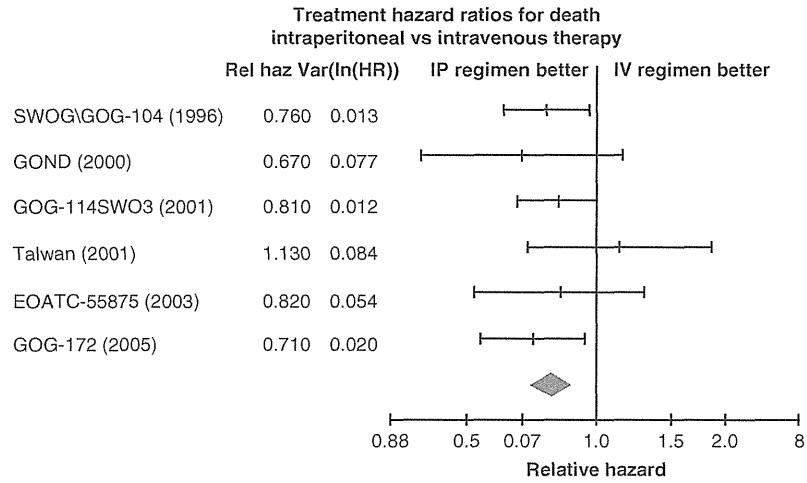

Figure 2. Result of meta-analysis for i.p. chemotherapy published as a NCI clinical announcement.

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.

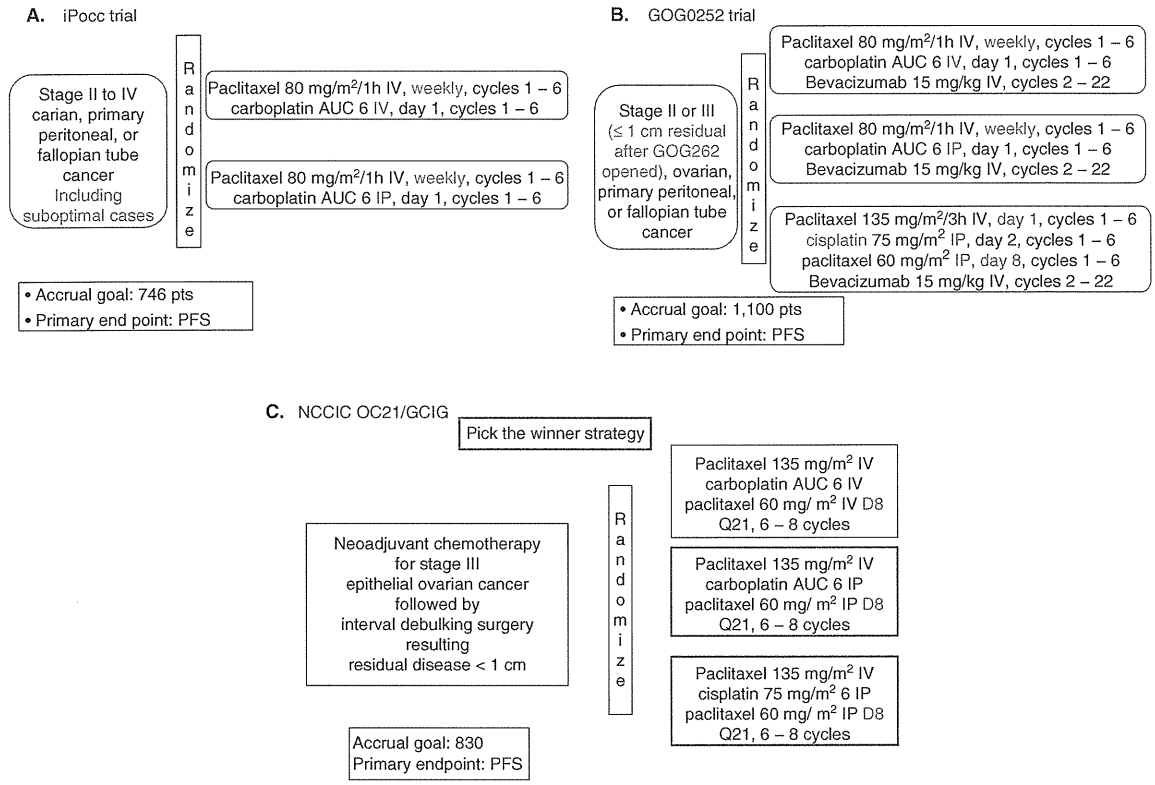

Figure 3. A. Schematic study design of iPocc trial. **B.** Schematic study design of GOG252 trial. **C.** Schematic study design of OV21 trial.

