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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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Phase III Trial of Upfront Debulking Surgery Versus Neoadjuvant Chemotherapy for Stage III/IV Ovarian, Tubal and Peritoneal Cancers: Japan Clinical Oncology Group Study JCOG0602

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On the basis of promising results of neoadjuvant chemotherapy (NAC) in our previous study (JCOG0206), we have been performing a Phase III study of treatment starting with NAC versus standard treatment starting with primary debulking surgery (PDS) for Stage III/IV müllerian carcinomas (ovarian, tubal and peritoneal carcinomas) since November 2006. The purposes are to prove the non-inferiority of the efficacy and to show the decrease in adverse effects resulting from reduced surgical invasiveness of treatment starting with NAC. Three hundred patients with advanced müllerian carcinomas will be randomized during 3 years. NAC arm patients undergo four cycles of NAC with paclitaxel plus carboplatin followed by interval debulking surgery and an additional four cycles of postsurgical chemotherapy. Standard arm patients undergo PDS and eight cycles of postsurgical chemotherapy with or without interval debulking surgery. The primary endpoint is overall survival. The major secondary endpoints are the incidence of adverse events and parameters representing surgical invasiveness.

Key words: ovarian neoplasms – neoadjuvant therapy – interval debulking surgery – primary debulking surgery

INTRODUCTION

The current standard treatment for advanced müllerian cancer is primary debulking surgery (PDS) followed by postsurgical chemotherapy. Better prognosis can be expected in cases in which optimal debulking can be achieved. Unfortunately, optimal debulking in the primary surgery can be achieved in only 30–60% of Stage III/IV müllerian cancers in average institutions (1,2), and the prognosis of patients with advanced müllerian cancers is poor. Neoadjuvant chemotherapy (NAC) has been recognized as a possible approach to improve the prognosis of these patients. In initial studies, NAC was chosen for patients with apparently unresectable bulky tumors or poor performance status as an alternative treatment to primary surgical debulking. Retrospective analyses (3–7) revealed that progression-free and overall survival were comparable between patients treated with NAC followed by interval debulking surgery (IDS) and those treated with PDS, though the former group had more advanced disease and poorer performance status. On the basis of these favorable results of NAC for patients with advanced disease or poor performance status, the target disease was extended to all cases of advanced disease, including patients without apparently unresectable tumors and good performance status in prospective studies. The European Organization for Research and Treatment of Cancer (EORTC) is conducting a Phase III study comparing neoadjuvant setting treatment with standard treatment for advanced müllerian cancers (8). We conducted a Phase II study of NAC with paclitaxel plus carboplatin followed by IDS and postsurgical chemotherapy as the study of the Japan

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Clinical Oncology Group (JCOG0206) (9). In the study, we assessed the safety and efficacy of NAC treatment, and also assessed whether we can accurately diagnose advanced müllerian cancer based on clinical findings, including imaging studies, cytologic findings and tumor markers. Although the final survival results of this Phase II study are awaited, we have started the Phase III trial on the basis of the efficacy and diagnostic accuracy shown in the study (10). Our study is basically similar to the EORTC study, with the aim of comparing NAC treatment with standard treatment for advanced müllerian cancer. One of the distinct points of our study is omitting the diagnostic surgical procedure, such as laparoscopy or laparotomy, based on the results of our above-mentioned previous study. This means the elimination of an extra procedure for the purpose of the clinical trial in both treatment arms and it has the advantage of making it possible to start NAC treatment earlier. In our study, it is possible to compare the two treatment protocols under clinically relevant conditions. Another distinct point is the number of cycles of chemotherapy. Since the study subjects are patients with evidently advanced disease according to clinical findings, we administer a total of eight cycles of chemotherapy in both treatment arms instead of the standard of six cycles.

The study protocol was designed by the Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG), approved by the Protocol Review Committee of JCOG on 18 October 2006 and activated on 17 November 2006. This trial was registered at the UMIN Clinical Trials Registry as UMIN000000523 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF THE JCOG0602

Purpose

The purposes are to prove the non-inferiority of the efficacy and to show the decrease in adverse effects due to reduced surgical invasiveness of treatment starting with NAC with paclitaxel plus carboplatin compared with standard treatment starting with PDS for stage III/IV müllerian carcinomas.

Study Setting

A multi-institutional (30 centers) randomized Phase III trial.

Resources

Health Sciences Research Grants for the Third Term Comprehensive Control Research for Cancer (Nos. h16-035, h19-028) and Grants-in Aid for Cancer Research (Nos. 17S-1, 17S-5, 17-12), from the Ministry of Health, Labor and Welfare, Japan.

Endpoints

The primary endpoint is overall survival among all eligible patients. Secondary endpoints concerning the efficacy of the treatments are as follows: (i) proportion of clinical complete remission (%cCR) among all eligible patients, (ii) progression-free survival among all eligible patients, (iii) response rate to NAC among patients assigned to the NAC arm. Clinical complete remission is defined as the disappearance of all lesions by computed tomography (CT) or magnetic resonance imaging (MRI), no pleural effusions by chest radiography and normal serum CA125 level (<20 U/ml) after completion of the protocol treatment. Secondary endpoints concerning the safety and surgical invasiveness of the treatments are as follows: (i) adverse events, (ii) number of times of surgery, (iii) total duration of the surgery, (iv) total amount of blood loss, (v) amount of blood transfusion during protocol treatment, (vi) amount of blood plasma, plasma expander and albumin infusion during protocol treatment, among all treated patients.

Eligibility Criteria

Inclusion Criteria

The study subjects are patients diagnosed with Stage III or IV ovarian, tubal or peritoneal carcinoma. The diagnosis is based on both imaging studies (CT or MRI, and chest radiography) and cytology/histology of ascites, pleural effusion or fluid/tissue obtained by tumor centesis. Malignancies of other origins, such as breast and digestive tract, should be excluded by endoscopy, opaque enema, or ultrasonography when these malignancies are suspected from symptoms, physical examination or imaging diagnosis. To rule out malignancies of digestive tract origin, the criteria for tumor markers are set to be CA125 >200 U/ml and CEA <20 ng/ml.

Further inclusion criteria are (i) the patient is clinically deemed to be a candidate for debulking surgery without evidence of brain, bone or bone marrow metastases, (ii) previously untreated for these malignancies and have no history of treatment with chemotherapy or radiotherapy for other diseases, (iii) age 20–75 years, (iv) Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, (v) adequate bone marrow, hepatic, renal, cardiac and respiratory functions and (vi) written informed consent.

Exclusion Criteria

Exclusion criteria are (i) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*, (ii) pregnant or nursing, (iii) severe mental disorder, (iv) systemic and continuous use of steroidal drugs, (v) positive for serum hepatitis B surface antigen, (vi) active infections, (vii) uncontrolled hypertension, (viii) diabetes mellitus, uncontrolled or controlled with insulin, (ix) history of cardiac failure, unstable angina, myocardial infarction within 6 months prior to registration, (x) intestinal occlusion requiring surgical treatment, (xi) hypersensitivity to polyoxyethylated castor oil and (xii) hypersensitivity to alcohol.

Treatment Methods

Standard Treatment Arm

Primary debulking surgery. PDS is performed within 4 weeks of study enrollment. Standard procedures for PDS consist of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and maximal debulking of metastatic tumors. Systematic pelvic and/or aortic lymphadenectomies are allowed.

Postsurgical chemotherapy. Eight cycles of a combination of paclitaxel (175 mg/m^2, Day 1) and carboplatin (AUC = 6, Day 1), namely the TC regimen, are administered every 3 weeks. Postsurgical chemotherapy is initiated within 3–5 weeks after PDS, according to the invasiveness of the surgery.

Interval debulking surgery. IDS is required when any of the standard procedures is not completed at PDS. IDS is allowed, as an option, when residual tumor larger than 1 cm is left at PDS. In such cases, IDS is performed 4–7 weeks after administration of the fourth cycle of postsurgical chemotherapy unless there is disease progression. The standard goal of IDS is completion of all standard procedures of PDS and maximal debulking of metastatic tumors. Systematic pelvic and/or aortic lymphadenectomies are allowed, but not included in the standard goal of IDS. Following IDS, four additional cycles of chemotherapy (TC regimen) is administered (eight cycles of chemotherapy in total). The chemotherapy is initiated within 3–5 weeks after IDS, according to the invasiveness of the surgery.

NAC Arm

Neoadjuvant chemotherapy. Four cycles of a combination of paclitaxel (175 mg/m^2, Day 1) and carboplatin (AUC = 6, Day 1) are administered every 3 weeks. NAC is initiated within 2 weeks of study enrollment.

Interval debulking surgery. IDS is performed 4–7 weeks after administration of the fourth cycle of NAC unless disease progression occurs during NAC. Standard procedures of IDS consist of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and maximal debulking of metastatic tumors. Systematic pelvic and/or aortic lymphadenectomies are allowed, but not included in standard procedures.

