性と判定した。さらに CDDP および paclitaxel については同時添加による相乗効果の有無を検索した。

（倫理面への配慮）

本検査を受けなくても不利益を受けないこと，いつでも検査は 希望により中止できることなどの倫理面への配慮を行った.

C. 研究結果

1．卵巣癌における抗癌剤感受性試験 CD-DST 測定結果

卵巣癌 22 例の中等度感受性以上は CDDP：5%，epirubicin：16%，etoposide：10%，paclitaxel：19%，irinotecan：

22%と CDDP の感受性は低値であったが，paclitaxel/CDDP の同時添加では 25%を示した。

2. 各組織型における抗癌剤感受性試験 CD-DST 測定結果

漿液性腺癌/類内膜腺癌 17 例における，中等度感受性以上は CDDP : 0%，epirubicin : 20%，etoposide : 13%，paclitaxel : 19%，irinotecan: 30%で，paclitaxel/ CDDP を用いた同時添加による感受性検索では 27%に相乗効果が認められた。粘液性腺癌例の 1 例で CDDP に中等度感受性，paclitaxel/ CDDP に相乗効果がみられた。一方，明細胞腺癌では 4 例中 1 例(25%)に paclitaxel, epirubicin に中等度感受性がみられたが，その他の薬剤では全て低感受性で paclitaxel/ CDDP による相乗効果は全く認められなかった。

D. 考察

CD-DST は，初代培養成功率が高く，少ない細胞数の薬剤評価，癌細胞のみの抗腫瘍効果の評価，生理学的薬剤濃度の評価が可能で，臨床効果とよく相関することなどの特徴を有している。膵・胆道癌，大腸癌，乳癌などで臨床応用されているが，婦人科領域ではあまり施行されていない。今回，卵巣癌における抗癌剤感受性分布を組織学的に検討した。

卵巣癌における各薬剤の中等度感受性以上は 5～22%と低値であったが，CDDP の低感受性症例において paclitaxel/ CDDP による同時添加では，相乗効果がみられ，全体として 25%に認められた。CDDP の低感受性症例において paclitaxel/ CDDP の同時添加の相乗効果のあった組織型は主に漿液性腺癌，類内膜腺癌であり，臨床効果とほぼ一致する。化学療法抵抗性があり，予後不良とされる明細胞腺癌で，paclitaxel における中等度感受性の 1 例を除く全薬剤は低感受性であり，また paclitaxel/CDDP 同時添加の相乗効果は全く認められていない。

2 剤の同時添加による相乗効果がみられているので全く感受性のない症例に対しては薬剤を選択して同時添加による効力をあらかじめ検索し、確認することが望まれる。以上の成績から，予後不良とされる明細胞腺癌の化学療法に対しては platinum を除いた paclitaxel/ irinotecan などの併用療法を今後考慮する必要がある。また，固形癌の heterogeneity などの問題もあり，薬剤の低感受性の評価については臨床応用する上で重要な課題である。

E. 結論

本法は治療前に有効な薬剤の選択がある程度可能であり，同時添加の検索では組織型による感受性の増加が認められた。薬剤抵抗性とされる粘液性腺癌，明細胞腺癌に対しては化学療法の個別化を図った上で，今後の臨床応用の可能性が推察された。

F. 健康危険情報

特記すべきことなし.

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H. 知的財産権の出願・登録状況（予定含）

１．特許取得

なし

２．実用新案登録

なし

３．その他

なし

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Katsumata.N	Dose-dense therapy is of benefit in primary treatment of ovarian cancer? In favor	Annals of Oncology	22	Viii29-Viii32	2011
Fujiwara.K. et al.	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	JJCO	41	278-282	2011
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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
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Dose-dense therapy is of benefit in primary treatment of ovarian cancer? In favor

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Paclitaxel and carboplatin given every 3 weeks is the current standard treatment in first-line chemotherapy regimens for ovarian cancer. The concept of 'dose-dense therapy' is based on the hypothesis that a shortening interval of the doses of cytotoxic agents will be more effective for tumor-cell kill. Recently published phase III trials in breast cancer have shown that dose-dense weekly paclitaxel improves response and survival. The Japanese Gynecologic Oncology Group reported a phase III study comparing the conventional 3-weekly paclitaxel and carboplatin schedule versus dose-dense weekly paclitaxel and 3-weekly carboplatin for advanced epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer. The progression-free survival, as the primary endpoint of this study, was significantly prolonged with the dose-dense treatment [28 versus 17.2 months; hazard ratio (HR): 0.71; 95% confidence interval (CI): 0.58–0.88; $P = 0.0015$], as was the overall survival at 3 years (72.1% versus 65.1%; HR 0.75; 95% CI: 0.57–0.98; $P = 0.03$). Dose-dense weekly paclitaxel plus carboplatin represents a new treatment option in women with advanced epithelial ovarian cancer.