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

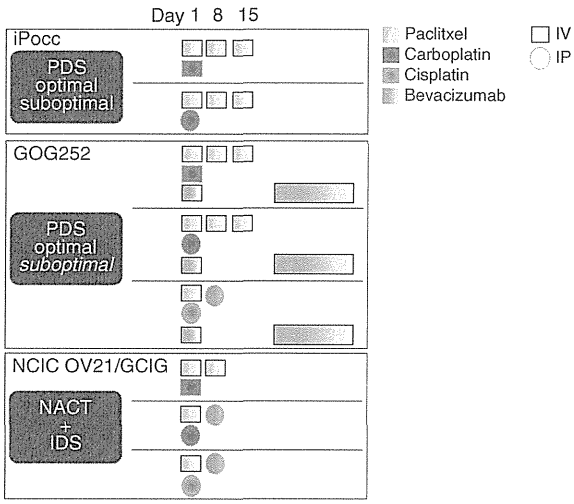

Figure 4. Comparison of iPocc, GOG252 and OV21 trial designs.

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.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 1996;335:1950-5

•• **This is the first randomized clinical trial that showed overall survival benefit of i.p. chemotherapy over conventional i.v. chemotherapy in ovarian cancer.**

2. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001;19:1001-7

•• **This is the first randomized clinical trial that showed improvement of PFS in combination of i.p. cisplatin plus paclitaxel over i.v. cisplatin plus paclitaxel, although overall survival was marginal.**

3. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006;354:34-43

•• **This trial is important because it showed significant improvement of overall survival in combination of i.p. cisplatin plus i.p. paclitaxel (day 8) and i.v. paclitaxel (day 1) over conventional i.v. cisplatin plus i.v. paclitaxel.**

4. Fujiwara K, Armstrong D, Morgan M, Markman M. Principles and practice of intraperitoneal chemotherapy for ovarian cancer. Int J Gynecol Cancer 2007;17:1-20

• **This is a comprehensive review of i.p. chemotherapy for ovarian cancer and will be useful to read together with current article.**

5. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1-6

6. Cannistra SA. Intraperitoneal chemotherapy comes of age. N Engl J Med 2006;354:77-9

7. NCI Clinical Announcement. Intraperitoneal Chmoetherapy for Ovarian Cancer. 2006.

•• **This is the first NCI clinical announcement that officially recommended the use of i.p. chemotherapy for ovarian cancer.**

8. Los G, Mutsaers PH, van der Vijgh WJ, et al. Direct diffusion of cis-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. Cancer Res 1989;49:3380-4

9. Markman M, Reichman B, Hakes T, et al. Evidence supporting the superiority of intraperitoneal cisplatin compared to intraperitoneal carboplatin for salvage therapy of small-volume residual ovarian cancer. Gynecol Oncol 1993;50:100-4

10. Bookman MA, McGuire WP III, Kilpatrick D, et al. Carboplatin and paclitaxel in ovarian carcinoma: a phase I study of the Gynecologic Oncology Group. J Clin Oncol 1996;14:1895-902

11. Miyagi Y, Fujiwara K, Kigawa J, et al. Intraperitoneal carboplatin infusion may be a pharmacologically more reasonable route than intravenous administration as a systemic chemotherapy. A comparative pharmacokinetic analysis of platinum using a new mathematical model after intraperitoneal vs. intravenous infusion of carboplatin–a Sankai Gynecology Study Group (SGSG) study. Gynecol Oncol 2005;99:591-6

• **This study provided an pharmacological evidence that support the use of i.p. carboplatin.**

12. Fujiwara K, Sakuragi N, Suzuki S, et al. First-line intraperitoneal carboplatin-based chemotherapy for 165 patients with epithelial ovarian carcinoma: results of long-term follow-up. Gynecol Oncol 2003;90:637-43

• **This is the first report that showed the possibility of carboplatin to be used i. p. route.**

13. Fujiwara K, Nagao S, Kigawa J, et al. Phase II study of intraperitoneal carboplatin with intravenous paclitaxel in patients with suboptimal residual epithelial ovarian or primary peritoneal cancer: a Sankai Gynecology Cancer Study Group Study. Int J Gynecol Cancer 2009;19:834-7