Postsurgical chemotherapy. Four additional cycles of chemotherapy (TC regimen) are administered (8 cycles of chemotherapy in total). Postsurgical chemotherapy is initiated within 3 to 5 weeks after IDS, according to the invasiveness of the surgery.

Study Design and Statistical Methods

The study is designed as a randomized Phase III non-inferiority study. Patients are randomized to each treatment arm by a minimization method with institution, Stage (III or IV), PS (0, 1 or 2, 3) and age (<60 or ≥ 60) as balancing factors at the JCOG Data Center. The planned accrual period is 3 years and the follow-up period is set as 5 years after completion of accrual. The hazard ratio between treatment arms and its confidence interval, estimated by the Cox proportional hazard model stratified with stage, PS and age is used to test the non-inferiority of the NAC treatment regarding overall survival. The significance level is set as 0.05 in a one-sided test because of the non-inferiority design of the study. Two hundred seventy-six events would provide a statistical power of 80%, to conclude that the NAC arm is not inferior to the standard arm in 3-year overall survival with a non-inferiority margin of 5%, and non-inferiority is concluded if the upper limit of the confidence interval of the hazard ratio does not exceed the limit of 1.161, which is in accord with the non-inferiority margin. A sample size of 298 patients is necessary to observe 276 events, considering the accrual and follow-up period, an estimated 3-year overall survival of 25% in the standard treatment arm and an expected 3-year overall survival of 30.3% in the NAC arm. Thus, the target sample size of 300 patients (150 patients per regimen) was set. Interim analysis is planned after half of the patients are enrolled, taking into account the multiplicity with the O'Brien Fleming type alpha spending function.

Study Monitoring

In-house interim monitoring is performed by the JCOG Data Center to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress according to standard JCOG procedures. Monitoring reports are submitted to the investigators in GCSG and the JCOG Data and Safety Monitoring Committee every 6 months.

Participating Institutions

Hokkaido University, Sapporo Medical University, Tohoku University, University of Tsukuba, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center, National Cancer Center Hospital, The Jikei University School of Medicine, Cancer Institute Hospital, University of Tokyo, Juntendo University, Kitasato University, Niigata Cancer Center Hospital, Shinshu University, Aichi Cancer Center, National Hospital Organization Nagoya Medical Center, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka City General Hospital, Osaka City University, Hyogo Cancer Center, Tottori University, National Hospital Organization Kure Medical Center, National Hospital Organization Shikoku Cancer Center, National Hospital Organization Kyushu Cancer Center, University of Kurume, Kyushu University, Saga University and Kagoshima City Hospital.

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Phase II Clinical Trial of Pegylated Liposomal Doxorubicin (JNS002) in Japanese Patients with Müllerian Carcinoma (Epithelial Ovarian Carcinoma, Primary Carcinoma of Fallopian Tube, Peritoneal Carcinoma) Having a Therapeutic History of Platinum-based Chemotherapy: A Phase II Study of the Japanese Gynecologic Oncology Group

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Objective: This study was conducted to evaluate the efficacy and safety of pegylated liposomal doxorubicin (PLD) in Japanese patients with Müllerian carcinoma having a therapeutic history of platinum-based chemotherapy.

Methods: Patients who were diagnosed with Müllerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube and peritoneal carcinoma) by histological examination and had received the initial platinum-based chemotherapy were included in the study. The study drug was administered to the patients at 50 mg/m^2 every 4 weeks.

Results: Seventy-four patients were enrolled in the study. All patients had received platinum-based chemotherapy as first-line regimen and more than 90% of patients had also received taxanes. The overall response rate was 21.9% (95% confidence interval, 13.1–33.1%) and 38.4% of patients had stable disease. The median time to progression was 166 days. The major non-haematological toxicities were hand-foot syndrome (Grade 3; 16.2%) and stomatitis (Grade 3; 8.1%). Myelosuppression such as leukopenia (Grade 3; 52.7%, Grade 4; 6.8%), neutropenia (Grade 3; 31.1%, Grade 4; 36.5%) and decreased haemoglobin (Grade 3; 14.9%, Grade 4; 2.7%) were the most common haematological toxicities.

Conclusion: We confirmed that a 50 mg/m^2 every 4 weeks regimen of PLD was active in Japanese patients with Müllerian carcinoma having a therapeutic history of platinum-based chemotherapy and toxicity was manageable by dose modification of PLD or supportive care.

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Key words: pegylated liposomal doxorubicin – Müllerian carcinoma – ovarian carcinoma – hand-foot syndrome – chemo-gynaecology – chemo-phase I-II-III – gynaecology

INTRODUCTION

Approximately 8000 cases of ovarian cancer are newly diagnosed in Japan and more than 4000 women die of this disease (1). From an embryologic perspective, epithelial ovarian carcinoma, primary carcinoma of fallopian tube and peritoneal carcinoma are generally recognized as a similar disease group, which is known as Müllerian carcinoma. In patients with primary carcinoma of the fallopian tube and peritoneal carcinoma, the experience with chemotherapeutic agents is largely limited to case reports and small studies due to the rarity of disease type (2,3). However, the overall experience closely parallels that of ovarian cancer, so treatment of primary carcinoma of the fallopian tube and peritoneal carcinoma is conducted according to that of ovarian cancer (2,3).

Advanced epithelial ovarian cancer is a highly chemosensitive solid tumour with response rates to first-line chemotherapy of ~80%. The majority of patients, however, eventually relapse and treatment with second-line agents becomes necessary. Furthermore, patients with recurrent ovarian cancer ultimately die of chemoresistant disease. Therefore, it is very important to recognize recurrent ovarian cancer therapy as palliative therapy and therapeutic agents are required to show efficacy as well as favourable toxicity profile. However, there are not many drugs approved in Japan for ovarian carcinoma, or recommended by the Japanese clinical practice guideline for as second-line treatment except platinum, taxane and irinotecan.

Pegylated liposomal doxorubicin (PLD) is a formulation of doxorubicin hydrochloride encapsulated in long circulating STEALTH® liposomes and formulated for intravenous administration. STEALTH® liposomes have liquid membranes coated with polyethylene glycol, which attracts water and renders resistance to mononuclear phagocytosis (4). The liposome's small diameter (~100 nm) and their persistence in the circulation allow their penetration into altered and often compromised, leaky tumour vasculature with entry into the interstitial space in malignant tissues (5). Therefore, pegylated liposomes are suitable for prolonged delivery of doxorubicin and have a prolonged circulation time (6,7). At these tumour sites, the accumulating liposomes gradually break down, releasing doxorubicin to the surrounding tumour cells (8,9). PLD has been designed to enhance the efficacy and to reduce the toxicities of doxorubicin such as myelosuppression, alopecia and cardiotoxicity by altering the plasma pharmacokinetics and tissue distribution of the drug.

Based on the data from the Phases II and III clinical trials in Europe and the USA, it is evident that PLD possesses promising activity and a favourable toxicity profile in the second-line treatment of ovarian cancer (10–15). Currently, PLD is provided as one of the standard treatment options in recurrent ovarian cancer treatment guidelines (16–18).

The result of the Phase I clinical trial in Japan was reported (19). In that study, recommended PLD dose was evaluated in 15 Japanese patients with solid tumours and resulted in 50 mg/m^2 every 4 weeks. In addition, one partial response (PR) and one normalization of CA125 were observed among six ovarian cancer patients enrolled in that study, and further trials with Japanese ovarian cancer patients were encouraged.

Based on the result from a Phase I clinical trial in Japan, we conducted the Phase II clinical trial of PLD in patients with recurrent or relapsed Müllerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube, peritoneal carcinoma) having a therapeutic history of platinum-based chemotherapy.

We conducted a multicentre, non-randomized, open-label study to evaluate efficacy and safety of a PLD 50 mg/m^2 every 4-week regimen in Japanese patients with Müllerian carcinoma who had previously been treated with platinum-based chemotherapy.

PATIENT AND METHODS

Study Design

This study was a multicentre non-randomized, open-label trial to evaluate efficacy and safety of PLD in Japanese patients with Müllerian carcinoma previously treated with platinum-based chemotherapy. The primary endpoint was the best overall response (response rate) and secondary endpoints included adverse events and adverse drug reactions (incidence, severity, seriousness and causality), time to response and duration of response. The final evaluation of the antitumour effect was performed by the independent radiological review committee. The study protocol was approved by the institutional review board at each site. This study was conducted based on ethical principles in the Declaration of Helsinki and in compliance with Good Clinical Practice.

