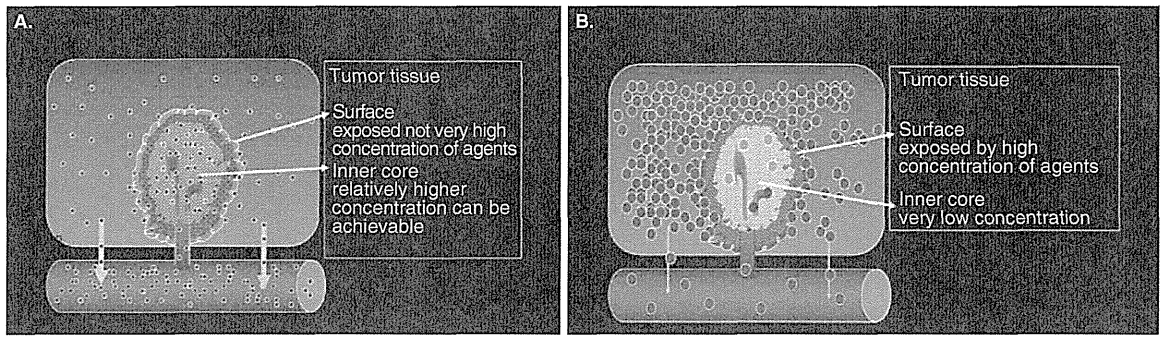

Figure 1. A. Schematic image of the distribution of chemotherapy agents with small molecular mass that was administered in the i.p. cavity. **B.** Schematic image of the distribution of chemotherapy agents with large molecular mass that was administered in the i.p. cavity.

Table 1. Ratio of drug level in peritoneal cavity:plasma by pharmacological characteristics of anticancer drugs.

Drug	Molecular mass	Water solubility	Ratio of drug level Peritoneal cavity:plasma	
			Peak	AUC
Cisplatin	300.05	+	20	12
Carboplatin	371.25	+	-	18
Mitomycin	334.33	±	71	-
Melphalan	305.20	-	93	65
Methotrexate	454.44	-	92	100
5-FU	130.08	±	298	367
Doxorubicin	543.53	±	474	-
Paclitaxel	853.92	-	-	1000
Mitoxantrone	517.40	-	-	1400

progression-free survival (PFS) (median: 28 vs 22 months; relative risk = 0.78; log rank $p < 0.01$, one tail) and overall survival (median: 63 vs 52 months; relative risk = 0.81; $p = 0.05$, one tail) of 426 assessable patients were observed in favor of the i.p. group. However, hematologic and non-hematologic toxicities ≥ grade 3 were significantly more frequent in the i.p. group. As a result, 18% of the patients received less than two courses of i.p. therapy. In spite of the significant survival improvement in this study, the gynecologic oncology community did not accept i.p. chemotherapy to be the standard treatment for ovarian cancer because there was a possibility that the addition of two cycles of carboplatin treatment may contribute to the improvement of survival and that toxicity was excessive in the i.p. arm.

The third trial was conducted by GOG [3]. In this study, 417 patients with optimally debulked stage III ovarian cancer were randomized either to i.v. paclitaxel (135 mg/m^2/24 h) followed by i.v. cisplatin (75 mg/m^2), or to i.v. paclitaxel (135 mg/m^2/24 h) followed by i.p. cisplatin (100 mg/m^2), plus i.p. paclitaxel (60 mg/m^2) on day 8. The relative risk of recurrence was 0.73 in the i.p. group as against i.v. group. The improvement in median overall survival was 15.9 months, with a treatment HR of 0.75 (95% CI: 0.58 – 0.97) favoring the i.p. study arm. The magnitude of improvement in median overall survival associated with i.p./i.v. administration of chemotherapy is similar to that observed with the introduction of either cisplatin or paclitaxel. The median duration of survival for the i.p. arm of this trial (66 months) was 10 months longer than that for the current standard treatment schedule (i.v. paclitaxel plus i.v. carboplatin treatment) arm of the GOG 158 trial (57 months). However, this survival advantage could be due to the addition of day 8 paclitaxel and not due to the i.p. delivery of cisplatin and paclitaxel. In addition, there were significantly more patients with grade 3/4 hematologic and non-hematologic toxicities in the i.p. arm compared to the i.v. arm. Because of these toxicities and/or catheter problems, 48% of patients in the i.p. arm received three or fewer i.p. treatments and only 42% patients received the planned six cycles of i.p. therapy. As discussed by Cannistra [6], 'it is remarkable that such a clinically meaningful survival advantage was observed, despite the high attrition rate in the intraperitoneal group, suggesting that a substantial benefit from intraperitoneal chemotherapy may occur within the first several cycles of treatment', and this trial raised important

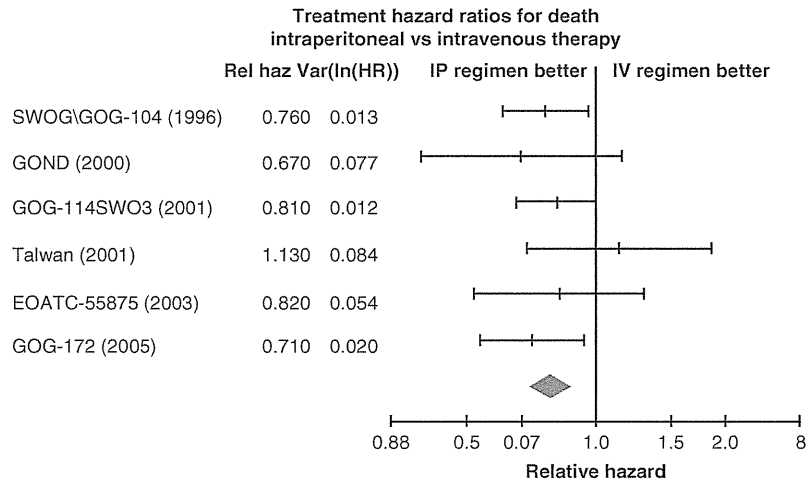

Figure 2. Result of meta-analysis for i.p. chemotherapy published as a NCI clinical announcement.

questions to be solved in the future because it is hypothesized that improving catheter complications may enhance the survival benefit by i.p. chemotherapy further.

Based on the results of these three large randomized trials and another five small studies, GOG and National Cancer Institute (NCI) conducted a meta-analysis and concluded that i.p. chemotherapy is beneficial for optimally debulked stage III ovarian cancer patients. This important information has been released as a clinical announcement from the NCI US in January 2006 [7]. As shown in Figure 2, i.p. therapy was associated with a 21.6% decrease in the risk of death (HR = 0.79; 95% CI: 0.70 – 0.89). The expected median duration of survival for women with optimally debulked ovarian cancer receiving standard treatment is ~ 4 years. Therefore, this size reduction in the overall death rate is expected to translate into about a 12-month increase in overall median survival.

Despite these promising results, i.p. chemotherapy has not been accepted as standard treatment for advanced ovarian cancer.

The most important drawback is the platinum agent used in the i.p. trials, which is cisplatin. As is well known, cisplatin is more toxic than carboplatin, which is the standard platinum agent when given intravenously. Therefore, it is reasonable to consider replacing cisplatin with carboplatin for i.p. use, but there have been two reasons why carboplatin was not used for i.p. chemotherapy for long time.

4. Reasons why carboplatin was not used for i.p. chemotherapy

There are two reasons why carboplatin was not used for i.p. chemotherapy. One of them was an animal experiment which showed that ~ 6 to 10 times more carboplatin was required to obtain equivalent tissue platinum concentration compared to cisplatin [8]. In this study, Los *et al.* measured platinum distribution in rat peritoneal tumors after i.p. treatment with equimolar doses of carboplatin and cisplatin and found that no platinum was detected 0.5 mm from the periphery after carboplatin treatment, whereas 14 ppm was detected after cisplatin treatment. They also measured the total platinum concentration in the tumor model after various doses of carboplatin and cisplatin were administered into the i.p. cavity of mice and found that 10 times more carboplatin than cisplatin had to be injected to obtain comparable platinum concentrations in the tumors. However, the tissue concentration has not been shown to be predictive of efficacy in this animal model.