14. Morgan MA, Sill MW, Fujiwara K, et al. A phase I study with an expanded cohort to assess the feasibility of intraperitoneal carboplatin and intravenous paclitaxel in untreated ovarian, fallopian tube, and primary peritoneal carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2011;121:264-8

• **This study is the first Phase I feasibility study for the combination of i.p. carboplatin and i.v. paclitaxel and became the rationale for future trials.**

15. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009;374:1331-8

16. Bookman MA. Dose-dense chemotherapy in advanced ovarian cancer. Lancet 2009;374:1303-5

17. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473-83

18. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96

19. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943-53

20. Fujiwara K, Aotani E, Hamano T, et al. A Randomized phase II/III trial of 3 weekly intraperitoneal versus intravenous carboplatin in combination with intravenous weekly dose-dense paclitaxel for newly diagnosed ovarian, fallopian tube and primary peritoneal cancer. Jpn J Clin Oncol 2011;41:278-82

• **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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INVITED COMMENTARY

Clinical Trials of Neoadjuvant Chemotherapy for Ovarian Cancer: What Do We Gain After an EORTC Trial and After Two Additional Ongoing Trials Are Completed?

Keiichi Fujiwara · Akira Kurosaki · Kosei Hasegawa

Abstract The aim of neoadjuvant chemotherapy is to reduce the tumor volume or spread of the disease before the main treatment, and it could possibly make the main procedures easier or less invasive. Although the standard therapeutic strategy for advanced ovarian cancer is a maximum primary debulking surgery followed by chemotherapy, a European Organisation for Research and Treatment of Cancer (EORTC) prospective randomized trial demonstrated that neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to the standard procedure. This study raised a number of controversies, particularly regarding the quality of debulking surgery. To solve the questions, we need to wait for the results of two additional ongoing randomized trials. However, the results of those two trials must be carefully assessed, because the quality of debulking surgery would significantly affect survival, and may make the interpretation of the trial results more confusing and difficult.

Introduction

The treatment outcome of ovarian cancer is very poor, because this disease is most commonly diagnosed in advanced stages [1].

Since 1999, the current standard treatment strategy for advanced ovarian cancer is so-called maximum effort of primary debulking surgery (PDS) followed by taxane plus carboplatin chemotherapy. To improve the therapeutic effect, new agents such as bevacizumab [2, 3] and intraperitoneal therapy [4] have been investigated. At the same time, the attempt to reduce the patient's burden has been investigated. This concept is important if the clinical outcome is the same regardless of the intensity or aggressiveness of the main therapy. These less invasive treatments will potentially improve the quality of life of patients. Neoadjuvant chemotherapy (NACT) is one of these approaches. In the Fourth Ovarian Consensus Conference statement [5], it was concluded that "delayed primary surgery following NACT is an option for selected patients with stage IIIC and stage IV ovarian cancer as included in EORTC 55971 [6]," although this was the only issue among the consensus conference where total consensus was not reached.

In this review, we discuss the concept, current status, and future perspectives of NACT in advanced ovarian cancer, focusing particularly on the quality of debulking surgery.

Neoadjuvant Chemotherapy

The general concept of NACT is to administer chemotherapy before the main treatment such as surgery or radiation therapy. The purpose of this strategy is to reduce the tumor size or extent of cancer spread before applying the radical main treatment, thus making the procedure easier or less invasive. It also provides the opportunity to know whether the chemotherapy is effective or not, which is not possible when the tumor is completely removed.

NACT has been studied in several types of cancer, such as breast, prostate, cervix, colorectal, lung, and esophageal cancers. Among those cancers, breast cancer would be best suited to NACT because it is now one of the standard treatment strategies.

In ovarian cancer, PDS followed by adjuvant chemotherapy is a gold standard procedure, and the role of NACT has been debated for years [7, 8]. However, the most interesting fact is that there have been no randomized trials demonstrating

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that PDS is better than NACT followed by interval debulking surgery (IDS). The European Organisation for Research and Treatment of Cancer (EORTC) 55971 trial is the first prospective randomized study of advanced (stage IIIC or IV) ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma to compare the overall survival between patients who received standard PDS followed by chemotherapy and those who received NACT plus IDS [6]. Most of the patients who entered this trial (n=670) had extensive stage IIIC or stage IV disease at the time of treatment. When we look at surgical achievement, a largest residual tumor 1 cm or less in diameter was achieved in 41.6 % of patients after primary debulking and in 80.6 % of patients after interval debulking. The hazard ratio for death in the NACT group as compared with the PDS group was 0.98 (90 % confidence interval, 0.84—1.13; P=0.01 for noninferiority), and the hazard ratio for progressive disease was 1.01 (90 % confidence interval, 0.89–1.15). Complete resection of all macroscopic disease (at primary or interval surgery) was the strongest independent variable in predicting overall survival. The rates of postoperative adverse events and mortality were higher after primary debulking than after interval debulking.