Patients

This study included patients who met all the following inclusion criteria: (i) having histological confirmation of Müllerian carcinoma (epithelial ovarian carcinoma, primary fallopian tube carcinoma and peritoneal carcinoma);

(ii) receiving first-line platinum-based chemotherapy and who would receive PLD as a second-line therapy if time to progression was within 12 months from the date of final administration of platinum therapy, excluding patients whose best response to first-line platinum-based chemotherapy was progressive disease (PD), or who received PLD as a third-line therapy; (iii) receiving 1 or 2 regimens with prior chemotherapy; (iv) having measurable lesions that conformed to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria; (v) ECOG performance status (PS) grade of 0–2; (vi) adequate functions of principal organs, defined by white blood cell (WBC) counts 3.0×10^3–$12.0 \times 10^3/mm^3$, neutrophil counts not less than $1.5 \times 10^3/mm^3$, haemoglobin not less than 9.0 g/dl, platelet count not less than $10.0 \times 10^4/mm^3$, serum AST, ALT and AP not more than 2.5 times the institutional upper limit of normal, total bilirubin not more than the institutional upper limit of normal, serum creatinine not more than 1.5 times the institutional upper limit of normal, left ventricular ejection fraction (LVEF) not less than 50%, electrocardiography (ECG) normal or minor change without symptoms that required any therapeutic intervention, and no evidence of cardiac disorder or Class 1 in New York Heart Association (NYHA) functional classification; (vii) no colony stimulating factor (CSF) agent or blood transfusion received within 2 weeks before the date of blood tests for screening; (viii) no previous treatment with hormonal agents, oral antimetabolic or immunotherapeutic agents for at least 2 weeks, with nitrosourea or mitomycin C at least 6 weeks, or with surgical therapy, radiation therapy or other chemotherapy for 4 weeks or more; (ix) abilities to stay in hospital for 4 consecutive weeks from the initial administration of PLD; (x) survival expectancy 3 months or longer; (xi) 20–79 of age years at enrolment in the trial; and (xii) received an explanation of this trial from the physicians with written informed consent forms and other relevant information and freely provided informed consent before the trial.

Patients who met any of the following exclusion criteria were excluded from the trial: (i) requiring drainage of pericardial fluid; (ii) having experienced myocardial infarction or angina attack within 90 days before the start of trial; (iii) receiving prior therapy with anthracycline (total anthracycline dose of more than 250 mg/m^2 as doxorubicin); and (iv) having known hypersensitivity to doxorubicin or any component of PLD.

Medication

PLD was intravenously administered to each subject at a dose of 50 mg/m^2 as doxorubicin hydrochloride on Day 1 of each cycle, followed by a treatment-free interval of 28 days including Day 1. This was repeated for at least two cycles if the subject did not meet the withdrawal criteria. PLD was administered at a rate of 1.0 mg/min from the start of infusion to completion, using an infusion pump in consideration of risks of development of infusion-related reactions. PLD was used by diluting with 250 ml of 5% glucose injection for a dose of less than 90 mg as doxorubicin hydrochloride or with 500 ml for a dose of 90 mg or more as doxorubicin hydrochloride.

After administration, PLD would be discontinued in subjects who met any of the following withdrawal criteria: (i) desiring to discontinue the study treatment or withdrawing consent; (ii) having LVEF decreased to less than 45% after administration of PLD or decreased by 20% or more than baseline; (iii) having no possibility for a subsequent cycle to be started within 6 weeks from the planned injection date because of adverse reactions or after 8 weeks for hand-foot syndrome (HFS) or stomatitis; (iv) having bilirubin increased to 3.0 mg/dl or more; (v) requiring a repeated reduction in the dose; (vi) the anticipated total dose of anthracycline antibiotics including PLD would exceed 500 mg/m^2 as doxorubicin hydrochloride (including doses from prior chemotherapy and pre/postoperative treatment); (vii) being judged by the physician to have difficulties continuing the trial due to serious (or significant) adverse events; (viii) being assessed to have difficulty continuing the trial due to concurrent illnesses (e.g. complications); (ix) having obvious progression of the underlying disease or development of new lesions (PD); (x) having any of the exclusion criteria which was discovered after enrolment; and (xi) being judged as unfavourable to continue the trial by the physician.

Prior to administration of the study drug in the next cycle, all the subjects were confirmed to meet all the following criteria: (i) HFS or stomatitis $\leq$Grade 1; (ii) neutrophil counts $\geq 1.5 \times 10^3/mm^3$; (iii) WBC counts $\geq 3.0 \times 10^3/mm^3$; (iv) platelet counts $\geq 7.5 \times 10^4/mm^3$; (v) bilirubin $\leq$1.5 mg/dl; and (vi) other adverse drug reactions $\leq$ Grade 2 (excluding fatigue, nausea, vomiting, anorexia, hypokalemia, hyponatremia and lymphopenia). If any of these criteria was not met, the scheduled administration of the study drug for the next cycle would be delayed for 2 weeks at the maximum. If any of the above criteria was still not met after a 2-week delay from the scheduled initial date of each cycle, the trial for the subjects would be discontinued. In case Grade 2 HFS or stomatitis was observed at 6 weeks from the initial date of each cycle, the scheduled administration of the test drug for the next cycle would be delayed for 2 weeks. As a result, when the subjects met all the above criteria, the next cycle would be started. Even if the subjects met all the criteria, the scheduled initial date could be delayed for a maximum of 2 weeks at the investigator's discretion.

As the subjects met any of the following dose reduction criteria, the previous dose would be reduced by 25% (37.5 mg/m^2) for the next cycle: (i) HFS or stomatitis $\geq$ Grade 3; (ii) neutrophil count $<500/mm^3$ or WBC count $<1000/mm^3$ that was maintained for at least 7 days; (iii) neutrophil counts $<1000/mm^3$ with 38.0°C or higher fever; (iv) platelet reduction $<2.5 \times 10^4/mm^3$; (v) other adverse drug reactions $\geq$ Grade 3 (excluding fatigue, nausea, vomiting, anorexia, hypokalemia, hyponatremia, lymphopenia and other adverse events associated with infusion-related reactions); and (vi) the physician judged that the dose should be

decreased. Dose reduction was permitted only once, and it was prohibited to increase the dose after the dose was reduced. If a further dose reduction was required after the dose was reduced, the trial for the subject would be discontinued.

Administration of CSF was admitted when patients met any of the following criteria: (i) neutrophil counts $<1000/mm^3$ with fever ($\geq 38°C$); (ii) neutrophil counts $<500/mm^3$; (iii) experience of either (i) or (ii) in the prior cycle and neutrophil counts $<1000/mm^3$ in the following cycle.

Evaluation of Response and Safety

Tumour response evaluation was performed according to the RECIST guidelines. Confirmed duration of stable disease (SD) was defined as the duration of 8 consecutive weeks or longer after the start of administration.

Severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

Sample Size and Statistical Analysis

Among the subjects enrolled in this trial, those who received platinum-based chemotherapy as the first-line chemotherapy and experienced disease progression between 6 and 12 months after the completion of the platinum regimen were classified as the platinum-sensitive group, and those who had progression during the first-line chemotherapy, received platinum-based chemotherapy as the first-line chemotherapy and experienced progression less than 6 months after the completion of the platinum regimen, or who would receive PLD as a third-line therapy were classified as the platinum-resistant group. A sample size to produce the expected response rate of 30 and 15% for the platinum-sensitive and platinum-resistant groups, respectively, with the threshold response rate of 5%, a significance level of 5% and power of 80% was determined to be 80 patients in total (20 and 60 patients for the platinum-sensitive and platinum-resistant groups, respectively).

For the response evaluation, statistical analysis was performed based on the evaluation for the full analysis set (FAS) by the independent radiological review committee. The primary endpoint was the response rate, the proportion of patients with complete response (CR) or PR in the response analysis set, and the point estimate and two-sided 95% confidence interval (CI) were calculated. The secondary endpoints included the duration of overall response, time to response and time to progression, and the progression-free survival was analysed using the Kaplan–Meier method, and descriptive statistics (median, minimum and maximum) were calculated. The safety of PLD was evaluated for all the subjects treated with PLD. Statistical analyses were performed using the SAS System for Windows release 8.02.

RESULT

Demographics and baseline characteristics of patients are shown in Table 1. Seventy-four patients were enrolled into the trial between January and December 2005, and 73 patients (11 for the platinum-sensitive group and 62 for the platinum-resistant group), excluding one patient who was confirmed to be ineligible after enrolment, were eligible for the trial, and defined as the FAS. All 74 patients who received PLD were defined as the safety analysis set. Although the targeted number of patients for the platinum-sensitive group was 20, only 11 patients were enrolled. That was because the study was closed at the end of 2005 when the patient enrolment in the platinum-resistant group reached the target number due to slow enrolment.

The median of patients' age was 57.0 years (range, 32–76). Among 74 patients enrolled, 62 had epithelial ovarian carcinoma and 12 had peritoneal carcinoma. Histological, 49 patients had serous carcinoma, eight had endometrioid carcinoma, eight had clear cell carcinoma, one had mucinous carcinoma and eight had other types of carcinoma. All 74 patients had received first-line chemotherapy including platinum regimen, 70 (94.6%) had also received taxanes as the first-line chemotherapy, and only three had received anthracycline in the prior chemotherapy. A total of 334 cycles of PLD was administered to 74 patients, and the median number of cycles administered was 4.0 (range, 1–10 cycles). Administration of PLD was completed or discontinued in all 74 patients before statistical analysis. The dose of PLD was reduced to 37.5 mg/m^2 in 26 of 74 patients (35.1%). The scheduled administration of PLD was delayed in 49 of 74 patients (66.2%) and in 154 of 334 cycles (46.1%).