Based on this result, Markman *et al.* retrospectively analyzed their clinical data of a small number of patients and showed that the response rate was better in the cisplatin-based regimen [9], concluding that carboplatin may be inferior to cisplatin when used intraperitoneally. However, these studies assume equivalency of dose between carboplatin and cisplatin. For example, in the Los *et al.* study, the dose of cisplatin and carboplatin administered to the mice was calculated based on weight. The dose of carboplatin that was required to achieve the equivalent tissue platinum concentration that was achieved by administering cisplatin at 5 mg/kg was between 30 and 49.2 mg/kg. By comparison, standard i.v. doses of platinum agents as designed in contemporary clinical trials with paclitaxel are: cisplatin 75 mg/m^2 and carboplatin AUC of 6 to 7.5 mg/mL min. Since carboplatin is principally cleared through the kidneys, more reliable toxicity and efficacy data have been gained through dosing based on renal function. Based on a Phase I study by Bookman *et al.*, the dose of carboplatin at AUC of 7.5 was equivalent to 471 mg/m^2 and AUC of 6 was equivalent to 400 mg/m^2

[10]. Therefore, the dose of carboplatin must be at least 5 to 6 times more to achieve the equivalent clinical efficacy even when the cisplatin or carboplatin is administered intravenously. In the Markman *et al.* study, the dose of carboplatin was also too small (200 – 300 mg/m^2), comparing it to a considerably high dose of cisplatin (100 mg/m^2). The study also has another limitation because it was a retrospective analysis using a small number of patients. Therefore, an adequate evaluation of i.p. carboplatin using a reasonable dose and sample size is necessary.

5. Reasons why we believe carboplatin will be suitable for i.p. chemotherapy

5.1 Pharmacological analysis of i.p. carboplatin

Miyagi *et al.* published their pharmacological analysis of platinum concentrations in the serum and i.p. cavity after carboplatin was administered intravenously or intraperitoneally [11]. In this study, they demonstrated that 24 h platinum AUC in the serum was exactly the same regardless of i.p. or i.v. administration of carboplatin. However, 24 h platinum AUC in the peritoneal cavity was ~ 17 times higher when carboplatin was administered via the i.p. route.

Based on this result, they concluded that i.p. infusion of carboplatin is feasible, not only as an i.p. regional therapy but also as more reasonable route for systemic chemotherapy.

5.2 Clinical efficacy of i.p. carboplatin-based chemotherapy

Fujiwara *et al.* published the survival data of 165 patients with epithelial ovarian cancer who underwent i.p. carboplatin-based chemotherapy as a first-line treatment. They treated patients with stages I – IV epithelial ovarian cancer with either i.p. carboplatin alone (n = 22) or in combination with cyclophosphamide (n = 116) or paclitaxel (n = 27) [12]. In this retrospective analysis, the median survival of the patients with small (< 2 cm) residual disease was 51 months. Although the median survival of patients in this population treated with a dose of < 400 mg/m^2 carboplatin was 24.5 months, the median survival was not reached until 84 months when the carboplatin was dosed ≥ 400 mg/m^2.

In the 90 stage III/IV patients, including both small and bulky residual disease, median survival was 25 months with carboplatin dosed under 400 mg/m^2, whereas it was 51 months with carboplatin ≥ 400 mg/m^2 (p = 0.0137). The authors analyzed the potential reasons for the difference in outcome with different doses such as performance status, age and tumor grades between stage III/IV patients who received i.p. carboplatin ≥ 400 mg/m^2 and < 400 mg/m^2 and found that they were not significantly different. They concluded that the most significant prognostic factor by both univariate and multivariate analysis was carboplatin dosed above 400 mg/m^2. Although this study is a retrospective analysis, it is reasonable to argue that the data further support the prospective evaluation of i.p. carboplatin administration.

5.3 Toxicity of i.p. carboplatin plus i.v. paclitaxel

Two Japanese studies demonstrated toxicities with a combination of carboplatin and paclitaxel.

Fujiwara *et al.* performed a preliminary toxicity analysis of i.p. carboplatin in combination with i.v. paclitaxel [13]. In this study, a fixed dose of paclitaxel (175 mg/m^2) was analyzed for toxicity with escalating doses of carboplatin ranging from AUC of 5 to 7.5. Dose-limiting toxicity (DLT) was primarily thrombocytopenia requiring platelet transfusion. Three of the six patients in the cohort of AUC 7.5 experienced DLT. One of the six patients in the cohort at AUC 7 showed grade 3 thrombocytopenia. The incidence of grade 4 neutropenia was 33.3% for both cohorts. Therefore, the recommended dose of i.p. carboplatin in combination with 3 h i.v. paclitaxel infusion at 175 mg/m^2 could be AUC of 6 – 7.

Based on this study, the GOG conducted a Phase I/feasibility study for i.p. carboplatin to determine the optimal dose with i.v. paclitaxel for future studies (GOG9917) [14]. In this study, they tried to find an appropriate dose for i.p. carboplatin in combination with fixed dose of paclitaxel at 175 mg/m^2. Twenty-one patients were entered on the dose-escalating phase for first cycle. Maximum tolerated dose of carboplatin at AUC 8, was tolerated for the first cycle, although thrombocytopenia was the dose-limiting factor over multiple cycles. An additional 69 patients were treated in expanded cohorts to assess the toxicities over four cycles. Four-cycle DLT required de-escalation to a carboplatin AUC of 6, and even at that dose, there were 14 dose-limiting toxic effects in 40 patients (35%). Seven DLTs were due to neutropenia and 6 DLTs were due to grade 3/4 thrombocytopenia. Six cycles of therapy were completed in 75% of eligible patients but dose adjustments were required. Therefore, by using an i.p. carboplatin dose of AUC 6 in combination with paclitaxel, the regimen can be administered with a high completion rate over multiple cycles. Because neutropenia is a frequent DLT, the addition of hematopoietic growth factors may permit a high completion rate, while maintaining this dose. Only 5 of 90 (5.6%) patients discontinued treatment because of a port problem.

6. New evidence surrounding i.p. chemotherapy strategies since NCI Clinical Announcement 2006

6.1 Dose-dense weekly administration of chemotherapy

Japanese Gynecologic Oncology Group (JGOG) conducted a randomized Phase III trial to compare the therapeutic effect and safety of administering carboplatin every 3 weeks in combination with conventional administration of paclitaxel at 175 mg/m^2 every 3 week versus dose-dense weekly

administration of paclitaxel at 80 mg/m^2 in patients with stage II – IV ovarian, fallopian tube or peritoneal cancers (JGOG3016) [15]. A total of 637 patients were randomized and 631 were eligible (dose-dense regimen, n = 312; conventional regimen, n = 319). Median PFS was longer in the dose-dense treatment group (28 months; 95% CI: 22.3 – 35.4) than in the conventional treatment group (17.2 months, 15.7 – 21.1; HR = 0.71; 95% CI: 0.58 – 0.88; p = 0.0015). Overall survival at 3 years was higher in the dose-dense regimen group (72.1%) than in the conventional treatment group (65.1%; HR = 0.75; 0.57 – 0.98; p = 0.03).

This result impacted on the design of i.p. chemotherapy trials that were planned to be conducted at that time. Since the winner arm of GOG172 trial had administered i.p. paclitaxel on day 8, it was unclear whether the survival benefit was obtained because of the i.p. administration of cisplatin or paclitaxel, or because of day 8 administration of paclitaxel [16].

6.2 Bevacizumab

GOG218 and ICON7 were the trials that investigated the efficacy and safety of incorporating an antiangiogenic agent, bevacizumab, in combination with paclitaxel and carboplatin followed by bevacizumab maintenance alone.

The GOG218 trial was a double-blind, placebo-controlled, Phase III trial. They randomly assigned patients with newly diagnosed stage III (incompletely resectable) or stage IV epithelial ovarian cancer having undergone debulking surgery to receive one of three treatments [17].

In this study, 1873 women were enrolled. The median PFS was 10.3 months in the control group, 11.2 in the bevacizumab-initiation group and 14.1 in the bevacizumab-throughout group. Relative to control treatment, the HR for progression or death was 0.908 (95% CI: 0.795 – 1.040; p = 0.16) with bevacizumab initiation and 0.717 (95% CI: 0.625 – 0.824; p < 0.001) with bevacizumab-throughout. At the time of analysis, 76.3% of patients were alive, with no significant differences in overall survival among the three groups. Toxicities were acceptable.

In the ICON7 trial, women with ovarian cancer were randomly assigned to carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m^2), given every 3 weeks for six cycles, or to this regimen plus bevacizumab (7.5 mg/kg), given concurrently every 3 weeks for five or six cycles and continued for 12 additional cycles or until progression of disease [18]. The primary end point was PFS.

A total of 1528 women from 11 countries were randomly assigned. PFS at 36 months was 20.3 months with standard therapy, as compared with 21.8 months with standard therapy plus bevacizumab (HR for progression or death with bevacizumab added = 0.81; 95% CI: 0.70 – 0.94; p = 0.004 by the log-rank test). In the updated analyses, PFS (restricted mean) at 42 months was 22.4 months without bevacizumab versus 24.1 months with bevacizumab (p = 0.04 by log-rank test). In patients at high risk for progression, the benefit was greater with bevacizumab than without it, with PFS (restricted mean) at 42 months or 14.5 months with standard therapy alone and 18.1 months with bevacizumab added, with respective median overall survival of 28.8 and 36.6 months. They concluded that bevacizumab improved PFS in women with ovarian cancer. The benefits with respect to both PFS and overall survival were greater among those at high risk for disease progression.