This study raised considerable controversies [9–11]; thus, additional phase III trials are necessary to clarify the benefit of the NACT strategy. Fortunately, two prospective randomized trials have already completed accrual. One is a UK trial and another is a Japanese trial.

The UK trial (CHORUS: chemotherapy or upfront surgery) is similar to the EORTC 55971 trial. The patients were randomly assigned to either immediate PDS followed by six cycles of chemotherapy, or three cycles of NACT followed by IDS, and then an additional three cycles of chemotherapy. For patients assigned to NACT, however, histological or cytological confirmation of target diseases was necessary before treatment started. The accrual target was 550 patients. The data will be combined with those from the EORTC 55971 study to reliably exclude a 5–6 % difference in 3-year overall survival. Analysis of the data is awaited.

The Japanese Clinical Oncology Group (JCOG) conducted a randomized trial (JCOG0602) [12] in which patients with stage III/IV ovarian, tubal, or primary peritoneal cancer were allocated either to a PDS arm followed by eight cycles of chemotherapy or to an NACT arm with four cycles of chemotherapy followed by IDS plus an additional four cycles of chemotherapy. This study is designed as a noninferiority trial with 300 patients in total. Accrual was completed in 2011.

Hopefully, these two trials will be able to answer the question of whether NACT followed by IDS is truly as efficacious as the standard primary debulking strategy, but things do not appear to be that simple. We may have to be careful to interpret upcoming data, because the difference in the accomplishment of optimal cytoreduction surgery may lead to an explanation of the results in the wrong direction.

Quality of Debulking Surgery Issue

The one of the most interesting observations in the EORTC trial was the fact that the debulking rate was substantially different from country to country (Table 1). Belgium was the only country that achieved a debulking rate for no residual disease of more than 50 %. As the hazard plot in Fig. 1 shows, the survival of patients in Belgium was exactly the same regardless of whether the patients were in the PDS arm or the NACT arm. However, in those countries in which the debulking rate was substantially lower, such as Spain, the UK, and Canada, prognosis of the patients in the upfront surgery arm tended to be better than that of those in the NACT arm.

There is no good explanation for this observation, but one can hypothesize that it occur because the debulking rate at the time of IDS was also substantially lower in these countries. In other words, the outcome of the NACT–IDS strategy was not sufficient because removal of chemoresistant tumor was not successful. In fact, as Table 1 shows, the debulking rates for the NACT arm (i.e., at the time of IDS) for no residual disease were almost half of that in Belgium. Therefore, the quality of IDS may be more critical. It is clear that the success of debulking surgery to leave no residual

Table 1 Debulking rate by country

Characteristics	Primary debulking surgery (n=310)	Neoadjuvant chemotherapy (n=322)
Residual disease (≤10 mm) per country—n (%)		
Belgium	44 (71.0)	73 (92.4)
The Netherlands	19 (37.3)	49 (75.4)
Norway	12 (32.4)	35 (79.5)
Italy	6 (37.5)	12 (66.7)
Spain	13 (43.3)	17 (70.8)
UK	15 (30.6)	33 (78.6)
Canada	11 (30.6)	30 (71.4)
No residual disease per country—n (%)		
Belgium	39 (62.9)	69 (87.3)
The Netherlands	2 (3.9)	18 (27.7)
Norway	3 (8.1)	22 (50)
Italy	1 (6.3)	7 (38.9)
Spain	3 (10.0)	10 (41.7)
UK	5 (10.2)	18 (42.9)
Canada	4 (11.1)	13 (40.5)

Data from Table 1 in the supplementary appendix of [6]