Response

The antitumour effect (best overall response) and response rate are shown in Table 2. The best overall response in 73 patients of FAS was CR in two patients, PR in 14, SD in 28, PD in 27 and not evaluable (NE) in two patients. The response rate was 21.9% (16 of 73) (95% CI: 13.1–33.1%). The response rate (two-sided 95% CI) by patient group was 27.3% (3 of 11) (95% CI: 6.0–61.0%) in the platinum-sensitive group and 21.0% (13 of 62) (95% CI: 11.7–33.2%) in the platinum-resistant group. The proportion of patients with CR, PR or SD was 60.3% (44 of 73) in FAS, and 54.5% (6 of 11) in the platinum-sensitive group and 61.3% (38 of 62) in the platinum-resistant group.

The results from subgroup analysis sets by platinum-free interval were as follows. In a subgroup analysis set where patients received PLD as a second-line therapy, the response rate by platinum-free intervals was 8.3% (1 of 12) and 27.3% (3 of 11) in patients with the platinum-free interval of within 6 months and of 6–12 months, respectively. In another subgroup analysis set where patients received PLD as a third-line therapy, the response rate was 7.1% (1 of 14),

Table 1. Demographics and baseline characteristics of patients

Characteristics	Total ($n = 74$)	Platinum sensitive ($n = 11$)	Platinum resistant ($n = 63$)
Age, years			
Median (range)	57.0 (32–76)	55.0 (40–72)	58.0 (32–76)
Primary cancer (%)			
Epithelial ovarian carcinoma	62 (83.8)	11 (100.0)	51 (81.0)
Peritoneal carcinoma	12 (16.2)	0 (0.0)	12 (19.0)
Tumour histology (%)			
Serous	49 (66.2)	6 (54.5)	43 (68.3)
Endometrioid	8 (10.8)	3 (27.3)	5 (7.9)
Clear cell	8 (10.8)	1 (9.1)	7 (11.1)
Mucinous	1 (1.4)	0 (0.0)	1 (1.6)
Other	8 (10.8)	1 (9.1)	7 (11.1)
Initial FIGO stage (%)			
I	7 (9.5)	1 (9.1)	6 (9.5)
II	1 (1.4)	1 (9.1)	0 (0.0)
III	50 (67.6)	6 (54.5)	44 (69.8)
IV	16 (21.6)	3 (27.3)	13 (20.6)
Previous chemotherapy (%)			
1 regimen	23 (31.1)	11 (100.0)	12 (19.0)
2 regimen	50 (67.6)	0 (0.0)	50 (79.4)
3 regimen	1 (1.4)	0 (0.0)	1 (1.6)
Previous chemotherapy with antracycline (%)			
Yes	3 (4.1)	0 (0.0)	3 (4.8)
No	71 (95.9)	11 (100.0)	60 (95.2)
Platinum-free interval (days)			
Median (range)	263 (28–2792)	315 (216–441)	235 (28–2792)
CA-125 at baseline (U/ml)			
Median (range)	243.6 (5.8–7809.8)	192.1 (22.2–808.0)	261.0 (5.8–7809.8)

FIGO, Federation Internationale de Gynecologie et d'Obstetrique.

Table 2. Response rate

	Total	Platinum sensitive	Platinum resistant
Number of patients	73	11	62
Best overall response: *n* (%)			
CR	2 (2.7)	0 (0.0)	2 (3.2)
PR	14 (19.2)	3 (27.3)	11 (17.7)
SD	28 (38.4)	3 (27.3)	25 (40.3)
PD	27 (37.0)	4 (36.4)	23 (37.1)
NE	2 (2.7)	1 (9.1)	1 (1.6)
Response rate			
n (%) (95% CI)	16 (21.9) (13.1–33.1)	3 (27.3) (6.0–61.0)	13 (21.0) (11.7–33.2)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable; 95% CI, confidence interval.

15.4% (2 of 13) and 36.8% (7 of 19) in patients with the platinum-free interval of within 6 months, of 6–12 months and more than 12 months, respectively.

The response rate by histological type was 29.2% (14 of 48) and 25.0% (2 of 8) in patients with serous carcinoma and with endometrioid carcinoma, respectively. In patients

Table 3. Time to response, duration of response and time to progression

	Total	Platinum sensitive	Platinum resistant
Number of patients	73	11	62
Time to response (day)			
Patient (%)[a]	16 (21.9)	3 (27.3)	13 (21.0)
Median (range)	54.0 (20–162)	56.0 (54–59)	52.0 (20–162)
Duration of response (day)			
Patient (%)[a]	16 (21.9)	3 (27.3)	13 (21.0)
Median (range)	149.0 (56–309)	– (92–159)	149.0 (56–309)
Withdrawal (%)	11 (68.8)	2 (66.7)	9 (69.2)
Time to progression (day)			
Patient (%)[b]	71 (97.3)	10 (90.9)	61 (98.4)
Median (range)	166.0 (14–358)	159.0 (16–217)	168.0 (14–358)
Withdrawal (%)	30 (42.3)	4 (40.0)	26 (42.6)

[a]Responder only. [b]Excluded two patients due to unable calculation for time to progression.

with clear cell carcinoma, SD was observed in two of eight patients, and the time to progression in the two patients was 350+ and 87+ days, respectively. In patients with mucinous carcinoma, SD was observed in one of one patient and the time to progression was 135+ days.

The median and range of the duration of response, time to response and time to progression are shown in Table 3.

The median time to response (CR or PR) was 54.0 days. The median time to response was 56.0 days in the platinum-sensitive group and 52.0 days in the platinum-resistant group.

The median duration of overall response was 149.0 days. The median duration of overall response in the platinum-resistant group was 149.0 days, however, that in the platinum-sensitive group could not be calculated. The Kaplan–Meier curve for time to progression is shown in Fig. 1. The median time to progression was 166.0 days: 159.0 days in the platinum-sensitive group and 168.0 days in the platinum-resistant group. The median survival could not be calculated.

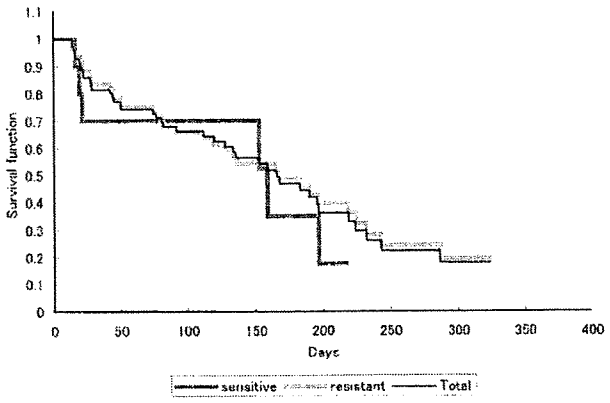

Figure 1. Kaplan–Meier estimates of time to progression.

Safety

Adverse drug reactions were reported from all 74 patients treated with PLD. The major adverse drug reactions observed in the study are shown in Table 4.

The most common Grade 3 or 4 adverse reactions were due to haematological toxicity: neutropenia in 50 patients (67.6%), leukopenia in 44 (52.7%), lymphopenia in 35 (47.3%), decreased haemoglobin in 13 (17.6%), thrombocytopenia in five (6.8%) and erythropenia in three patients (4.1%). The median time to nadir for neutrophils, WBCs, haemoglobin and platelets from the start of administration in the first cycle was 21.0 days, 21.0, 15.0 and 22.0 days, respectively. The median time to recovery to the level at which the administration of PLD in the next cycle was permitted was 7.0–8.0 days for any haematological event.

Grade 3 or 4 adverse drug reactions due to non-haematological toxicity included: HFS in 12 patients (16.2%), stomatitis in six (8.1%), febrile neutropenia, nausea, ALT (GPT) increased and blood potassium decreased in two each (2.7%) and deep venous thrombosis rash, herpes zoster, infection, upper respiratory tract infection, impaired glucose tolerance, diarrhoea, small intestinal obstruction, vomiting, fatigue, AST (GOT) increased, decreased blood sodium and increased γ-GTP in one each (1.4%). Only deep venous thrombosis was Grade 4. The median time to occurrence of HFS, rash and stomatitis from the start of administration was 34.0 days (2.0 cycles), 33.0 days (2.0 cycles) and 16.0 days (1.0 cycle), respectively. The median time to the Grade 2, 3 or 4 adverse reactions (Grade 3 or 4 for rash), which required delay of next administration, was 64.5 (3.0 cycles), 84.0 (3.0 cycles) and 43.0 (2.0 cycles), respectively and the median duration for those reactions was 15.0, 8.0 and 8.0 days, respectively.