Key words: advanced epithelial ovarian cancer, dose-dense therapy, paclitaxel

introduction

Currently, the combination of paclitaxel and carboplatin (TC) is the standard first-line chemotherapy for ovarian cancer. In its most recent consensus statements on the management of ovarian cancer during the Fourth International Ovarian Cancer Consensus Conference, the Gynecologic Cancer InterGroup (GCIG) confirmed this. GCIG recommended the use of 175 mg/m^2 paclitaxel, given intravenously (i.v.) over 3 h, followed by carboplatin as an i.v. infusion over 30–60 min at a dose adjusted to produce an area under the plasma concentration–time curve (AUC) of 5–6 mg·ml/min and to repeat this every 3 weeks for six cycles [1]. Moreover, GCIG considered intraperitoneal therapy in patients with small-volume residual disease and dose-dense weekly paclitaxel in combination with 3-weekly carboplatin acceptable treatment options.

the concept of dose-dense therapy

'Dose-dense therapy' is a strategy to enhance antitumor activity and prolong the survival of patients. The theoretical basis for this dose-dense chemotherapy strategy is derived from the Gompertzian model, which is based on Norton–Simon's hypothesis [2, 3]. In the Gompertzian model, smaller tumors grow faster and so tumor regrowth between treatment cycles is more rapid when cell kill is greatest. Increased dose density is achieved by reducing the interval between each dose of chemotherapy. The cumulative drug dose remains constant, but the same amount of drug is administered over a shorter period. Mathematical models of tumor growth have provided the basis for the clinical application of dose-dense chemotherapy. The Norton–Simon model suggests that increasing the dose density of chemotherapy will increase efficacy by minimizing the opportunity for regrowth of tumor cells between cycles of chemotherapy. This concept has been applied in adjuvant therapy, in sequential administration of chemotherapy and in dose-dense administration of chemotherapy, in particular for breast cancer. The Cancer and Leukemia Group B C9344 study demonstrated that the sequential use of paclitaxel following doxorubicin and cyclophosphamide as adjuvant therapy for breast cancer improved survival [4]. Weekly paclitaxel as compared with every-3-weeks administration of paclitaxel improved survival in two phase III trials of breast cancer [5, 6]. A meta-analysis of dose-dense chemotherapy in non-metastatic breast cancer demonstrated a better overall and disease-free survival [7].

dose-dense paclitaxel for ovarian cancer

The weekly administration of paclitaxel has been investigated from preclinical studies to clinical trials. The results from some *in vitro* studies indicate that increasing the number of short paclitaxel infusions results in a greater response rate than the normal 24-h administration period [8]. Preclinical studies have suggested that the duration of exposure is an important determinant of the cytotoxic activity of paclitaxel [9]. Adequate cytotoxicity can be achieved at relatively low concentrations of paclitaxel, provided that the exposure is prolonged [9, 10]. It

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has also been suggested that in addition to its microtubule-stabilizing action, paclitaxel may have other cytotoxic effects, such as inducing apoptosis and inhibiting angiogenesis, which are even observed at very low concentration levels of paclitaxel and even under weekly administration [11].

A phase I study conducted at the Memorial Sloan Kettering Cancer Center by Leiser et al. [12], included 16 relapsed ovarian cancer patients. Weekly paclitaxel escalating dose of 50–80 mg/m^2 and carboplatin AUC 4–6 every 3 weeks were administered. Febrile neutropenia and grade 4 thrombocytopenia according to the National Cancer Institute common toxicity criteria were the dose-limiting toxicities at dose levels 3 and 4 with no mucositis, nausea, vomiting or peripheral neuropathy observed greater than grade 2. They recommended weekly paclitaxel 80 mg/m^2 in combination with carboplatin AUC 5 every 3 weeks for further study. Kikuchi et al. [13] conducting a similar phase I trial, in Japanese patients with advanced non-small cell lung cancer, recommend a dose of weekly paclitaxel 100 mg/m^2 on days 1, 8, and 15 in combination with carboplatin AUC 6 every 4 weeks.