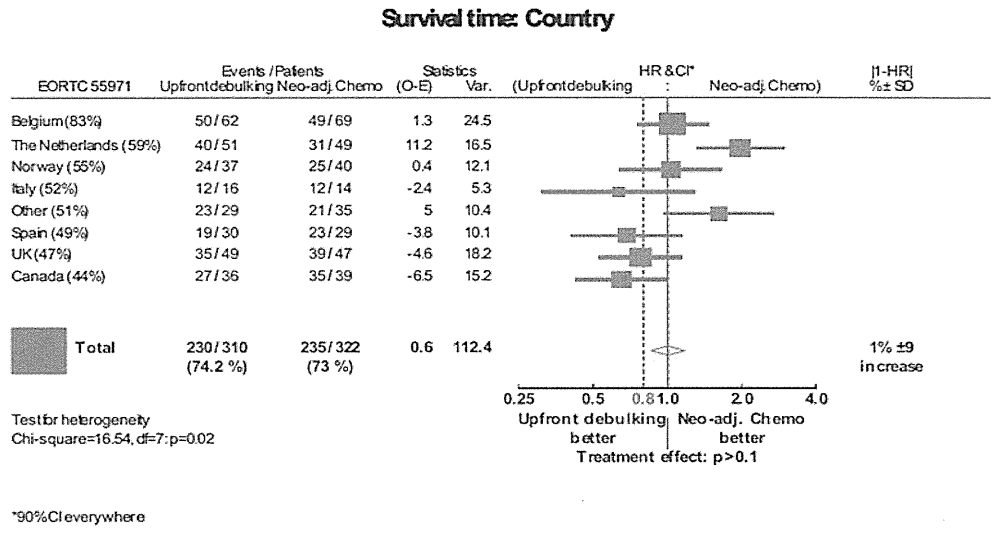

Fig. 1 Survival plot by country. (Reproduced from Fig. 9 in the supplementary appendix of [6] with permission)

disease is the most important prognostic factor for both the PDS arm and the NACT arm.

Another important determinant factor for prognosis is postoperative mortality. It is assumed that extensive surgery causes more postoperative complications and mortality. Figure 2 shows the hazard in the PDS arm at 2 months after randomization is greater than that in the NACT arm, probably because of the postoperative deaths.

In the countries where the PDS rates were lower, most of the patients assigned to the PDS arm received less invasive surgery; therefore, it is supposed that rates of postoperative death were less than expected and the prognosis was better. Also, it is assumed that those patients who received successful PDS had less extensive disease only.

On the other hand, this trend was reversed around month 5, and then the difference disappeared at later time (Fig. 2). This reversed trend was probably due to disease progression in patients who had chemoresistant disease in the NACT arm, whereas it might have been removed in the PDS arm.

On the basis of these assumptions, we need to build the future strategy thoughtfully. It is not difficult to avoid postoperative death by not performing too radical PDS. The question is how we select the patients who should undergo radical PDS because the disease is anticipated to be resistant to chemotherapy to prolong survival. This is the most important research question for the future.