These two important trials influenced the study design of GOG252 i.p. trials, which incorporated the bevacizumab in all three arms of the trial.

6.3 Neoadjuvant chemotherapy

Although primary debulking surgery (PDS) followed by adjuvant chemotherapy (ACT) is a standard treatment strategy for advanced ovarian cancer, there has been a great deal of controversy about whether neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) and additional ACT should be beneficial for the selected patient population.

EORTC55071 is a prospective randomized trial, which compared treatment efficacy and quality of life of standard PDS + ACT versus NACT + IDS + ACT in the patients with stage IIIC or stage IV disease [19]. Of the 670 patients randomly assigned to a study treatment, 632 (94.3%) patients were eligible and started the treatment. The largest residual tumor was ≤ 1 cm in diameter in 41.6% of patients after PDS and in 80.6% of patients after IDS. Postoperative rates of adverse effects and mortality tended to be higher after PDS than after IDS. The HR for death (intention-to-treat analysis) in the group assigned to NACT followed by IDS, as compared with the group assigned to PDS + ACT, was 0.98 (90% CI: 0.84 – 1.13; p = 0.01 for noninferiority). Complete resection of all macroscopic disease (at primary or interval surgery) was the strongest independent variable in predicting overall survival.

This trial influenced the trial design of the Canadian OV21 trial.

These new data impacted on the trial design of i.p. studies. Among the three results, the most important one was the dose-dense weekly concept.

7. Trial designs of currently ongoing i.p. chemotherapy trials

GOG114 and GOG172 trials had a problem of trial design because of the addition of other factors such as two cycles of carboplatin at AUC9 (GOG114 trial) or administration of i.p. paclitaxel on day 8 (GOG172 trial). It is desirable to have a trial to show the pure advantage of i.p. chemotherapy with less toxicity. Also, it is important to incorporate new evidence that became available recently.

Currently, there are three ongoing randomized trials worldwide attempting to find the best strategy in the treatment for ovarian cancer.

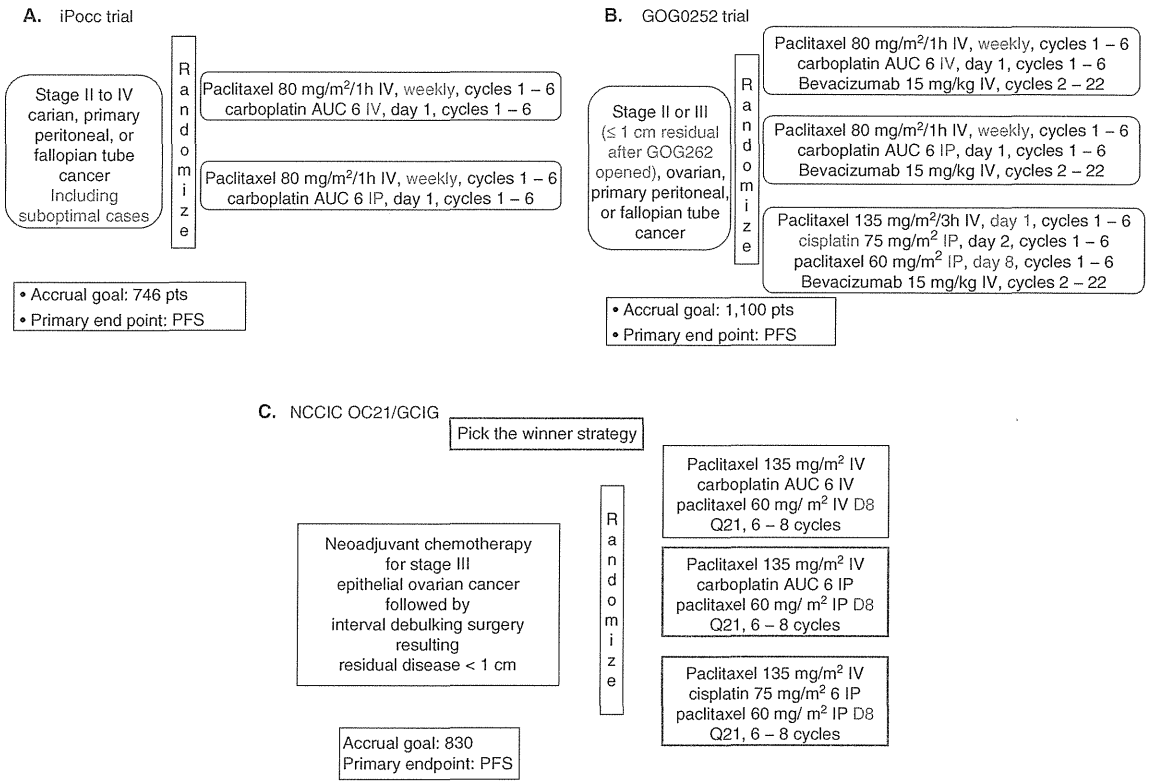

Figure 3. A. Schematic study design of iPocc trial. **B.** Schematic study design of GOG252 trial. **C.** Schematic study design of OV21 trial.

7.1 iPocc trial (GOTIC-001/JGOG3019)

After the JGOG3016 result became available, JGOG declared that dose-dense weekly administration of paclitaxel should be the standard chemotherapy regimen for the future JGOG trials. Accordingly, a new Japanese i.p. trial, iPocc trial (GOTIC-001/JGOG3019), was started in 2010 to compare the efficacy and safety of i.p. administration of carboplatin with standard i.v. administration in combination with dose-dense i.v. administration of paclitaxel [20]. The dose of paclitaxel is 80 mg/m^2 given every week for both arms, and carboplatin at AUC of 6 will be given every 3 weeks either intravenously (control arm) or intraperitoneally (experimental arm) (Figure 3A).

Unlike the other two ongoing trials, this is the trial that purely investigates the role of carboplatin for i.p. administration. In addition, this is the first trial that will include suboptimal stage III and stage IV patients to test the hypothesis that was proposed by Miyagi *et al.* [11].

7.2 GOG252 trial

The GOG252 Trial is a three-arm randomized Phase III study to compare the efficacy and safety of two i.p. chemotherapy regimens with standard i.v. chemotherapy. The standard chemotherapy arm and one of the i.p. arms are exactly the same as in the iPocc trial except for incorporating the administration of bevacizumab. Administration of bevacizumab is similar to the GOG218 trial [17], by being administered at 15 mg/kg every 3 weeks with carboplatin at AUC of 6 in combination with weekly dose-dense administration of paclitaxel at 80 mg/m^2 for five cycles followed by maintenance bevacizumab for 17 cycles (Figure 3B). Another i.p. chemotherapy regimen is the modified dosing schedule of the winner arm of the GOG172 trial [3]. The dose of cisplatin was reduced from 100 mg/m^2 to 75 mg/m^2. Bevacizumab was administered with a similar dosing schedule to the other two arms.

This trial was originally designed to administer paclitaxel every 3 weeks, but it was amended to utilize dose-dense weekly administration after the JGOG3016 trial was presented at American Society of Clinical Oncology (ASCO) 2006. The GOG252 trial has been already closed for accrual and for the data to be matured.

7.3 OV21 trial

The OV21 trial is an international study with Gynecologic Cancer Intergroup. The study design is somewhat unique (Figure 3C). Eligible patients are those with clinically stage III

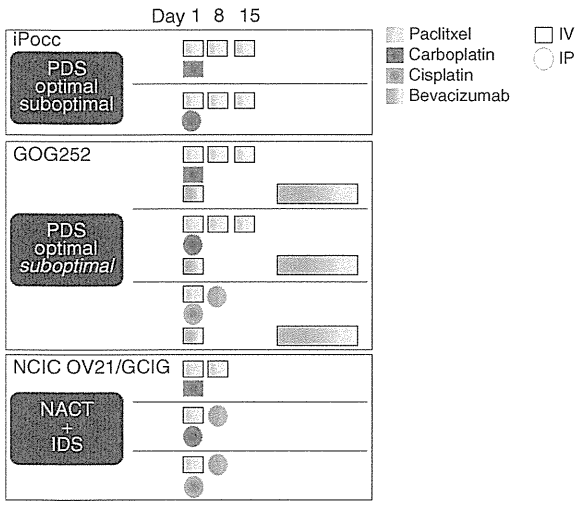

Figure 4. Comparison of iPocc, GOG252 and OV21 trial designs.

ovarian cancer who had received NACT followed by IDS, which resulted in the residual disease being < 1 cm (optimal). Those patients will be randomly assigned to either the i.v. arm or one of two i.p. arms. In the i.v. (control) arm, paclitaxel at 135 mg/m^2 and carboplatin at AUC 6 will be administered intravenously on day 1 followed by i.v. paclitaxel administration at 60 mg/m^2 on day 8. The original study was designed to administer paclitaxel at 175 mg/m^2 and carboplatin at AUC 6 on day 1, repeating every 3 weeks. However, it was amended to the current schedule when the JGOG3016 trial was presented at ASCO 2006. One of the i.p. arms is the replacement of administration of carboplatin from i.v. to i.p. Another arm is the modified GOG172 winner arm, similar to the GOG252 study, administering i.v. paclitaxel at 135 mg/m^2 on day 1 followed by i.p. administration of cisplatin at 75 mg/m^2 on day 2 and i.p. administration of paclitaxel at 60 mg/m^2 on day 8. These two i.p. arms are the objects to be chosen at the end of Phase II part, and winner will be compared with control arm as a Phase III study.