Several phase II clinical trials of dose-dense weekly paclitaxel and carboplatin administration have shown promising efficacy and favorable tolerability in women with ovarian cancer [14–16]. We reported a phase II study of 80 mg/m^2 paclitaxel and carboplatin AUC 2, which were administered every week in recurrent ovarian cancer patients [14]. The objective response rate was 67% (22/33). Grade 3–4 leukopenia was observed in 25% of patients and grade 3–4 neutropenia in 57% of patients. However, no patient was given granulocyte-colony stimulating factor. Febrile neutropenia was not observed. Grade 3 neurotoxicity was observed in 4% of patients. All patients were treated in the outpatient clinic. In another study, Sehouli et al. [16] reported weekly administration of 100 mg/m^2 paclitaxel and weekly carboplatin AUC 2, and showed substantial activity and tolerability of this regimen when treating patients in the primary disease setting. A treatment delay of only 2.8% was observed and the incidence of grade 3 neurotoxicity was even lower than that in our study. In addition, Pignata et al. reported that weekly carboplatin at a dose of AUC 2 and weekly paclitaxel at a dose of 60 mg/m^2 on days 1, 8 and 15, every 4 weeks, had a favorable toxicity profile in elderly ovarian cancer patients, when treated in first line [17].

randomized phase III trial of dose-dense weekly paclitaxel in combination with carboplatin for advanced ovarian cancer

The Japanese Gynecologic Oncology Group (JGOG) conducted a randomized phase III trial of dose-dense weekly paclitaxel in combination with 3-weekly carboplatin for advanced ovarian cancer [JGOG 3016; New Ovarian Elaborate (NOVEL) trial] [18].

Patients with stage II–IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer were randomly assigned to receive six cycles of either paclitaxel plus carboplatin, given on day 1 of a 21-day cycle [conventional TC (c-TC)] or dose-dense paclitaxel, given on days 1, 8 and 15, plus carboplatin given on day 1 of a 21-day cycle [dose-dense TC (dd-TC)]. Both groups received carboplatin at a dose calculated to produce an AUC of 6 mg·ml/min on day 1 of each 21-day cycle. Carboplatin was given as an i.v. infusion over 1 h. The conventional therapy group received paclitaxel given as a 3 h i.v. infusion at a dose of 180 mg/m^2 body surface area on day 1. In the dose-dense therapy group, paclitaxel was given as a 1 h i.v. infusion at a dose of 80 mg/m^2 body surface area on days 1, 8 and 15. The dose of carboplatin was calculated with the Calvert formula [19], using the creatinine clearance instead of the glomerular filtration rate (GFR). The creatinine clearance was calculated with the Jelliffe formula [20]. The treatments were repeated every 3 weeks for six cycles. Patients with measurable lesions who had a partial response or a complete response received three additional cycles of chemotherapy. The primary endpoint was progression-free survival. Secondary endpoints were overall survival, response rate and adverse