Infusion-related reactions were seen in 14 patients (18.9%) only during the first cycle. Serious reactions were not seen.

Table 4. Grades 3 and 4 adverse drug reactions

Adverse Reaction (MedDRA/J Ver9.0)	Number of patients ($n = 74$)			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	8 (10.8)	11 (14.9)	23 (31.1)	27 (36.5)
Lymphocytopenia	15 (20.3)	16 (21.6)	29 (39.2)	6 (8.1)
Leukopenia	5 (6.8)	20 (27.0)	39 (52.7)	5 (6.8)
Haemoglobin decreased	23 (31.1)	27 (36.5)	11 (14.9)	2 (2.7)
Thrombocytopenia	27 (36.5)	13 (17.6)	4 (5.4)	1 (1.4)
Deep vein thrombosis	0 (0)	0 (0)	0 (0)	1 (1.4)
Hand-foot syndrome	20 (27.0)	26 (35.1)	12 (16.2)	0 (0)
Stomatitis	29 (39.2)	22 (29.7)	6 (8.1)	0 (0)
Erythropenia	42 (56.8)	11 (14.9)	3 (4.1)	0 (0)
Nausea	37 (50.0)	6 (8.1)	2 (2.7)	0 (0)
ALT (GPT) increased	16 (21.6)	1 (1.4)	2 (2.7)	0 (0)
Blood potassium decreased	10 (13.5)	0 (0)	2 (2.7)	0 (0)
Febrile neutropenia	0 (0)	0 (0)	2 (2.7)	0 (0)
Rash	17 (23.0)	19 (25.7)	1 (1.4)	0 (0)
Fatigue	28 (37.8)	5 (6.8)	1 (1.4)	0 (0)
Vomiting	11 (14.9)	5 (6.8)	1 (1.4)	0 (0)
γ-GTP increased	13 (17.6)	4 (5.4)	1 (1.4)	0 (0)
Diarrhoea	12 (16.2)	4 (5.4)	1 (1.4)	0 (0)
AST (GOT) increased	18 (24.3)	2 (2.7)	1 (1.4)	0 (0)
Upper respiratory tract infection	0 (0)	2 (2.7)	1 (1.4)	0 (0)
Blood sodium decreased	15 (20.3)	0 (0)	1 (1.4)	0 (0)
Small intestinal obstruction	0 (0)	0 (0)	1 (1.4)	0 (0)
Herpes zoster	0 (0)	0 (0)	1 (1.4)	0 (0)
Infection	0 (0)	0 (0)	1 (1.4)	0 (0)
Glucose tolerance impaired	0 (0)	0 (0)	1 (1.4)	0 (0)

Of these patients, one patient had Grade 2 events and other patients had Grade 1 events. Symptoms associated with infusion-related reactions included hot flushes, facial flushing and hot feeling. These symptoms were restored on the day of occurrence or the following day. PLD was discontinued in one patient who had nausea, low back pain, chest tightness and facial flushing as Grade 2 infusion-related reactions. These symptoms were rapidly restored by supportive care with drip infusion of physiological saline. Although slow-down in the PLD infusion rate was required in two patients, the other 11 patients completed the infusion without any intervention. Among 14 patients with infusion-related reactions, 11 patients received the next cycle without recurrence of infusion-related reactions.

Cardiac toxicity was seen in 17 of 74 patients (23.0%), all of which were Grade 1. Increase in the incidence of cardiac toxicity associated with accumulation of PLD was not observed. Alopecia was seen in 18 patients (24.3%), which was Grade 1 in all of them.

There was no death due to adverse events reported during the trial period. Fourteen serious adverse reactions were seen in 11 patients (14.9%): two events each of nausea, HFS, small intestinal obstruction and stomatitis; and one event each of neutropenia, leukopenia, vomiting, pneumonitis, deep venous thrombosis and anorexia.

PLD was discontinued due to adverse reactions in 16 (21.6%). Common adverse reactions that required the discontinuation of PLD included: decreased haemoglobin in six patients (8.1%), leukopenia in four (5.4%) and HFS and neutropenia in three each (4.1%). The PLD dose was reduced in 24 patients (32.4%) due to adverse drug reactions such as HFS in 10 patients (13.5%), decreased haemoglobin and stomatitis in five each (6.8%) and neutropenia in three patients (4.1%). Administration of PLD was delayed in 49 patients (66.2%) in 111 cycles of 334 cycles due to adverse reactions mainly including leukopenia in 68 cycles (20.4%), neutropenia in 56 cycles (16.8%), HFS in 40 cycles (12.0%) and stomatitis in eight cycles (2.4%).

DISCUSSION

We evaluated the efficacy and safety of PLD in Japanese patients with Müllerian carcinoma (epithelial ovarian carcinoma, primary fallopian tube carcinoma and peritoneal carcinoma) previously treated with platinum-based chemotherapy.

Currently, platinum and taxane therapies are used for the standard first-line chemotherapy for treatment of ovarian carcinoma, though the results of Phase III clinical trials conducted in the US and Europe demonstrated the effectiveness of PLD, gemcitabine and topotecan in patients resistant to these drugs (13,14,20). However, these drugs have not been approved and the results from prospective studies of their use in patients with ovarian carcinoma previously treated with platinum and taxane therapy have not been reported in Japan. Our study was intended to provide the outcome in patients who had recurrent Müllerian carcinoma after the standard first-line chemotherapy (90% of patients in our study had received first-line chemotherapy with platinum and taxane).

In this trial, the response rate was 21.9% (95% CI: 13.1–33.1%) for all patients in FAS. The response rate in the platinum-sensitive and platinum-resistant groups was 27.3% (95% CI: 6.0–61.0%) and 21.0% (95% CI: 11.7–33.2%), respectively. Better response was obtained in patients with longer platinum-free interval when PLD was administered as second- or third-line chemotherapy. Clinical studies conducted in the US and Europe showed that the response rate of PLD was 28.4% in the platinum-sensitive group and 6.5–18.3% in the platinum-resistant group (11,12,13). These response rates were similar to those obtained in our trial.

Common adverse reactions reported in this study were haematological toxicities (leukopenia, neutropenia and decreased haemoglobin), HFS and stomatitis.

The median time to nadir for WBC, neutrophils and haemoglobin after the start of administration of PLD was 15–22 days, and the median time to recovery to baseline after reaching the nadir was 7–8 days. Repeated cycles did not lead to worsening the events. Most patients could receive PLD continually by concomitant use of G-CSF and dose modification, such as dose reduction and delay of next administration.

In the previous Phase III study (13), HFS and stomatitis occurred in 49% (Grade 3 or higher: 23%) and 40% (Grade 3 or higher: 8%) of patients, respectively. Although these toxicities were seen in 78.3 and 77.0% of patients in our study, only 16.2 and 8.1% of patients experienced Grade 3 or higher toxicities, respectively. Most patients could continually receive PLD treatment by dose modification of PLD and supportive care, and the patients discontinued due to toxicities were few.

Infusion-related reaction that is known as toxicity specific to PLD was seen in 14 patients (18.9%) during the first cycle, all of which were resolved on the day of the occurrence or the following day. The second cycle was administered in 11 of 14 patients with infusion-related reactions. No recurrence of infusion-related reactions was seen in all 11 patients. It is important to use PLD with close attention to the condition of patients at the first administration of PLD. Infusion-related reaction is related to the initial infusion rate of PLD. It has been reported that decreasing the infusion rate reduces the risk of the infusion-related reaction (21).

It has been reported that cardiac toxicity, which is a significant problem with the use of conventional doxorubicin, associated with PLD is mild (22). Also in this trial, all cardiac toxicities observed were Grade 1, and had no effect on continuation of the trial. Furthermore, no patients experienced Grade 2 or higher alopecia, and Grade 3 or higher gastrointestinal toxicities were rarely seen in our trial. These toxicities are frequently induced by treatment of conventional doxorubicin.

These results suggest that toxicity of PLD is manageable by dose modification of PLD and supportive care.

Most patients with ovarian carcinoma exhibited response to first-line chemotherapy, however, the incidence of recurrence is high and prognosis is poor. It might be important to recognize that the chemotherapy would be palliative treatment for treatment of recurrent ovarian carcinoma. PLD has a safety profile that is different from that of platinum and taxanes, which are used for the standard first-line chemotherapy. PLD has a low risk of enhancing cumulative toxicities (haematological toxicity or neurotoxicity) associated with first-line chemotherapy. PLD is expected to have a beneficial effect against disease progression as the proportion of patients with CR, PR or SD and time to progression were 60.3% and 166 days (median). Furthermore, PLD might make it easy to provide long-term outpatient chemotherapy since PLD would reduce a patient burden by dosing once every 4 weeks.