8. Future directions

These three trials have different designs, so it is not possible to answer all the questions regarding i.p. chemotherapy. However, as shown in Figure 4, it might be possible to resolve some of the questions by cross trial comparison, although it is not perfect because the power is not satisfactory. For example, the role of bevacizumab with i.p. chemotherapy with carboplatin will be elucidated by comparing the i.p. arms of iPocc and GOG252 trials. The role of the day 15 paclitaxel may be elucidated by comparing iPocc and OV21 trials.

9. Expert opinion

In spite of an enormous effort to improve the survival of ovarian cancer patients, prognosis of ovarian cancer is still poor. The i.p. chemotherapy is one of these approaches. Three large clinical trials conducted in the United States, GOG104, 114 and 172 trials, and meta-analysis showed survival benefit by giving cisplatin-based i.p. chemotherapy for optimally debulked stage III ovarian cancer patients.

As described in this review article, the main issue to improve in the i.p. chemotherapy is how we overcome the toxicities, mainly those caused by cisplatin. The most important question to solve the cisplatin-based toxicities is whether carboplatin can replace cisplatin. Based on the retrospective Phase I or Phase II studies, there are three Phase III trials to test whether i.p. carboplatin improves the survival over i.v. carboplatin administration.

Also, new evidence has been published, since the meta-analysis was conducted in 2006. These data include dose-dense weekly administration of paclitaxel, incorporation of bevacizumab and integration of NACT for selected patient population. It is important to incorporate this evidence into the future i.p. trial, but we believe it is most important to answer whether carboplatin can be a less-toxic substitute to cisplatin.

Currently ongoing three randomized Phase III trials will provide extremely important information about whether the i.p. carboplatin regimen will be beneficial. The iPocc trial will be the basis of other trials. Since GOG252 incorporated bevacizumab, the role of bevacizumab can be speculated by comparing iPocc trial and GOG252 trial. The role of i.p. therapy in patients with NACT can be estimated by comparing with iPocc and OV21. Although the GOG252 trial has been already closed for enrollment due to the full accrual, investigators of the gynecologic oncology field encourage participation in the iPocc or OV21 trial if one of them is available.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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• **This study is the randomized Phase III trial that purely compare the efficacy of i.p. versus i.v. carboplatin and trial design is discussed.**

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ORIGINAL ARTICLE

Paclitaxel–carboplatin for advanced or recurrent carcinosarcoma of the uterus: the Japan Uterine Sarcoma Group and Tohoku Gynecologic Cancer Unit Study

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Abstract
Background Paclitaxel and carboplatin (PC) have shown antitumor activity in carcinosarcoma of the uterus (CS). The purpose of this prospective multi-institutional study was to determine the response rate (RR), progression-free survival (PFS) and overall survival (OS) and to assess the toxicity of paclitaxel and carboplatin in patients with CS.
Methods We conducted a phase II study in which patients were administered paclitaxel 175 mg/m^2 over a 3-h period followed by carboplatin (area under the serum concentration–time curve = 6) intravenously over a 30-min period on day 1 of each treatment cycle (3 weeks) until disease progression or adverse effects prohibited further therapy. Eligible patients had histologically confirmed, advanced stage (III or IV), persistent or recurrent measurable disease, and no prior chemotherapy.
Results Six patients were enrolled between February 2006 and April 2009. The median age of the patients was 61 (range 48–77) years; one patient was stage IIIC (17 %) and five were stage IVB (83 %). Three patients (50 %) (1 at stage IIIC and 2 at stage IVB) received total abdominal hysterectomy plus bilateral salpingo-oophorectomy as part of the initial treatment; five (83 %) had homologous tumors and one (17 %) had a heterologous tumor. The median cycle number administered was 4.8 (range 2–7). The RR was 66.7 % (complete response, 2; partial response, 2); the PFS was 9.1 months and OS was not reached. The frequently observed Grade 4 toxicities were

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neutropenia (3 patients, 50 %). Manageable neutropenic sepsis developed in one patient.
Conclusion This is the first prospective multi-institutional study in Asia showing that PC may be effective and tolerable for the treatment of advanced or recurrent CS.

Keywords Carcinosarcoma of the uterus · Paclitaxel + carboplatin · Prospective multi-institutional study

Introduction

Carcinosarcoma of the uterus (CS), also known as malignant mixed Mullerian tumor, is a rare and aggressive neoplasm that contains both carcinomatous and sarcomatous histologic elements. Overall, the survival of women of Caucasian ethnic groups is significantly better than that of African–American women according to the surveillance, epidemiology, and end results (SEER) data [1]. CSs are monoclonal in original rather than true collision tumors [2, 3], suggesting that CS may be metaplastic, with the implication that the sarcomatous elements of CS are derivatives of the carcinomatous elements [4]. Even with surgery and adjuvant radiotherapy, the overall prognosis of CS is extremely poor due to its tendency to metastasize and its high local and distant relapse rate [5]. While initially grouped with sarcomas in early clinical trials, the clinical behavior of carcinosarcomas has subsequently been shown to be a reflection of the carcinomatous element. In light of this, carcinosarcomas have now been classified for staging purposes with carcinomas of the endometrium. Consequently, chemotherapeutic regimens for aggressive high-grade endometrial carcinoma, including the combination paclitaxel–carboplatin (PC), may also be effective in CS [6–8]. The Gynecologic Oncology Group (GOG) has reported a series of phase II trials to identify potentially active cytotoxic agents for the treatment of advanced or recurrent CS: ifosfamide [response rate (RR) 32 %] [9–12]; doxorubicin, 19 % [13, 14]; cisplatin, 8 % [15, 16], paclitaxel, 18 %] [17]. In addition, the GOG reported two large phase III trials. In these trials, the cisplatin–ifosfamide combination demonstrated significant improvements in RR (54 vs. 36 %) and progression-free survival (PSF) over cisplatin alone, but no statistical difference was seen in overall survival (OS) [18]. The combination of Ifosfamide–paclitaxel–filgrastim also demonstrated significant improvements in RR (45 vs. 29 %), PFS (6 vs. 4 months), and OS (14 vs. 8 months) over ifosfamide alone [19]. The toxicity, multiday schedule, and limited activity of these regimens, however, support further investigation of new treatments. A recent GOG study by Powell et al. [20] and our retrospective pilot study suggest that PC has activity in CS patients (RR 80 %; four of five evaluable patients) with minimal toxicity [21]. We therefore designed the present prospective multi-institutional study for CS to determine the RR, PFS and OS in CS treated with PC and to assess the toxicity of this treatment.

Patients and methods

Eligibility

Eligible patients had histologically confirmed, advanced stage III, IV, or recurrent CS with a measurable target lesion of $\geq$20 mm when measured by computed tomography (CT) and magnetic resonance imaging or of $\geq$10 mm when measured by spiral CT. Patients had to have at least one target lesion to assess response on this protocol, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [22]. Two gynecologic pathologists performed a pathologic slide review of the primary malignancy for all patients. Patients who had received prior cytotoxic chemotherapy were ineligible for entry into the study, and patients with a history of another invasive malignancy within the previous 5 years other than a non-melanoma skin cancer were also excluded. Patients of childbearing potential had to undergo a negative serum pregnancy test before entry onto the study and had to be practicing some effective form of contraception. A minimum Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, granulocytes of $\geq$1,500/μL, platelets of $\geq$100,000/μL, serum creatinine of $\leq$1.5× institutional upper limit of normal (ULN), and adequate liver function [bilirubin of $\leq$1.5× institutional ULN and aspartate aminotransferase and alkaline phosphatase of $\leq$2.5× the institutional ULN] were also required. Patients were to have recovered from previous treatments and have no evidence of infection. Patients with neuropathy (sensory or motor) Grade $\geq$1, according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 were excluded. All patients who entered the study provided written informed consent consistent with institutional review board regulations before study entry.