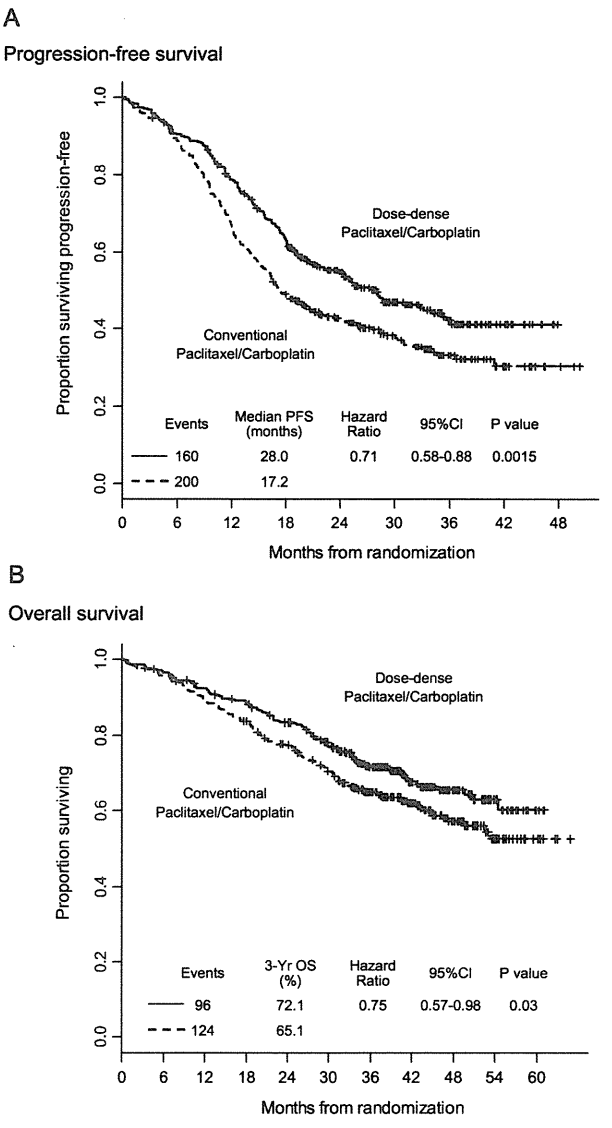

Figure 1. Progression-free and Overall Survival.

events. A total of 600 patients were required to detect a 5-month prolongation of progression-free survival with an 80% power, using a two-sided log-rank test, with an α level of 0.05, an accrual period of 3 years and a follow-up period of 1.5 years.

A total of 637 patients were randomized either to the dd-TC arm with 312 eligible patients or to the c-TC arm with 319 eligible patients. The overall response rate evaluated by classical World Health Organisation criteria was not significantly different in both arms (56% versus 53%; $P = 0.72$). Progression-free survival was substantially improved in the dd-TC arm (28 versus 17.2 months; hazard ratio: 0.71; 95% confidence interval: 0.58–0.88; $P = 0.0015$; Figure 1). The overall survival was immature because of lacking sufficient events at the time of presentation at the American Society of Clinical Oncology meeting in 2008 [18]; however, the 2-year overall survival was better in the dd-TC arm than in the c-TC arm of the study (83.6% versus 77.7%; $P = 0.049$) . Updated overall survival with a median follow-up of 42 months was significantly better in the dd-TC arm (72.1%) than in the c-TC arm (65.1%) ($P = 0.03$ by the log-rank test) (Figure 1) [21]. Early discontinuation of treatment occurred in 165 patients in the dose-dense regimen group and in 117 patients in the conventional regimen group. Withdrawal because of toxicity was higher in the dose-dense regimen group (113 versus 69), but reasons for dropout were otherwise balanced between the groups. Neutropenia was the most frequently observed adverse event [dose-dense regimen, 286 (92%) of 312 patients; conventional regimen, 276 (88%) of 314 patients]. Compared with the conventional treatment group, the dose-dense treatment group had a higher frequency of grade 3 and 4 anemia [214 (69%) versus 137 (44%); $P < 0.0001$]. Other toxic effects, including neuropathy, occurred with similar frequencies in both groups.

carboplatin for Japanese patients

Hematologic toxicity was more frequently observed in the JGOG trial than in previous trials using the same chemotherapy doses in Western countries [22, 23]. There are well-known discrepancies in the observed toxicity of carboplatin-based chemotherapy between Japanese and Western patients [24], which can be explained in part by the different techniques used to assay creatinine. Two techniques are commonly used to measure serum creatinine levels: (i) the kinetic Jaffe method; and (ii) the enzymatic peroxidase–antiperoxidase (PAP) method. The creatinine clearance measured by the PAP method overestimates the GFR in subjects with normal renal function [25], and most clinical laboratories in Japan use the PAP method. Therefore, the carboplatin dose calculated with the Calvert formula using the PAP method would be overdosed in the JGOG trial and induce more myelotoxicity. Several methods to estimate GFR more accurately from serum creatinine have been proposed [26–29]; however, there is no global consensus on the best method for assessing renal function as the basis for determining the dosage of carboplatin. One should be cautious in interpreting carboplatin-induced toxicities and take into account the method used to determine serum creatinine concentrations when using creatinine clearance estimations with the Calvert formula.