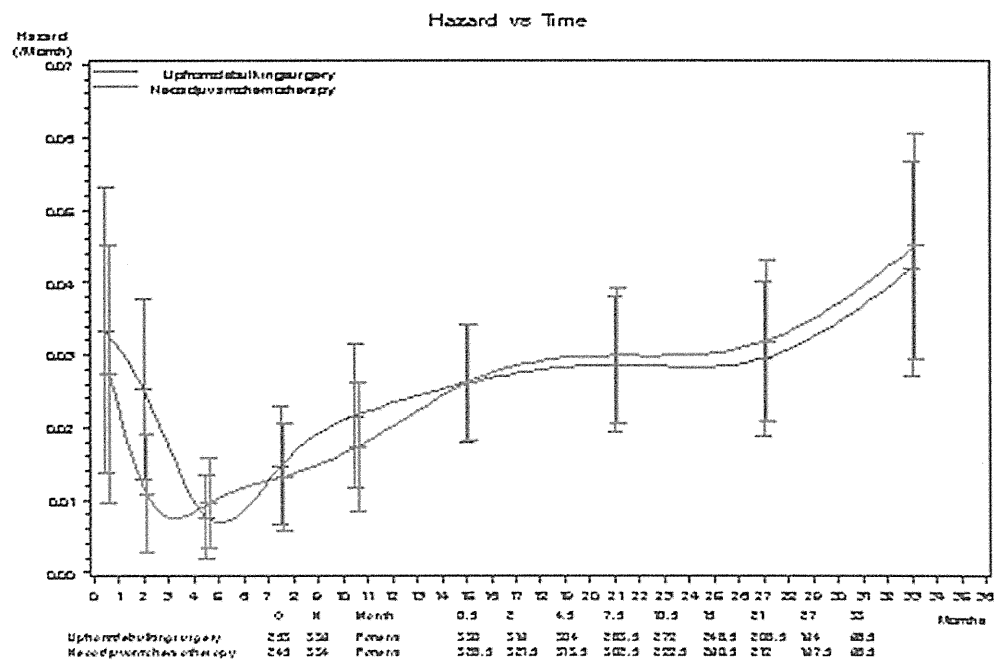

Fig. 2 Hazard plot of primary debulking surgery (*red*) and neoadjuvant chemotherapy (*blue*) arms by time. (Reproduced from Fig. 16 in the supplementary appendix of [6] with permission)

Conclusions

From the above-mentioned discussions, it is anticipated that prognosis in the PDS arm of currently ongoing NACT trials will become better if the ratio of PDS to no visible disease is low. However, this should not be interpreted as PDS being better than the NACT–IDS strategy; rather it should be interpreted as being due to reduction of the rate of postoperative death and the lower debulking rate in IDS.

To resolve these contradictory assumptions, we strongly believe that an NACT trial has to be conducted in a group where aggressive PDS can be accomplished as homogeneously as possible (such as in Belgium). It is of regret that the concept of the GOG NACT trial was rejected by the US Cancer Therapy Evaluation Program.

Conflict of Interest Keiichi Fujiwara has been a consultant for Auro and Amgen and has received honoraria from Sanofi, Boehringer-Ingelheim, Taiho, Kyowa Kirin, Chugai, Zeria, Janssen, and GlaxoSmithKline.

Akira Kurosaki declares no conflict of interest.

Kosei Hasegawa declares no conflict of interest.

References

1. Stuart GC, Kitchener H, Bacon M, et al. 2010 Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. Int J Gynecol Cancer. 2011;21:750–5.
2. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365:2473–83.
3. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365:2484–96.
4. Armstrong DK, Brady MF. Intraperitoneal therapy for ovarian cancer: a treatment ready for prime time. J Clin Oncol. 2006;24:4531–3.
5. Thigpen T, duBois A, McAlpine J, et al. First-line therapy in ovarian cancer trials. Int J Gynecol Cancer. 2011;21:756–62.
6. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363:943–53.
7. Onda T, Yoshikawa H. Neoadjuvant chemotherapy for advanced ovarian cancer: overview of outcomes and unanswered questions. Expert Rev Anticancer Ther. 2011;11:1053–67.
8. Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis. Gynecol Oncol. 2006;103:1070–6.
9. Chi DS, Bristow RE, Armstrong DK, Karlan BY. Is the easier way ever the better way? J Clin Oncol. 2011;29:4073–5.
10. Chi DS, Musa F, Dao F, et al. An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT). Gynecol Oncol. 2012;124:10–4.
11. Vergote I, Trope CG, Amant F, Ehlen T, Reed NS, Casado A. Neoadjuvant chemotherapy is the better treatment option in some patients with stage IIIc to IV ovarian cancer. J Clin Oncol. 2011;29:4076–8.
12. Onda T, Matsumoto K, Shibata T, et al. 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. Jpn J Clin Oncol. 2008;38:74–7.

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Applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer: The SGSG-012/GOTIC-004/Intergroup study

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HIGHLIGHTS

- We reviewed the clinical data of second-line platinum-based chemotherapy in patients with recurrent endometrial cancer.
- The concept of "platinum sensitivity" is applicable to recurrent endometrial cancer.

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ABSTRACT

Objective. The concept of "platinum sensitivity" has been widely applied in the management of recurrent ovarian cancer. This study aimed to evaluate the applicability of this concept to recurrent endometrial cancer.

Patients and methods. In this multicenter retrospective cohort study, the clinical data of patients with recurrent endometrial cancer, who had a history of receiving first-line platinum-based chemotherapy and who received second-line platinum-based chemotherapy at the time of recurrence between January 2005 and December 2009 were reviewed.