Therapy

One treatment cycle consisted of 3 weeks. Paclitaxel 175 mg/m^2 was delivered over a 3-h period followed by carboplatin dosed to an area under the serum concentration–time curve (AUC) = 6 intravenously over a 30-min interval on day 1 of each treatment cycle until disease progression or adverse effects prohibited further therapy. The dosing of carboplatin was calculated according to the Calvert formula to reach a target AUC of concentration multiplied by time using an estimated glomerular filtration rate (Cockgroft–Gault equation); a minimum creatinine value of 0.6 was stipulated. The maximum body surface

area used for paclitaxel dose calculations was set at 2.0 m^2. The number of cycles given beyond a clinical complete response (CR) was at the discretion of the principal physician. Patients with a partial response (PR) or stable disease were encouraged to continue unless adverse effects prohibited further therapy.

Dose modification and evaluation

Subsequent doses were modified for prolonged (>7 days) Grade 4 granulocytopenia, Grade 4 thrombocytopenia, or select non-hematologic toxicity. Grade ≥2 peripheral neuropathy required the reduction of one dose level of both paclitaxel and carboplatin and a delay in subsequent therapy for a maximum of 2 weeks until recovery to Grade 1. Dosing modifications for patients with renal, hepatic, and hypersensitivity reaction were mandated. Granulocyte-colony stimulating factor (G-CSF) was permitted in the setting of febrile neutropenia and/or recurrent documented Grade 4 neutropenia persisting for ≥7 days (after initial dose reduction). A history and physical exam and a laboratory evaluation were performed before each cycle of chemotherapy. CT or magnetic resonance imaging was performed every other cycle. Hematologic parameters were checked weekly. Response was determined according to RECIST criteria. CR and PR were classified as responses. Adverse effects were categorized and graded according to CTCAE v3.0.

Histopathology

Disease stage was determined using the clinical staging system of the International Federation of Gynecology and Obstetrics (FIGO) [23]. All slides in this study were examined by two pathologists (K.I. and H.N.) to review the histologic types of carcinomatous and sarcomatous components. Carcinomatous components were classified histologically as endometrioid adenocarcinoma and clear cell adenocarcinoma, respectively. All endometrioid adenocarcinomas were graded based on the proportion of nonsquamous solid growth pattern (Grade 1, ≤5 %; Grade 2, 6–50 %; Grade 3, >50 %) according to the World Health Organization classification [24]. Clear cell adenocarcinomas were classified as Grade 3 because the prognosis in these histologic types is reported to be poor [25]. Sarcomatous components were classified into homologous and heterologous types, respectively.

Statistical design

The primary endpoint was defined as RR, including CR and PR for patients with measurable disease. Toxicity and PFS were secondary endpoints. According to the historical GOG RR, the expected efficacy rate was set at 50 % and the threshold efficacy rate at 30 % for the study treatment under the conditions of $\alpha = 0.05$ and $\beta = 0.20$; the required number of subjects was 34. We targeted an enrollment of 35 subjects, anticipating one case of dropout.

Results

The study was closed in April 2009 due to slow accrual. Simultaneously, the GOG began a multicenter phase II trial studying this same combination of drugs for CS in 2005 that completed accrual in 2008 [20]. We also conducted a feasibility study with PC for CS patients who underwent an optimal surgery around the same time as this study. Fifty-one patients were enrolled from 30 institutions, of whom 22 and five were stage III and IV patients, respectively; all patients underwent optimal surgery (unpublished data). Our surgeons are particularly skilled and achieved high rates of optimal surgery; therefore, very few patients had residual tumors.

Six patients were enrolled in the study between February 2006 and April 2009. Table 1 summarizes the patient characteristics for the eligible patients. The median age of the patients was 61 (range 48–77) years. Of these six patients, five (83.3 %) had newly diagnosed disease (stage IVB), and one patient (16.7 %) had recurrent disease (stage IIIC) after post-surgical pelvic radiation therapy. Three patients (50 %; 1 at stage IIIC; 2 at stage IVB) underwent a total abdominal hysterectomy plus bilateral salpingo-oophorectomy as part of the initial treatment. The remaining three IVB patients could not undergo surgery because of the wide dissemination of their tumors (2 had lung metastases and 1 had peritonitis carcinomatosa). Even though surgical intervention after PC was not permitted in the protocol, we performed surgical intervention in two PR patients (no. 2 and 5) and in one patient with stable disease (SD; no. 6) because of their anxiety concerning surgical resection. We estimated the best response at the time of surgical intervention. Considering that both patients with optimal surgery (no. 5 and 6) had no evidence of disease after surgery, the RR of this study may have been higher.

The carcinomatous component was endometrioid adenocarcinoma in five patients (83.3 %), and one patient (16.7 %) had endometrioid plus clear cell adenocarcinoma. All endometrioid adenocarcinomas were Grade 1 adenocarcinoma. The sarcomatous component was undifferentiated homologous sarcoma in five tumors and contained rhabdomyosarcoma in one tumor. Unfortunately, we could not find any histopathologic characteristic relationships in this study. Table 2 summarizes the number of chemotherapy cycles each patient received and the best responses. The median number of cycles was 4.8 (range 2–7).

Table 1 Characteristics of the six patients enrolled in the study

Patient no.	Age (years)	Performance status	Stage	Carcinomatous component/ grade	Sarcomatous component	Pre-protocol treatments	Target lesion	Non-target lesion
1	68	0	IIIC	Endo./1	Homozygous	TAH + BSO + PLA, WP40 Gy	PAN	
2	54	0	IVB	Endo./1	Homozygous	None	Uterus, Rt. Ischial and Sacral bone	Lung
3	60	0	IVB	Endo. + Clear/ 3	Homozygous	TAH + BSO	Uterus, PLN-Subclavicular LN	
4	60	0	IVB	Endo./1	Heterozygous	TAH + BSO + OMT	Pelvis	
5	77	1	IVB	Endo./1	Homozygous	None	Uterus, Pelvis	Peritonitis carcinomatosa
6	48	0	IVB	Endo./1	Homozygous	None	Uterus, Lt. PLN, PAN	Lung
	61.2 (average)							

Endo. Endometrioid adenocarcinoma, *Clear* clear cell adenocarcinoma, *TAH* total abdominal hysterectomy, *BSO* bilateral salpingo-oophorectomy, *PLA* pelvic lymphadenectomy, *OMT* omentectomy, *LN* lymph node, *PLN* pelvic lymph node, *PAN* para-aortic lymph node

Table 2 Clinical treatments and results for all six patients

Patient no.	Cycles of PC (*n*)	Best response	Reason for discontinuation	Post-treatment		Status	Progression-free survival	Overall survival
				Surgery	Chemotherapy			
1	2	PD	Progressive disease	None	None	DOD		
2	7	PR	Patient's reason	TAH + BSO	Weekly PC	DOD		
3	6	CR	Complete remission	None	None	NED		
4	4	CR	Bone marrow suppression	None	PC × 2	AWD		
5	4	PR	Change of therapeutic strategy	TAH + BSO + PLA	PC × 5	NED		
6	6	SD	Change of therapeutic strategy	SemiRH + BSO	None	NED		
	4.8 (average)						9.1 months (50 % of patients)	Not reached (67 %)

CR Complete response, *PR* partial response, *SD* Stable disease, *PD* progressive disease, *AWD* alive with disease, *NED* no evidence of disease, *DOD* dead of disease, *PC* Paclitaxel-carboplatin

Treatment was discontinued for the following reasons: disease progression (1 patient, 16.7 %), change of therapeutic strategy to surgery (2 patients, 33.3 %), person reason (1 patient, 16.7 %), and toxicity (1 patient, 16.7 %). The RR was 66.7 % (CR, 2; PR, 2), and one patient (16.7 %) achieved SD. One patient (16.7 %) had progression of disease (PD). Four patients were alive (3 without and 1 with PD), and two had died due to complications from their cancer at the time of this analysis. The median PFS was 9.1 months, and the median OS was not reached. All reported adverse events are summarized in Table 3. The frequently observed Grade 3 and 4 toxicities were neutropenia (5 patients, 83.3 %), anemia (1 patient, 33.3 %), thrombocytopenia (1 patient, 33.3 %), and motor neuropathy (1 patient, 33.3 %). There was no Grade 4 motor and sensory neuropathy. One patient developed neutropenic sepsis (Grade 3) that responded to treatment.