summary

In conclusion, dose-dense TC is an effective treatment with improved progression-free survival in patients with advanced ovarian cancer. Confirmatory studies are ongoing in Western countries. GOG 262 (trial registration: NCT01167712; Figure 2) is comparing carboplatin AUC 6 plus 175 mg/m^2 paclitaxel given every 3 weeks with carboplatin AUC 6 plus weekly 80 mg/m^{2}paclitaxel given every 3 weeks for suboptimal stage III or IV ovarian cancer. Additional bevacizumab is an option in the study. MITO 7 (trial registration: NCT00660842; Figure 3) is comparing carboplatin AUC 5 plus 175 mg/m^2 paclitaxel with weekly carboplatin AUC 2 plus weekly 60 mg/m^2 paclitaxel. ICON 8 is preparing to start a three-armed randomized trial comparing carboplatin AUC 5 plus 175 mg/m^2 paclitaxel with carboplatin AUC 5 plus weekly 80 mg/m^2 paclitaxel and with weekly carboplatin AUC 1.67 plus weekly 80 mg/m^2 paclitaxel for stage IC to IV ovarian cancer. It is reasonable to conclude that if these studies confirm the Japanese phase III trial data, then weekly paclitaxel administration is an appropriate strategy to consider in the standard treatment of advanced ovarian cancer.

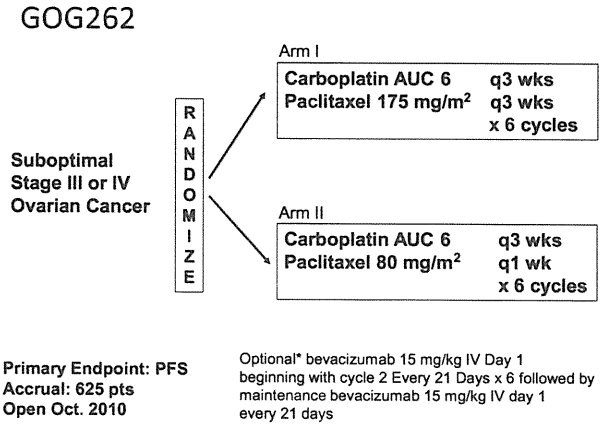

Figure 2. The GOG 262 study.

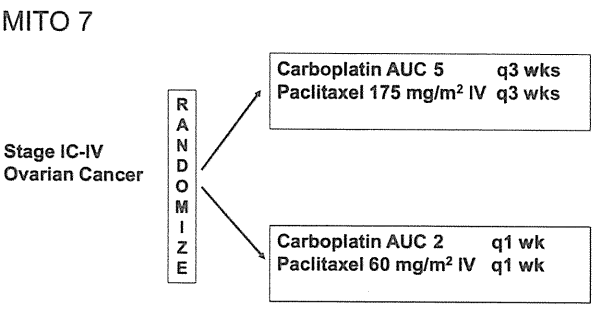

Figure 3. The MITO 7 study.

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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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The chemosensitivity of nodal metastases in recurrent epithelial ovarian cancer

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Summary

Purpose: In this study, we compared second-line chemotherapy effects of nodal metastases with other metastases sites. *Methods:* The medical records of 44 women with recurrent ovarian cancer who received second-line chemotherapy were retrospectively reviewed. *Results:* Median age at the time of second-line chemotherapy was 55 years (range: 31-74). Recurrent sites were as follows: 29 patients had a solitary site (abdominal cavity: 8; lymph node: 3; pelvic cavity: 10; liver: 4; lung: 4) and 15 patients had multiple sites In total, the response rate was 30% (CR: 8, PR: 5). The response rate in sensitive cases was higher than in refractory/resistant cases (50% vs 5% p = 0.002). However, age, chemotherapy regimen, histologic type and number of diseases were not related with chemotherapy effect. In all diseases, response rate tended to be higher in lymph node disease than in the others (44% vs 27%). In both sensitive and refractory/resistant cases, response rate tended to be higher in lymph node disease. *Conclusion:* The response rate for lymph node diseases tended to be relatively high. Further study analyzing survival will be required to conclude the chemotherapy effect.