Results. A total of 262 patients from 30 centers with initial FIGO stage classifications of I (29), II (23), III (122), and IV (88) were enrolled. In total, 153 endometrioid adenocarcinomas, 34 serous adenocarcinomas, 17 clear cell adenocarcinomas, 36 carcinosarcomas, and 22 "other" tumors were documented. The response rates for patients with platinum-free intervals of <6 months, 6–11 months, 12–23 months, and ≥24 months were 25%, 38%, 61%, and 65%, respectively. The median progression-free survival after second-line platinum-based chemotherapy for patients with platinum-free intervals of <12 months and ≥12 months was 4.4 (95% confidence interval (CI) = 3.7–5.8) months and 10.3 (95% CI = 8.2–12.6) months, respectively (log-rank $P < 0.0001$), and the median overall survival was 13.8 (95% CI = 10.6–18.1) months and 40.9 (95% CI = 25.3–54.2) months, respectively (log-rank $P < 0.0001$).

Conclusion. Platinum-free interval is a predictor of response and survival after second-line platinum-based chemotherapy in patients with recurrent endometrial cancer. The concept of "platinum sensitivity" could be applicable to recurrent endometrial cancer.

Introduction

One of the most important factors for predicting the outcome of recurrent ovarian cancer is the platinum-free interval, which is defined as the period between the completion of platinum-based primary chemotherapy and disease recurrence. Women with ovarian cancer and a platinum-free interval of >6 months are classified as "platinum sensitive" and they usually undergo platinum-based second-line chemotherapy as well; their response rates ranging from 27% to 65% along with a median survival of 12–24 months [1,2]. On the other hand, patients with a platinum-free interval of <6 months are classified as "platinum

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resistant". Their median survival is 6–9 months along with and a 10%–30% probability of response to second-line chemotherapy.

Recently, a number of important developments in chemotherapy for endometrial cancer have been observed. In the Gynecologic Oncology Group study 122, the effects of chemotherapy with doxorubicin plus cisplatin were compared with whole abdominal radiation therapy in patients with stage III–IV endometrial cancer along with a <2 cm residual tumor [3]. In this trial, compared with radiation therapy, chemotherapy was associated with superior progression-free survival (PFS: 50% vs. 38% at 5 years; $P = 0.007$) and overall survival (OS: 55% vs. 42% at 5 years; $P = 0.004$). In addition, the Japanese Gynecologic Oncology Group compared pelvic radiotherapy and chemotherapy with cyclophosphamide, doxorubicin, and cisplatin in a cohort of women with stage IC–IIIC endometrial cancer [4]. Although overall survival revealed no significant difference between both methods, the investigators noted a survival advantage of adjuvant chemotherapy in the women from the high-to-intermediate risk group (stage IC, >70 years of age, grade 3, stage II, or positive cytology with >50% myometrial invasion). The results of this trial have had a significant impact on clinical practice in the Japanese gynecologic oncology community.

In recent years, more patients with endometrial cancer have undergone adjuvant chemotherapy instead of radiation therapy. Concurrently, more patients have received salvage chemotherapy after recurrence as well; however, data regarding the efficacy of second-line platinum-based chemotherapy for endometrial cancer are lacking. Therefore, we conducted this retrospective study to evaluate the applicability of the "platinum sensitivity" concept to recurrent endometrial cancer.

Patients and methods

Study design

This is a retrospective cohort study evaluating the relationship between platinum-free interval and response to second-line platinum-based chemotherapy, as well as PFS and OS after second-line chemotherapy. The platinum-free interval was defined as the period from the completion of first-line platinum-based chemotherapy to the date of diagnosis of recurrence. PFS was measured from the start date of second-line chemotherapy to the date of subsequent radiologic relapse, progression, or to the date of last contact for disease-free patients. OS was defined as the period from the start date of second-line chemotherapy to death or the date of last contact.

Patients

Consecutive patients with histologically confirmed endometrial cancer or uterine carcinosarcoma, who received second-line platinum-based chemotherapy between January 2005 and December 2009, were registered (histological confirmation of recurrence was not required). All patients had received primary platinum-based chemotherapy. Concurrent chemoradiation therapy was not regarded as a platinum-based chemotherapy even if it included a platinum agent. There was no restriction regarding the type of therapy administered after completion of second-line chemotherapy. Patients were excluded if they had a uterine sarcoma or another concurrent invasive cancer.

Factors analyzed

Data regarding the following clinicopathological parameters were recorded for analysis: (1) type of primary therapy, (2) presence of a residual tumor after surgery, (3) FIGO stage at primary diagnosis, (4) histologic type and grade, (5) first-line chemotherapy regimen received, (6) date of completion of first-line chemotherapy, (7) information regarding radiation therapy, if received, (8) age at the time of diagnosis of recurrence, (9) site of recurrence, (10) second-line chemotherapy regimen and number of cycles administered, (11) start date of second-line chemotherapy, (12) response to second-line chemotherapy assessed according to RECIST version 1.1 or WHO criteria, (13) date of subsequent radiologic relapse or progression, (14) date of death or last contact, and (15) cause of death.