Discussion

Carcinosarcoma of the uterus is aggressive and frequently diagnosed at an advanced stage. The 5-year disease-free survival of CS by stage is poor (stage I, 56 %; stage II,

Table 3 Adverse events

Adverse events	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Leukocytes (total white blood cells)	0	0	2	4	0	67
Neutrophils/granulocytes	0	0	1	2	3	83
Hemoglobin	0	1	3	2	0	33
Platelets	3	0	1	1	1	33
Anorexia	3	1	2	0	0	0
Nausea/vomiting	3	1	2	0	0	0
Constipation	3	3	0	0	0	0
Diarrhea	5	1	0	0	0	0
Fatigue	3	2	1	0	0	0
Hair loss/alopecia	1	2	3	0	0	0
Mucositis/stomatitis	6	0	0	0	0	0
Febrile neutropenia	6	–	–	1	0	17
Neuropathy–motor	5	0	0	1	0	17
Neuropathy–sensory	3	3	0	0	0	0
Allergic reaction/hypersensitivity	4	2	0	0	0	0

Table 4 Responses of chemotherapeutic trials in uterine carcinosarcoma

Drug/drug combination	First and/or second-line therapy	Response rate	Progression-free survival (months)	Overall survival (months)
Doxorubicin (GOG0087A) [6]	First	5/26 (19 %)	5	NR
Ifosfamide (GOG0087B) [3]	First	9/28 (32 %)	NR	NR
Cisplatin (GOG0026C) [9]	First	5/63 (8 %)	NR	NR
Paclitaxel (GOG0130B) [10]	First/second	8/44 (18 %)	4.2	NR
Ifosfamide/cisplatin (GOG0180) [11]	First	50/92 (54 %)	6	9.4
Ifosphamide/paclitaxel (GOG0261) [12]	First	40/88 (45 %)	5.8	13.5
Carboplatin/paclitaxel (Tohoku University) [19]	Retrospective	4/5 (80 %)	18	25
Carboplatin/paclitaxel (GOG0232B) [21]	First	25/46 (54 %)	17 %, 7.6	35 %, 14.7
Carboplatin/paclitaxel [24]	Retrospective	8/13 (62 %)	7.9	15
Carboplatin/paclitaxel (this study)	First	4/6 (67 %)	50 %, 9.1	67 %, not reached

31 %; stage III, 13 %; stage IV, 0 %) [26, 27], and most patients present with extrauterine disease. The GOG reported that the combination of cisplatin, ifosfamide, and paclitaxel has significant activity, and these agents were evaluated in subsequent phase III trials (Table 4) [10, 13, 16–21, 28]. Sutton et al. reported on the cisplatin–ifosfamide combination, which resulted in a significant increase in PFS (6 vs. 4 months), but no difference was seen in OS (RR 0.80; 95 % upper confidence limit 1.03; $p = 0.07$). Based on these results, ifosfamide–paclitaxel–filgrastim demonstrated statistically significant improvements in all three parameters (RR, PFS, and OS) over ifosfamide alone, establishing this regimen as the standard comparator regimen for further GOG trials.

In our retrospective study published in 2004, PC showed the potential for significant activity in the treatment of CS (RR 80 %, four of five evaluable patients) [21]. The study we report here is the first prospective study in Asia for advanced or recurrent CS. Taking into account data from the SEER publication, we suggest that Japanese patients may have survival rates that are comparable to or higher than those of Caucasian women [1] (Table 4). Our results suggest that PC for advanced or recurrent CS is feasible. PC is highly tolerable and may be administered on an outpatient basis. In addition, paclitaxel-induced neuropathy is generally mild.

Powell et al. [20] recently reported that the RR of CS to PC (AUC = 6) in patients with prior radiation therapy was 25 of 46 (54 %; CR, 6; PR,19) and that the PFS was 7.6 months. Lacour et al. [29] also reported on the RR of PC (AUC = 5) in patients with prior radiation therapy; in this study the RR of PC was 8 of 13 (62 %; CR 3; PR, 5) and the time to tumor progression was 7.9 months. Our results in terms of RR (66.7 %) and PFS (9.1 months) are comparable; however, the strength of our conclusions is limited by our small sample

size. While these results are promising, there is clearly still room for improvement that will likely be achieved through the incorporation of targeted therapeutics.

Although data in the literature are conflicting, recent studies have found that the behavior and overall prognosis of uterine carcinosarcoma is much more dependent on the characteristics of the epithelial elements than on those of the stromal elements [30]. In neoplasms where the epithelial element is Grade 3 endometrioid, serous, or clear cell in type, there is a higher frequency of metastasis and deep myometrial and cervical involvement. The results of older studies suggested that the presence of heterologous elements was associated with more aggressive behavior [31, 32], but more recent studies have found that the histologic features of the stromal component have no relationship to the likelihood of metastasis or overall prognosis [2, 4, 33]. Thus, it is still controversial whether the characteristics of the epithelial and stromal components impact survival; we could not find any histopathologic characteristic relationships in this study.

Novel molecular-targeted agents, including imatinib mesylate, sorafenib, VEGF-Trap, AZD0530, sunitinib, temozolomide, liposomal doxorubicin (+ carboplatin), lapatinib + ixabepilone, and bortezomib + gemcitabine are now also under investigation in trials of CS (clinicaltrials.gov). PC is one of the most common regimens in gynecologic malignancies, since severe adverse events are well characterized, predictable, and manageable. The results of our study indicate that PC is an effective and well-tolerated regimen for the treatment of advanced and recurrent CS and is therefore a likely candidate for use in conjunction with novel targeted agents. A randomized phase III trial of paclitaxel + carboplatin versus ifosfamide + paclitaxel in chemotherapy-naïve patients with newly diagnosed stage I–IV, persistent or recurrent carcinosarcoma of the uterus or ovary (GOG0261) is ongoing. We anticipate opening additional trials in Asia with targeted therapeutics in the near future.

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Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Feasibility study of gemcitabine plus docetaxel in advanced or recurrent uterine leiomyosarcoma and undifferentiated endometrial sarcoma in Japan

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Abstract
Background Uterine leiomyosarcoma (LMS) and undifferentiated endometrial sarcoma (UES) are rare, aggressive malignancies. Both are treated similarly; however, few chemotherapy agents are effective. Recently, the combination of gemcitabine (900 mg/m^2, days 1 and 8) plus docetaxel (100 mg/m^2, day 8) with granulocyte colony-stimulating factor (G-CSF, 150 μg/m^2, days 9–15) has been shown to have activity in LMS. In Japan, neither prophylactic G-CSF at a dose of 150 μg/m^2 nor docetaxel at a dose of 100 mg/m^2 are approved for use. For this reason, we evaluated the combination of 900 mg/m^2 gemcitabine plus 70 mg/m^2 docetaxel regimen without prophylactic G-CSF support in advanced or recurrent LMS and UES in Japanese patients.
Methods Eligible women with advanced or recurrent LMS and UES were treated with 900 mg/m^2 gemcitabine on days 1 and 8, plus 70 mg/m^2 docetaxel on day 8, every 3 weeks. The primary endpoint was overall response rate, defined as a complete or partial response.
Results Of the eleven women enrolled, 10 were evaluated for a response. One complete response and 2 partial responses were observed (30 %) with an additional 4 (40 %) having stable disease. Mean progression-free survival was 5.4 months (range 1.3–24.8 months), and overall survival was 14 months (range 5.3–38.4 months). Grade 4 neutropenia was the major toxicity (50 %). The median number of cycles was 5 (range 2–18). Twenty-two cycles (44 %) employed G-CSF.
Conclusion The gemcitabine plus docetaxel regimen without prophylactic G-CSF support was tolerable and highly efficacious in Japanese patients with advanced or recurrent LMS and UES.

Keywords Chemotherapy · Uterine leiomyosarcoma · Gemcitabine · Docetaxel · G-CSF · Japanese patients

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Introduction

Uterine leiomyosarcoma (LMS) and undifferentiated endometrial sarcoma (UES) together account for approximately 1 % of all uterine malignancies [1–3] and thus are diagnosed in only a few hundred women each year in Japan [4]. Systemic therapy for LMS and UES is similar [5]. Women who present with advanced disease and those with recurrence have a poor prognosis [6]. Median

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survival among women with advanced disease is less than 1 year.

Single-agent doxorubicin remains the standard first-line therapy in many treatment settings, with first-line response rates of approximately 25 %. The combination of doxorubicin plus ifosfamide (response rate 28–30 %) has not been shown to improve outcomes among patients with soft tissue sarcoma compared with doxorubicin alone [7, 8] (Table 1). Other single agents with moderate activity in leiomyosarcoma include ifosfamide (response rate 17.2 %) [9], gemcitabine (bolus infusion achieved a 20 % response rate) [10], trabectedin (response rate of 8 % among patients without prior treatment, and 45 % second-line treatment) [11, 12] and temozolomide (15.5 % objective response with daily oral treatment) [13]. Multiple chemotherapy agents, including cisplatin [14–16], liposomal doxorubicin [17], intravenous etoposide [18], oral etoposide [19], paclitaxel [20, 21], topotecan [22], trimetrexate [23], sunitinib malate [24], and thalidomide [25] have been tested in the first- and second-line settings with negligible activity demonstrated.