In conclusion, this trial demonstrated that PLD (50 mg/m^2 every 4 weeks) was expected to have antitumour effect in Japanese patients with Müllerian carcinoma previously treated with platinum-based chemotherapy and that toxicities associated with PLD are manageable by dose modification and supportive care. In the USA and Europe, combination chemotherapy with PLD and platinum has recently been investigated in the platinum-sensitive group where PLD is considered to be more effective (23,24,25). It is desirable to investigate the optimal regimen of the combination therapy in Japan.

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Conflict of interest statement

None declared.

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Emerging drugs for ovarian cancer

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Background: Long-term survival of patients with ovarian cancer remains poor and therapy disappointing despite decades of experience with various chemotherapies, including the current gold standard, carboplatin/paclitaxel (TC). *Objective*: To review current and emerging therapies for ovarian cancer in search of ways to improve outcome, reduce toxicity, and maintain quality of life. *Methods*: This is a review of the current status of chemotherapy for ovarian cancer, the ongoing clinical studies, emerging therapies, and proposals for future research. *Results/conclusion*: Novel chemotherapeutic agents are needed to reduce toxicity and improve efficacy. Effective biological agents must be found and tested, either in combination with TC or as maintenance therapy after TC. An appropriate regimen and number of repeat treatment cycles for intraperitoneal chemotherapy is urgently needed, and an effective regimen must be established for patients with clear cell/mucinous adenocarcinoma. The main strategy for recurrent ovarian cancer is to find the gene related to drug resistance, then treat the cancer based on its molecular biology.

Keywords: bevacizumab, biological agents, carboplatin, chemotherapeutic agents, ovarian cancer, paclitaxel

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1. Background

Since the 1980s, adjuvant chemotherapy with cyclophosphamide (CPA) and cisplatin (CDDP) (CP regimen) or CPA, doxorubicin (DXR), and CDDP (CAP regimen) has been the standard initial chemotherapy for epithelial ovarian cancer [1,2]. Carboplatin (CBDCA) was introduced in the 1980s, and adjuvant therapy using CBDCA and CPA has been the standard in the United States and Canada because of its equivalent efficacy, less frequent adverse events and ease of administration [3,4]. In Europe, CBDCA monotherapy is standard because efficacy did not differ between the CAP regimen and CBDCA monotherapy, as shown in the Second International Collaborative Ovarian Neoplasm Study [5]. In the late 1990s, paclitaxel (TXL) for initial treatment was established.

The advantage of adjuvant therapy with TXL and CDDP (TP regimen) over the CP regimen was demonstrated [6,7], and thereafter first-line chemotherapy with TXL and CBDCA (TC regimen) was recommended because of its nonhematotoxicity and ease of administration [8,9]. To evaluate neurotoxicity and patient quality of life (QoL), a comparative study of chemotherapy with docetaxel (TXT) and CBDCA (DC regimen) was conducted using the TC regimen as the control arm. No significant difference in efficacy was found (Scottish Randomized Trial in Ovarian Cancer, SCOTROC); hence, the DC regimen is optional [10]. A regimen that includes TXL prolongs the survival period, but its efficacy is inadequate (Figure 1).

Many studies have attempted to establish an effective initial chemotherapy, but no ideal therapy has yet been found. For example, a regimen in which epirubicin was added to TC (TEC regimen) proved ineffective [11]. In another large randomized controlled trial (RCT) with five study arms using the TC regimen,

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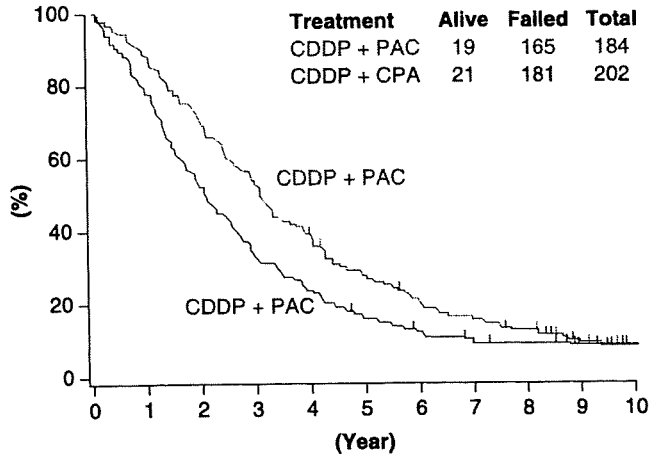


Figure 1. Gynecologic Oncology Group (GOG) 111: survival of patients with suboptimal stage III/IV disease.
McGuire WP, Educational session, ASCO 2002.

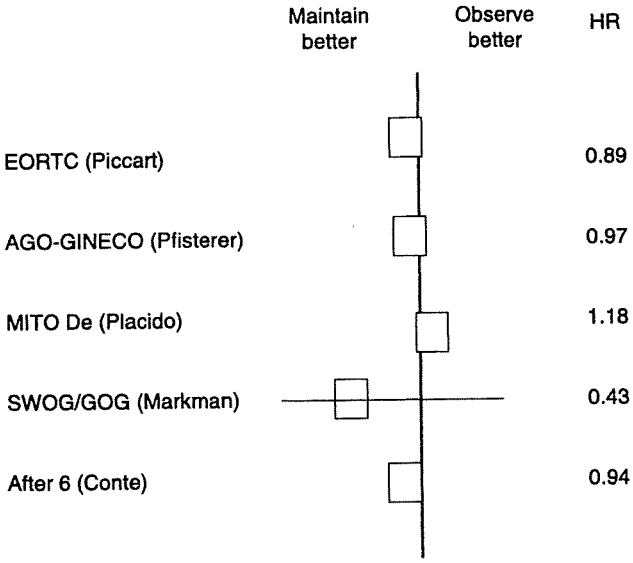


Figure 2. Randomized controlled trials of maintenance chemotherapy: progression-free survival.
Conte PF. ASCO 2007 (Chicago).

the advantage of triplet arm (carboplatin/paclitaxel/gemcitabine and carboplatin/paclitaxel/pegylated liposomal doxorubicin) and a sequential doublet arm (carboplatin/topotecan → TC and carboplatin/gemcitabine → TC) was inconclusive [12]. In a randomized clinical trial (GOG178) of five maintenance chemotherapies in patients with no evidence of disease (NED) after the initial chemotherapy, the therapy using paclitaxel was found to prolong progression-free survival (PFS); however, no such improvement was found in other studies (Figure 2) [13-17].

The route of chemotherapy administration has also been studied. Intraperitoneal administration would seem to be a logical approach, because ovarian cancer spreads throughout the abdomen. Intraperitoneal chemotherapy reportedly did prolong the survival period significantly compared with intravenous chemotherapy (Figure 3) [13,18-22]. However, this route is not recommended as the standard because of the resulting toxicity and complications, such as severe hematotoxicity and reservoir obstruction. Clinical trials using various injection routes and conducted according to complex study designs are inconclusive regarding efficacy and toxicity. Consequently, as of 2008, the TC regimen (TXL 175 mg/m^2/3 h + CBDCA area under the curve (AUC) 6) administered intravenously is recommended as the standard regimen for ovarian cancer.

Many patients (> 60%) suffer a recurrence after initial therapy and require second-line chemotherapy. However, no optimal chemotherapy for recurrent ovarian cancer has yet been found. At the time of recurrence, the treatment-free interval (TFI), residual toxicity from the first-line therapy, tumor volume, and serologic relapse (CA125) are considered before initiating second-line therapy. TFI is the most important factor in selecting a drug [23,24] because patients with TFI > 6 months generally have a relatively chemosensitive tumor that may respond to platinum therapy. One report on the effectiveness of second-line therapy is that of a RCT comparing TXL/platinum combination therapy and conventional platinum-based therapy (CAP and CBDCA monotherapy, etc.) in sensitive recurrent cancer. The former therapy resulted in a better response rate (66 vs 54%) and an improved 2-year survival rate, thus the authors recommend the TC regimen [25]. In another comparative study of gemcitabine/CBDCA (GC regimen) and CBDCA monotherapy, the GC regimen significantly improved the response rate (47 vs 31%) and PFS (HR: 0.72) compared with CBDCA monotherapy [26]. From these results, for patients with platinum-sensitive recurrent cancer, CBDCA combination therapy is recommended rather than CBDCA monotherapy. In contrast, patients with a TFI < 6 months or no response to the initial therapy (chemo-resistant or -refractory tumor) have an extremely poor outcome, so a drug without cross-resistance to taxane/platinum is required.