Key words: Second-line chemotherapy; Recurrence; Lymph node; Recurrent site.

Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy, accounting for 7,000 new diagnoses and 4,000 deaths annually in Japan. Patients are usually treated with cytoreductive surgery, followed by platinum and paclitaxel chemotherapy. The initial response rate to standard treatment exceeds 70% [1]. Despite initial high responses, the majority of cases experience relapse, with a median disease-free interval of 18 to 24 months. Some retrospective studies demonstrated a survival benefit for patients undergoing optimal secondary cytoreductive surgery [2-8]. Based on NCCN guidelines, secondary cytoreductive surgery may be considered as a treatment option for clinically focal recurrence after a disease-free interval > 6 months. Recently, retrospective studies have shown that secondary cytoreductive surgery for isolated nodal recurrence is effective [9-12]. Morice et al. reported that nodal metastases of EOC are chemoresistant lesions [13]. However, Blanchard *et al.* reported that good chemotherapy response rates could be obtained in recurrent nodal metastases [10]. Thus, it is controversial if chemotherapy is effective for lymph node disease.

Cancer consists of founder cancer cells and stroma including blood and lymph endothelial cells, inflammatory cells, immunocytes and macrophages, and fibroblasts. Recently, the role of stroma is thought to be associated with tumor progression including invasion or metastatsis as well as response to therapy [14-16]. In addition, the chemotherapy effect is thought to be related to drug delivery status. From these findings, it can possibly be deduced that chemotherapy effects may differ among the locations of target disease. In this study, we compared the chemotherapy effect of nodal metastases with other metastasis sites.

Materials and Methods

Patients

We retrospectively reviewed the medical records of women with recurrent ovarian cancer who received second-line chemotherapy Recurrent cases who received surgery were excluded from the study. Forty-four patients who initiated second-line chemotherapy between February 1998 and October 2008 were included in this study All patients underwent initial surgery and primary chemotherapy consisting of a platinum/taxane regimen. All patients were followed-up at the Department of Obstetrics and Gynecology, Keio University Hospital, Tokyo. Treatment decisions for second-line chemotherapy were usually made by the attending clinician Data were collected on age, International Federation of Obstetricians and Gynaecologists (FIGO) , histologic type, the extent and outcome of surgery, prior chemotherapeutic treatments, recurrent sites, intervals between primary and secondary treatments and overall survival after receiving the second-line drug.

Definition of chemotherapy sensitivity of primary chemotherapy

Refractory, resistant, and sensitive in the first recurrence were defined as follows. Refractory: partial response, progression or stable disease on primary chemotherapy; Resistant: complete remission and relapse < 6 months after stopping primary chemotherapy; Sensitive: complete remission and relapse ≥ 6 months after stopping primary chemotherapy.

Evaluation of response of second-line chemotherapy

Response was based on two-dimensional measurements of the lesions on computed tomography (CT) or magnetic resonance imaging (MRI) images. Complete response (CR) was

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defined as no evidence of disease on imaging studies, with normalization of the serum CA125 level. Partial response (PR) was defined as a > 50% decrease in tumor size. Progressive disease (PD) was defined as a > 25 increase in tumor size or the appearance of a new lesion. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The CA125 response criteria were not used; however, patients were not considered as having PR or SD if there was an increase of CA125.

Statistical analysis

The relationship between response rate or non-PD rate and chemosensitivity, age, regimen, histology, and disease site were analyzed by Fisher's exact testStatistical calculations were performed using SPSS Statistics software version 17.0 for Windows (SPSS, Chicago, IL).

Results

Patients

Median age at the time of second-line chemotherapy was 55 years (range: 31-74). Clinical stage and histology were as follows: clinical stage (I: 5; II: 3; III: 24; IV: 12); histology (serous: 22; clear cell: 12; endometrioid: 8; undifferentiated: 2). At first recurrence, 24 patients were platinum-sensitive and 20 patients were platinum-resistant. Recurrent sites were as follows: 29 patients had a solitary site (abdominal cavity: 8; lymph node: 3; pelvic cavity: 10; liver: 4; lung 4) and 15 patients had multiple sites. Performance status (PS) was zero-one in 40 cases, and two in four cases at second-line chemotherapy Twenty-four patients received a platinum/taxane regimen, 13 patients received cisplatin+irinotecan, four patients received cisplatin+doxorubicin+cyclophosphamide, and three patients received irinotecan, doxil or topotecanas second-line chemotherapy.