Docetaxel disrupts mitosis by the promotion of abnormal microtubular assembly and suppression of the depolymerization of microtubular bundles to free tubulin [26]. Gemcitabine is an S-phase-specific, fluorine-substituted pyrimidine analog, which is phosphorylated by deoxytidine kinase to the active diphosphate and triphosphate metabolites. This metabolite inhibits ribonucleotide reductase and DNA synthesis [27]. The clinical development of the gemcitabine–docetaxel regimen is outlined, and data demonstrating the efficacy of this regimen in soft tissue sarcoma are reviewed [28–30].

Table 1 Responses of chemotherapeutic trials in LMS

Drugs	Treatment lines	Response rate	Progression-free survival (months)
Doxorubicin [7]	First/second	7/28 (25 %)	3.5
Doxorubicin [36]	First	5/26 (19 %)	5
Cisplatin [16]	First	1/33 (3 %)	Not reported
Ifosfamide [9]	First	6/35 (17 %)	Not reported
Liposomal doxorubicin [17]	First	5/32 (16 %)	4.1
Etoposide IV [18]	First	0/28 (0 %)	2.1
Etoposide PO [19]	First/second	2/29 (7 %)	2.1
Paclitaxel [20]	First/second	3/33 (9 %)	Not reported
Topotecan [22]	First	4/36 (11 %)	Not reported
Trimetrexate [23]	Second	1/24 (4.3 %)	2.2
Paclitaxel [21]	First	4/48 (8 %)	1.5
Gemcitabine (bolus infusion) [10]	First/second	9/42 (20 %)	Not reported
Gemcitabine (fixed-dose rate, 10 mg/m^2/min) [37]	Second	4/21 (19 %)	5.5
Sunitinib malate [24]	Second	2/23 (8.7 %)	1.5
Temozolomide [13]	Second	1/13 (8 %)	Not reported
Thalidomide [25]	Second	0/29 (0 %)	1.7
Trabectedin [11]	Second	6/35 (17.1 %)	Not reported
Trabectedin [12]	Second	5/11 (45 %)	Not reported
Vincristine/dactinomycin/cyclophosphamide [38]	First	29 %	Not reported
Doxorubicin/dacarbazine [7]	First/second	24 %	Not reported
Doxorubicin/cyclophosphamide [36]	First	5/26 (19 %)	Not reported
Doxorubicin/ifosfamide [8]	First	10/33 (30 %)	4
Mitomycin/doxorubicin/cisplatin [39]	First	8/35 (22.8 %)	Not reported
DMAP, sargramostim (GM-CSF) [40]	First	5/18 (28 %)	5.9
Doxorubicin/ifosfamide [41]	First	12/25 (48 %)	Not reported
Gemcitabine + docetaxel [31]	First	18/34 (53 %)	5.6
Gemcitabine + docetaxel [33]	Second	13/48 (26 %)	5.6+
Gemcitabine + docetaxel [34]	First	15/42 (36 %)	4.4
Gemcitabine + docetaxel [37]	Second	5/21 (24 %)	4.7
Gemcitabine + docetaxel (this study)	Second/third	3/10 (30 %)	5.4

LMS Leiomyosarcoma, *DMAP* dacarbazine, mitomycin, doxorubicin, and cisplatin, *GM-CSF* granulocyte–macrophage colony-stimulating factor

A single-institution study of gemcitabine plus docetaxel yielded high objective response rates among patients with advanced LMS in both the second-line [31] and first-line settings [32]. Recently, gemcitabine plus docetaxel has been shown to yield higher response rates, and longer progression-free and overall survivals than single-agent gemcitabine in a randomized trial for patients with soft tissue sarcoma who had received up to three prior regimens [30]. In a Gynecologic Oncology Group (GOG) phase II trial for women with advanced leiomyosarcoma who had received one prior cytotoxic regimen, gemcitabine plus docetaxel achieved objective responses in 28 % of patients, with an additional 50 % having stable disease (SD). The high dose of docetaxel (100 mg/m$^{2)}$ in this study, however, produced profound myelosuppression necessitating the use of growth factor support [33].

A prospective study of gemcitabine plus docetaxel has been eagerly anticipated in Japan. However, such studies have not been conducted because the GOG regimen, as either prophylactic G-CSF at a dose of 150 μg/m^2 or docetaxel at a dose of 100 mg/m^2, is not approved in Japan. The maximum approved dose of docetaxel in Japan is 70 mg/m^2.

Therefore, the aim of this single-institution study was to evaluate the efficacy and toxicity of a regimen of gemcitabine 900 mg/m^2 plus dose-reduced docetaxel 70 mg/m^2 without prophylactic G-CSF support in Japanese patients with advanced or recurrent LMS and UES.

Patients and methods

Patients

Women with measurable advanced or recurrent LMS and UES with non-resectable disease were eligible. All tumors were histologically confirmed. Patients were permitted to have had prior chemotherapy and pelvic radiotherapy; however, patients previously treated with either docetaxel or gemcitabine were excluded. Patients were required to have an ECOG performance status of 0–2, and adequate bone marrow function [absolute neutrophil count (ANC) greater than or equal to 1500/μl, and platelets greater than or equal to 100,000/μl]; renal function (creatinine less than or equal to 1.5 × the institutional upper limit of normal); hepatic function (bilirubin less than or equal to 1.5 × the institutional upper limit of normal, and serum glutamic oxaloacetic transaminase [sGOT] and alkaline phosphatase less than or equal to 2.5 × the institutional upper limit of normal); and neurological function [baseline neuropathy, sensory and motor, less than or equal to National Cancer Institution Common Toxicity Criteria version 3.0 (CTC 3.0) grade 1]. Patients with a history of another invasive malignancy within the past 5 years were not eligible. All patients provided written, informed consent. The protocol and consent were reviewed and approved annually by Institutional Review Boards of Tohoku University Hospital.

Treatment

All participants had baseline imaging with a computed tomography (CT) scan of the chest, abdomen, and pelvis, within 4 weeks of starting therapy. CT imaging was repeated following every other cycle of treatment to assess response. A history was taken, and a physical examination and assessment of toxicities were performed at each cycle. Complete blood counts and comprehensive metabolic panels were monitored weekly. Participants received gemcitabine 900 mg/m^2 on days 1 and 8 intravenously infused over 90 min, followed by docetaxel 70 mg/m^2 on day 8 intravenously infused over 60 min. Treatment cycles were repeated approximately every 3 weeks, and patients continued on the study treatment until disease progression, achievement of discontinuation criteria as defined in the study protocol, or at the discretion of the investigator. Recommended pre-medication for the docetaxel was dexamethasone 8 mg orally twice a day starting the day prior to docetaxel. Early intervention with diuretics was encouraged for signs of docetaxel-related fluid retention. Patients received the day 1 treatment of each cycle provided the ANC was greater than or equal to 1500/μl and the platelet count was greater than or equal to 100,000/μl. Patients received full-dose day 8 treatment provided the ANC was greater than or equal to 1000/μl and platelet count greater than or equal to 100,000/μl. Seventy-five percent of the planned day-eight dose was given if the ANC was between 500 and 1000/μl or the platelet count was between 50,000 and 100,000/μl, and provided bilirubin levels from day 1 or after were within institutional normal limits. Day-8 treatment with docetaxel was omitted if the bilirubin remained above normal on day 8. Day-8 gemcitabine and docetaxel were both omitted if the day-8 ANC was under 500/μl or the platelet count was less than 50,000/μl. Patients were given therapeutic and second-line prophylactic G-CSF if they had grade 4 neutropenia. Doses of both docetaxel and gemcitabine were reduced by 25 % in subsequent cycles if a patient experienced grade 3 elevations in sGOT, serum glutamic pyruvic transaminase (sGPT), or alkaline phosphatase, and treatment was not resumed until such grade 3 elevations had resolved to grade 1 or less. Patients who experienced grade 2 or worse neurotoxicity had treatment held for a maximum of 2 weeks and could resume treatment at 75 % of the prior docetaxel dose if the neuropathy had improved. Other non-hematological toxicities with an impact on organ function of grade 2 (or greater) required 25 % dose reduction and delay in subsequent therapy for a maximum of 2 weeks until it recovered to no worse than grade 1.