2. Existing treatment

2.1 First-line chemotherapy

Combination therapy consisting of paclitaxel (175 mg/m^2/3 h) and carboplatin ACU 6 (TC regimen) is the current gold standard [8,9]. At limited stages of disease – that is, among high-risk patients – treatment consists of three to six cycles of combination therapy every 3 weeks, while advanced cases are treated with six to eight cycles every 3 weeks. When paclitaxel-induced neurotoxicity and hypersensitivity occur, the combination therapy of docetaxel 60 – 70 mg/m^2 and carboplatin ACU 5 – 6 is effective [10]. In patients with

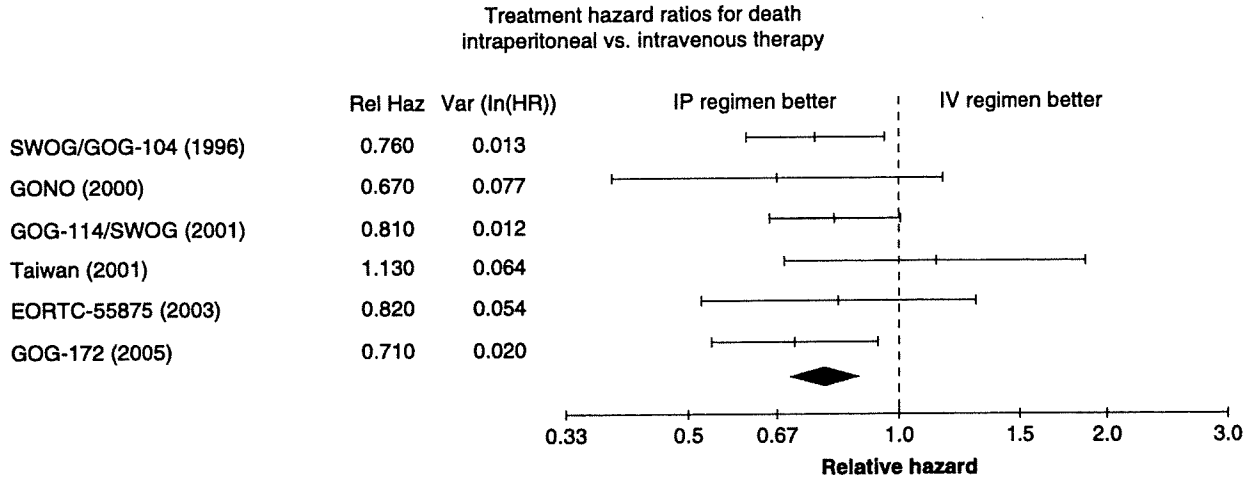


Figure 3. Intraperitoneal chemotherapy for ovarian cancer.

$m^2_{heterogeneity\ (5\ d.f.)} = 3.1$, $p = 0.68$.

Hazard ratio is not reported for the GONO study but it is calculated from the available data reported.

Hazard ratio is not reported for the Greek study.

HR = 0.784 (95% CI, 0.693 – 0.886).

NCI Clinical Announcement, 2006 [60].

serous adenocarcinoma and endometrioid adenocarcinoma, these regimens produced clinical response rates of ≥ 70%, whereas drug sensitivity was low in patients with clear cell carcinoma and mucinous adenocarcinoma.

The results of large-scale randomized studies of the efficacy of a tri-weekly TC regimen reported a PFS of 21 – 23 months and OS of 52 – 57 months in patients with optimal disease (residual tumor diameter < 1 cm) who underwent the first surgery [8,9], while on the other hand, PFS was 18 months and OS was 38 months in patients with suboptimal disease [6]. In a study in patients with both optimal and suboptimal disease (GOG182), PFS was 16 months [12]. We presented the results of the Japanese Gynecologic Oncology Group (JGOG) protocol 3016 study in both optimal and suboptimal disease in the ASCO in 2008 [27]. The PFS of patients treated with dose-dense weekly TC chemotherapy was 28 months, significantly superior to that of those receiving standard tri-weekly TC chemotherapy (17 months). This result suggested a dose-dense effect of paclitaxel in initial therapy, and warrants further investigation.

2.2 Consolidation/maintenance therapy

No data show that maintenance and consolidation therapy improves overall survival in ovarian cancer. Four of five studies of this therapy for ovarian cancer reported negative data (Figure 2) [13-17]. Finally, a meta-analysis of paclitaxel studies is needed to determine paclitaxel's antiangiogenic effect.

2.3 Intraperitoneal chemotherapy

Since 1994, seven RCTs for intraperitoneal (IP) therapy have been reported, mainly in the United States. In all trials except one, survival in the IP therapy group was good; in three large-scale trials in the United States (GOG104, GOG114, GOG172), the survival period of the IP group was significantly longer than that of the intravenous group [13,18-22]. Based on the results of these RCTs and a National Cancer Institute (NCI) meta-analysis (Figure 3), NCI submitted a clinical recommendation in January 2006 for IP chemotherapy with cisplatin and paclitaxel for patients who were having optimal surgery (residual tumor < 1 cm). The winner arm in GOG-172 was IV paclitaxel (day 1) + IP cisplatin (day 2) + IP paclitaxel (day 8), which is considered to be the control arm for IP therapy in the United States and Canada [22]. However, an appropriate regimen, cycle number, and reservoir setting method have not been established and no standards have yet been proposed.

2.4 Second-line chemotherapy

For patients with chemosensitive disease (TFI > 6 months), a TC regimen and combination therapy of gemcitabine (1000 mg/m^2) and carboplatin AUC 4 are recommended [25,26]. On the other hand, for patients with chemoresistant disease (TFI < 6 months), it is necessary to select a drug that is not cross-resistant to paclitaxel and carboplatin. The goal of therapy is to delay disease progression, relieve symptoms, and improve QoL. Generally, monotherapy is selected because it is less toxic than combination therapy. Pegylated liposomal doxorubicin (doxil), and weekly paclitaxel, have been approved by the US FDA. Topotecan is also an approved agent in the United States, where weekly topotecan is often utilized to decrease hemologic toxicity. In addition, gemcitabine, oral etoposide, and docetaxel are often used. In

Table 1. Phase II studies of biological agents conducted by the Gynecologic Oncology Group (GOG).

Protocol #	Agent	Response
146-H	Bryostatin (Pyrazoacridine)	Inactive
146-N	Bortezomib (Velcade)	Minimum activity
146-O	Irofulven	Too early
146-P	Cetuximab (Erbitux®)	Modest activity
160	Trastuzumab (Herceptin®)	PR 9.7%, SD 31.8%
170-B	IL-12	PR 3.8%, SD 50%
170-C	Gefitinib (Iressa®)	PR 3.7%, SD 30%
170-D	Bevacizumab (Avastin®)	PR 21%, SD 52%
170-E	Imatinib (Gleevec®)	PR 1.8%, SD 12.5%
170-F	BAY43-9006	Too early
170-G	Lapatinib (Tykerb®)	Insufficient efficacy
170-H	Vorinostat	Insufficient efficacy
170-I	Temsirolimus (CCI-779)	Too early
170-J	Enzastaurin	Too early
170-K	Mifepristone	Too early
170-L	AMG706	Too early
186-C	CT-2103	Modest activity
186-D	Karenitecin	Limited activity

Japan, weekly irinotecan is frequently used. Regarding molecular-target drugs, bevacizumab is confirmed to be effective, so it is used in monotherapy or combination therapy with anticancer drugs [28-33]. GOG Phase II studies of bryostatin (GOG 146-H), lapatinib (GOG 170-G), and vorinostat (GOG 170-H) had insufficient effect to warrant further investigation of recurrent ovarian cancer,; karenitecin (GOG 186-D) has limited activity in third-line treatment; and studies of cetuximab (GOG 146-P), trastuzumab (GOG 160), gefitinib (GOG 170-C), imatinib (GOG 170-E) and CT-2103 (GOG 186-C) have also shown only modest effects (Table 1).

Regarding toxicity, palmar-plantar erythrodysesthesia (PPE) develops during doxil therapy, peripheral neuropathy and arthralgia develop during paclitaxel therapy, and diarrhea develops during irinotecan therapy. According to the previous studies of bevacizumab, gastrointestinal perforation occurred in 16 of 299 patients (5.4%).

3. Medical need and current research goals

Medical need and the current research goals in this field are outlined below.

3.1 First-line chemotherapy

- To prolong survival using biological agents combined with TC therapy or alone as maintenance therapy.
- To determine an optimal regimen and administration cycle for IP chemotherapy, as well as IP positioning in the disease, by conducting RCTs comparing IP therapy with TC therapy.
- To develop a novel chemotherapy regimen for clear cell carcinoma and mucinous adenocarcinoma.

3.2 Second-line chemotherapy

- To find an effective biological marker and agents (Table 1).
- To find new cytotoxic agents with novel mechanisms of action (Table 2).
- To find effective combination regimens (cytotoxic and biologic agents).
- To minimize chemotherapy-induced toxicity.
- To establish assay-directed therapy.

4. Scientific rationale

The scientific rationale for each of the research goals is outlined below.