Relationships between clinical factors and the response rate or non-PD rate

Relationships between clinical factors and the response rate or non-PD rate of second-line chemotherapy are shown in Table 1. In total, response rate and non-PD rate were 30% and 51% (CR: 8, PR: 5, SD: 9), respectively. The response rate in sensitive cases was higher than in refractory/resistant cases (50% vs 5% $p = 0.002$) and the non-PD rate in sensitive cases was higher than in refractory/resistant cases (67% vs 30% $p = 0.03$). However, age, chemotherapy regimen, histologic type and number of diseases were not related with the chemotherapy effect.

Table 1. — *Effect of second-line chemotherapy.*

Clinical factor		CR+PR	CR+PR+SD
All cases		30% (13/44)	50% (22/44)
Sensitivity	Sensitive	50% (12/24)*	67% (16/24)**
	Refractory/Resistant	5% (1/20)*	30% (6/20)**
Age	Median >	23% (5/22)	36% (8/22)
	Median <	36% (8/22)	64% (14/22)
Regimen	Mono	0% (0/3)	33% (1/3)
	Comb	32% (13/41)	51% (21/41)
Histology	Serous	41% (9/22)	55% (12/22)
	Non-serous	18% (4/22)	45% (10/22)
Disease site	Solitary	31% (9/29)	48% (14/29)
	Multiple	27% (4/15)	53% (8/15)

= *0.002, p = **0.03.

Table 2. — *Relationship between chemotherapy response and recurrent site.*

Recurrent site	CR+PR	CR+PR+SD
All cases		
Lymph node	44% (4/9)	89% (8/9)
Other	27% (13/48)	50% (24/48)
Pelvic cavity	15% (2/13)	54% (7/13)
Abdominal cavity	41% (7/17)	53% (9/17)
Liver	10% (1/10)	30% (3/10)
Lung	38% (3/8)	63% (5/8)
Sensitive		
Lymph node	100% (4/4)	100% (4/4)
Other	44% (11/25)	64% (16/25)
Pelvic cavity	20% (1/5)	60% (3/5)
Abdominal cavity	55% (6/11)	73% (8/11)
Liver	33% (1/3)	33% (1/3)
Lung	50% (3/6)	67% (4/6)
Refractory/Resistant		
Lymph node	0% (0/5)	80% (4/5)
Other	8.7% (2/23)	35% (8/23)
Pelvic cavity	13% (1/8)	50% (4/8)
Abdominal cavity	17% (1/6)	17% (1/6)
Liver	0% (0/7)	29% (2/7)
Lung	0% (0/2)	50% (1/2)

Table 3. — *Relationship between chemotherapy response and recurrent site in multiple recurrent cases.*

No.	Age	Histology	Sensitivity	Site	Response
1	55	Clear	Sensitive	Lymph node	CR
				Abdominal cavity	CR
2	62	Clear	Resistant	Liver	SD
				Pelvic cavity	SD
3	36	Clear	Sensitive	Lymph node	CR
				Liver	CR
				Lung	CR
4	62	Clear	Sensitive	Abdominal cavity	SD
				Lung	SD
5	53	Serous	Sensitive	Pelvic cavity	PD
				Liver	PD
6	50	Clear	Resistant	Pelvic cavity	PD
				Abdominal cavity	PD
7	57	Clear	Resistant	Abdominal cavity	PD
				Liver	PD
8	38	Endometrioid	Resistant	Liver	PD
				Lung	SD
9	63	Clear	Resistant	Abdominal cavity	CR
				Liver	SD
10	31	Endometrioid	Resistant	Lymph node	SD
				Lung	PD
11	52	Serous	Resistant	Lymph node	SD
				Abdominal cavity	PD
12	56	Serous	Resistant	Lymph node (PAN)	SD
				Lymph node (virchow)	SD

Relationship between chemotherapy response and recurrent site

The relationship between response rate or non-PD rate and recurrent sites is shown in Table 2. In all diseases, the response rate and non-PD rate tended to be higher in