Assessment of response and toxicity

All patients who received at least 1 cycle of study treatment were considered assessable for response. Response was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST). Responses according to these criteria are defined as follows: Complete response (CR) is the disappearance of all target and non-target lesions and no evidence of new lesions documented by 2 disease assessments at least 4 weeks apart. Partial response (PR) is at least a 30 % decrease in the sum of the longest dimensions (LD) of all target measurable lesions taking as the reference the baseline sum of LD. There could be no unequivocal progression of non-target lesions and no new lesions. Documentation by 2 disease assessments at least 4 weeks apart is required. In the case where the only target lesion is a solitary pelvic mass measured by physical examination, and which is not radiographically measurable, a 50 % decrease in the LD is required. Progression of disease (PD) requires at least a 20 % increase in the sum of LD of target lesions taking as references the smallest sum of LD, the appearance of new lesions, death due to disease or global deterioration due to disease. SD is any condition not meeting the above criteria. All 11 patients enrolled in the study were included in the assessment of response, apart from 1 patient who was not treated because of ileus. The primary endpoint was the overall response rate (RR: CR + PR), and secondary endpoints were progression-free survival (PFS), overall survival (OS), and adverse events. Time to treatment failure (TTF) was defined as the time from enrollment to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death. Adding to PFS, TTF is generally not accepted as a valid endpoint, but was also included as an endpoint in this study because 3 SD patients electively opted to change chemotherapy. Toxicities were graded according to CTC 3.0.

Results

Patient characteristics

Between February 2009 and June 2011, 11 women were enrolled in this phase II study. One patient (No. 8) underwent and was diagnosed by intrauterine cytology and curettage. One patient (No. 11) developed a prolonged postoperative ileus shortly after enrollment and was not included in the analysis. The remaining cases were included in the calculation of the objective response rate (Table 2). The median age of the cohort was 60.1 years (range 50–74 years). Nine patients had an ECOG performance status of 0 or 1, one had a performance status of 2. Eight of 10 patients had confirmed LMS, and 2 had UES. Nine of 10 patients had undergone a total abdominal hysterectomy plus bilateral salpingo-oophorectomy. Five of 6 recurrent patients had received 1 or more prior cytotoxic regimens, and in the majority, the prior therapy had been doxorubicin and ifosfamide-based. Three IVB stage patients were enrolled for first-line treatment. The main target regions were lung (40 %), pelvis (40 %), liver (10 %), and omentum (10 %). After 3 cycles, 3 SD patients (Nos. 4, 6, and 7) requested to be switched to other chemotherapies, and 1 patient (No. 5) refused further treatment. One patient (No. 3) desired surgical resection of the downsized pelvic tumor. Nine of 10 (90 %) received three or more cycles of study treatment. The median number of cycles of study treatment delivered per patient was five (range 2–18 cycles).

Response and survival

The RECIST-measured objective RR was observed in 3 of the 10 patients enrolled (30 %). One patient had CR (10 %), 2 had confirmed PR (20 %), and 4 (40 %) had SD (Table 2). The disease control rate (DCR; CR + PR + SD) was 70 %. Three of 10 (30 %) had PD. Mean PFS was 5.4 months (range 1.3–24.8 months), and mean TTF was 3.1 months (range 2.4–15.4 months). Mean OS was 14 months (range 5.3–38.4 months). Among 3 objective responses, the median response duration was 19.7 months (range 5.9–28.3 months).

Adverse events

Among the total of 50 cycles, the median number of cycles per patient was 5 (range 2–18 cycles); 22 cycles (44 %, median 5 times/cycle: range 3–7 times) were for 4 patients who required G-CSF at a dose of 75 $\mu g/m^2$ (half the dose used in the GOG trials). Myelosuppression was the major toxicity: neutropenia grade 3 in 20 %, grade 4 in 50 %; anemia grade 3 in 10 %, grade 4 in 10 %; thrombocytopenia grade 3 in 10 %, grade 4 in 20 %. There were no cases of grade 4 febrile neutropenia. One patient had grade 3 liver toxicity (Table 3). No grade 3/4 pulmonary toxicity was observed.

Discussion

Efficacy

In Japan, prophylactic G-CSF at a dose of 150 $\mu g/m^2$ and docetaxel at a dose of 100 mg/m^2 are not approved for use. For this reason, we performed the current feasibility study of gemcitabine 900 mg/m^2 plus dose-reduced docetaxel

Table 2 Patient characteristics and results

No.	Age (years)	PS	Stage	Hist.	Preprotocol treatments	Target lesion	Cycles	BR	Reason for discontinuation	Post treatments		Status
										Surgery	Chemo./ irradiation	
1	51	0	IVB	LMS	TAH + BSO	Omentum	6	CR	NA	None	None	NED
2	66	0	Rec.	LMS	TAH + BSO IAP × 3, TC × 3	Lung	18	PR	PD	None	Irradiation	DOD
3	53	0	Rec.	LMS	TAH + BSO IAP × 6	Pelvis	6	PR	Change strategy	Lt. pelvic tumor resection	GD × 2	DOD
4	59	0	IVB	UES	TAH + BSO	Lung	3	SD	Patient preference	None	IP × 3	DOD
5	74	0	Rec.	LMS	TAH + BSO IAP × 3	Liver	3	SD	Patient's reason	None	None	DOD
6	51	0	Rec.	UES	TAH + BSO IAP × 3	Pelvis	3	SD	Patient preference	None	TC × 2	DOD
7	50	0	Rec.	LMS	TAH + BSO	Lung	3	SD	Patient preference	None	IA × 3	DOD
8	55	1	IVB	LMS	None	Uterus Pelvic LN	2	PD	PD	None	Irradiation	DOD
9	40	1	Rec.	LMS	TAH + BSO	Lung	3	PD	PD	Lt. lower lobectomy	None	DOD
10	74	1	Rec.	LMS	TAH + BSO, CPT11 × 8, AP × 3	Pelvic LN	3	PD	PD	None	None	DOD
11[a]	60	2	Rec.	LMS	TAH + BSO	Lung	0	NA	NA	None	None	DOD

PS Performance status, *Rec.* recurrence, Hist., histology, *LMS* leiomyosarcoma, *UES* undifferentiated endometrial sarcoma, *TAH* total abdominal hysterectomy, *BSO* bilateral salpingo-oophorectomy, *IAP* ifosfamide + doxorubicin + cisplatin, *TC* paclitaxel + carboplatin, *CPT-11* irinotecan, *AP* doxorubicin + cisplatin, *IP* ifosfamide + cisplatin, *IA* ifosfamide + doxorubicin, *GD* gemcitabine + docetaxel, *BR* best response, *NA* not applicable, *NED* no evidence of disease, *DOD* dead of disease, *CR* complete response, *SD* stable disease, *Lt.* left, *PD* progression of disease, *LN* lymph node

[a] Patient No. 11 developed a prolonged postoperative ileus shortly after enrollment and was not treated with gemcitabine and docetaxel

70 mg/m^2 without prophylactic G-CSF support in Japanese patients with advanced or recurrent LMS and UES.

The GOG conducted a phase II trial for women with advanced, unresectable LMS whose disease had progressed after one previous cytotoxic regimen (gemcitabine–docetaxel as second-line therapy) [33]. This study enrolled 51 patients, of whom 48 were evaluable for response. Ninety percent of the patients had received previous doxorubicin-based therapy. Patients were treated with gemcitabine 900 mg/m^2 on days 1 and 8 over 90 min, and docetaxel 100 mg/m^2 on day 8 of a 21-day cycle with G-CSF support. Patients who had received previous pelvic radiation were given 25 % lower doses. Three of 48 patients (6.3 %) achieved CR, and 10 (20.8 %) achieved PR for an overall objective RR of 27 %. An additional 50 % of women had SD lasting a median duration of 5.4 months. The median number of cycles per patient was 5.5 (range 1–22 cycles). The PFS rate at 12 weeks was 73 %, and at 24 weeks was 52 %. Median PFS was 5.6+ months (range 0.7–27+ months). The median duration of objective response exceeded 9 months (range 3.9–24.5+ months). The GOG has conducted a prospective phase II trial to assess the efficacy of first-line, fixed-dose-rate gemcitabine plus docetaxel in women with advanced LMS [34]. The doses and schedule are the same as in their previously reported second-line treatment study. Objective responses were observed in 35.8 % of patients, CR in 4.8 % and PR in 31 %. An additional 26.2 % had SD. Half of the patients received 6 or more cycles of study treatment. The median PFS was 4.4 months (range 0.4–37.2+ months). Among the patients with an objective response, the median response duration was 6 months (range 2.1–33.4+ months). Median OS exceeded 16 months (range 0.4–41.3 months). The RR (30 %, 27.1 % [33], 35.8 % [34]), PFS (5.4 months), DCR (70 %), OS (14 months), and duration of objective response (19.7 months) in our study nearly equaled those of the 2 prior GOG trials (RR: 27.1 % [33], 35.8 % [34]; PFS: 5.6+ [33], 4.4 months