4.1 Biological agents in first-line chemotherapy and maintenance therapy

A TC regimen with a third cytotoxic agent does not improve survival [12]. Similarly, a prolonged survival period was not found in NED patients who were treated with maintenance chemotherapy combined with cytotoxic agents after initial chemotherapy (Figure 2) [13-17]. Meta-analysis of studies with paclitaxel, which is expected to have an antiangiogenic effect, will be necessary after results have been obtained from ongoing comparative studies of paclitaxel (40 mg/m^2 weekly ×24) and surveillance in early cancer (GOG 175), as well as of paclitaxel (135 mg/m^2 every 28 days ×12), CTI-2103 (paclitaxel poliglumex: 135 mg/m^2 every 28 days ×12), and no treatment in advanced cancer (optimal disease < 1 cm) (GOG 212). A novel cytotoxic drug combination is needed as a first treatment. However, improved efficacy using cytotoxic agents is limited because of cumulative toxicities, and a promising biological agent is expected to emerge while Phase II studies of various biological agents (GOG 170 series) continue (Table 1). In future maintenance therapy, biological agents will play a leading role and a variety of biological agents must be introduced. At the present time, two RCTs of bevacizumab, which showed the highest efficacy of the biological agents tested so far, are now underway in the United States (GOG218, ICON7). A trial with erlotinib (OSI-774) is ongoing in Europe (European Organization for Research and Treatment of Cancer: EORTC 55041).

4.2 Intraperitoneal chemotherapy

A safe and effective IP regimen is urgently needed, and studies comparing IP carboplatin with cisplatin must be conducted. The GOG is planning an intergroup comparative study of three regimen groups in Stage III patients with optimal disease: cisplatin 75 mg/m^2 IP + paclitaxel 135 mg/m^2 (day 1, 24 h) + paclitaxel 60 mg/m^2 (day 8, IP), which is a

Table 2. Recently studied chemotherapeutic agents for ovarian cancer.

TLK 286: glutathione prodrug GSH analog
Pemetrexed: multitargeted antifol
Epothilones: tubulin inhibitors
ET-743: trabectedin – DNA binder
Novel taxanes: tubulin inhibitors
Abraxane – paclitaxel protein-bound particles
Platinum drugs
Novel topoisomerase I inhibitors

control arm and a cisplatin-reduced regimen from the winner arm in the GOG-172 study; paclitaxel 175 mg/m^2 (day 1, 3 h) + carboplatin AUC6 i.v. (the standard TC regimen); and paclitaxel 175 mg/m^2 (day 1, 3 h) + carboplatin AUC6 IP. In this study, bevacizumab is to be combined with all arms in the second cycle and after. The results of this study will probably resolve the question of whether the efficacy of IP cisplatin is equivalent to that of IP carboplatin, and whether IP dose-dense paclitaxel is effective. However, the effect of bevacizumab may mask the true differences among the three regimens.

4.3 Refractory cancers (clear cell carcinoma and mucinous adenocarcinoma)

The four types of adenocarcinomas are biologically different; that is, they are different adenocarcinomas. Of the four major histological subtypes, serous adenocarcinoma and endometrioid adenocarcinoma respond to a TC regimen, but clear cell carcinoma and mucinous adenocarcinoma do not respond as well. TC therapy, which was recently introduced as a standard regimen for epithelial ovarian cancer based on the results of RCTs, may, however, not be an optimal regimen for clear cell carcinoma and mucinous adenocarcinoma [8,9,34]. These two histologic subtypes account for only 3 – 5% of cases enrolled in randomized trials [34]. Therefore, poor prognosis is not reflected in the results of these prospective studies. Clinical trials for each of these refractory cancers should continue in international studies.

Based on previous reports on the fundamental and clinical efficacy of irinotecan in clear cell carcinoma [34-41], a trial for first-line chemotherapy is in progress for patients with clear cell carcinoma (Stages I – IV; GCIG/JGOG 3017: TC vs irinotecan/cisplatin [42]). In addition to bevacizumab to treat recurrent clear cell carcinoma, sunitinib, which is effective in renal cell carcinoma and whose molecular biology is similar to that of clear cell carcinoma, is thought to be effective [43,44]. Also regarding mucinous adenocarcinoma, a Phase II study is planned to test a regimen like that for gastrointestinal cancer. The candidate agents are 5-FU [45], irinotecan [46,47], oxaliplatin [48-50], capecitabine [51-54], and S-1 [55-58], which are effective in treating gastrointestinal cancer. The GOG will start a randomized Phase II trial comparing TC regimen with capecitabine plus oxaliplatin (GOG241). We are planning a Phase II study of S-1 plus oxaliplatin in Japan. More international clinical trials should be conducted by histological subtype. Regarding these refractory cancers, the establishment of molecular biology-based cross-organ treatment with cytotoxic/cytostatic agents is required.

4.4 Recurrent cancer

Cytotoxic agents combined with carboplatin for chemosensitive tumors, and cytotoxic and biological agents offering novel mechanisms of action against chemoresistant tumors, should be developed (Tables 1 and 2).

Finding an effective biological marker and agents is critical to understand and treat recurrent cancer. The introduction of assay-directed therapy for platinum-resistant disease is under discussion; however, some problems, including assay method and timing of tumor sampling, have not been solved. The conventional standard treatment has been monotherapy with doxil and topotecan. In the future, to reduce non-hematotoxicity and increase efficacy, dual therapy with a cytotoxic agent and combination therapy with a biologic agent should be investigated. Furthermore, a molecular biology-based approach is essential in order to find biological agents that can be combined with chemotherapy. The GOG has conducted trials of many biologic agents for recurrent ovarian cancer, of which bevacizumab is the only promising agent (Table 1), and relapsed patients with chemosensitive disease are included in a current RCT of a TC regimen with or without bevacizumab (GOG213).

5. Competitive environment

See Table 3 [59].

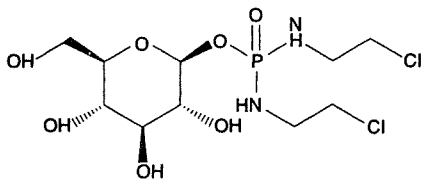
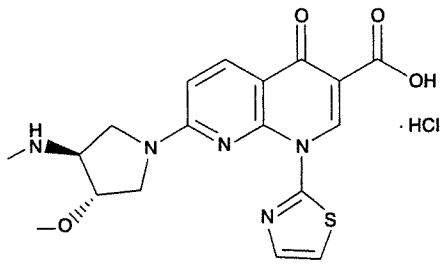
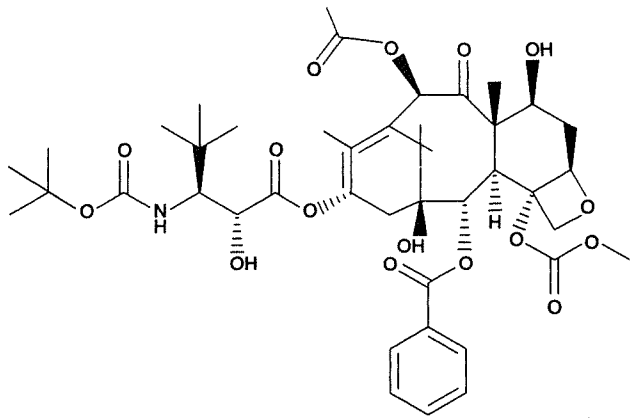
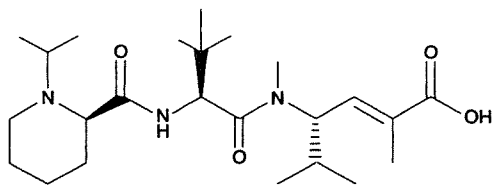
5.1 Alkylating agents

Glufosfamide is an alkylating agent in which carbohydrate chains are attached to ifosfamide synthesized by the German Cancer Research Center. Tumor cells possess a propensity to repeat glucose metabolism: glufosfamide enters tumor cells, inhibiting cancer proliferation. Adverse reactions associated with an alkylating agent may be reduced because glufosfamide attacks only cancerous lesions. Glufosfamide is similar in structure to oxazaphosphorine, but has a different mechanism of action. Glufosfamide possesses a cytocidal effect specific to tumor cells, an effect that has been confirmed not only in aerobic but also in hypoxic areas. In January 2007, a Phase II study began among ovarian cancer patients who are resistant to platinum-based regimens.

5.2 Topoisomerase inhibitor

SNS-595 is a topoisomerase II inhibitor, the basic structure of which is 1,8-naphthyridine-4-oxo-3-carboxylic acid with the thiazolyl group at the first position and the optically active 3-methoxy-4-methylaminopyrrolidinyl group at the

Table 3. Competitive environment.

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Glufosfamide	Threshold Pharmaceuticals, Inc.		Ovarian	Phase II	DNA synthesis inhibitor (alkylating)
SNS-595	Sunesis Pharmaceuticals, Inc.		Ovarian	Phase II	Topoisomerase II inhibitor
BMS-275183	Bristol-Myers Squibb		Ovarian	Phase I	Microtubule stabilization
E 7974	Eisai Co. Ltd.		Ovarian	Phase I	Microtubule binding inhibitor

Information contained in this table was taken from Cima Science [59].