Statistical analysis

To evaluate whether response to second-line platinum-based chemotherapy increased with longer platinum-free intervals, Cochran–Armitage test for trend was used. The PFS and OS probabilities were estimated using the Kaplan–Meier method, and log-rank trend test was used to test for a trend in PFS or OS across ordered platinum-free intervals. In addition, the probability of PFS or OS was estimated separately between groups with a platinum-free interval of <12 months and ≥12 months using the Kaplan–Meier method, and differences in PFS or OS between the two groups were evaluated by log-rank test. There may be significant differences between patient characteristics of the groups. Such differences must be adjusted to determine the effects of platinum-free interval. Therefore, the comparability of patient characteristics between the groups was conducted, and then, one-to-one matching was performed between groups to adjust one characteristic (existence or non-existence of residual tumor at primary surgery) that differed between the two groups. The probability of PFS or OS was estimated separately for each group using the Kaplan–Meier method, and differences in PFS or OS between the two groups were evaluated by log-rank test; P values < 0.05 were considered statistically significant.

Study management

The protocol was approved by the protocol committee of the Sankai Gynecologic Study Group in September 2010. The study was registered immediately with the University Hospital Medical Information Network (http://www.umin.ac.jp; No. 000005051). The trial was approved by the institutional review board of each participating institution. This report was prepared in accordance with the STORE statement [5].

Results

Patient characteristics

A total of 279 patients from 30 centers were registered. However, 17 patients were excluded from the analysis (2 patients did not receive first-line platinum-based chemotherapy, 9 did not receive second-line platinum-based chemotherapy, 3 received second-line chemotherapy after January 2010, and the presence of residual tumor after surgery was not reported for 3 patients). Finally, data from 262 patients were analyzed. Table 1 summarizes the major characteristics of the patients and their tumors. Most patients [210 (80%)] had advanced endometrial cancer (FIGO stage III or IV). More than half of the patients had type II endometrial cancer. Other histological types included 6 adenosquamous carcinomas, 1 undifferentiated carcinoma, and 15 indeterminate types of cancer. A total of 182 patients (70%) had no residual tumor after primary surgery. Remaining 78 patients (30%) either had a residual tumor or did not undergo surgery. In addition to chemotherapy, 14 patients (5%) received radiotherapy as a primary therapy. The median age at diagnosis of recurrence was 63 years (range: 37–86 years). Furthermore, 15 patients (6%) had a single recurrent tumor localized at the vaginal stump, but 134 patients (51%) had distant metastasis beyond the abdominal cavity. The median platinum-free interval was 9 months (range: 0–112 months). The patients were distributed in almost equal proportions across platinum-free intervals.

Chemotherapy

Table 2 lists the first- and second-line chemotherapy regimens. About three-quarters of patients received a carboplatin-based first-

Table 1
Patient characteristics (n = 262).

	N	%
FIGO stage at primary therapy		
I	29	11
II	23	9
III	122	47
IV	88	33
Histology		
Endometrioid	153	58
Grade 1	37	
Grade 2	62	
Grade 3	47	
Not determined	7	
Serous	34	13
Clear cell	17	7
Carcinosarcoma	36	14
Others	22	8
Radiotherapy in primary therapy		
Performed	14	5
Not performed	248	95
Site of recurrence (allowed for overlapping)		
Vaginal stump	26	10
Pelvic cavity	38	14
Abdominal cavity	74	28
Lymph nodes	68	26
Liver	24	9
Lung	78	29
Other sites	48	18
Unclear	1	0
Platinum free interval (months)		
<6 months	64	24
6 months ≤, <12 months	65	25
12 months ≤, <24 months	67	26
24 months ≤	66	25

line (81%) or second-line (70%) chemotherapy. Less than 20% patients received cisplatin and doxorubicin combination (AP therapy) at first- (16%) or second-line (20%) chemotherapy. About two-thirds of patients [143/212 (67%)] who received carboplatin and paclitaxel (TC therapy) or carboplatin and docetaxel (DC therapy) as first-line chemotherapy received the same TC or DC therapy as second-line chemotherapy.

Table 2
Regimen of chemotherapy (n = 262).

	N	%
First-line chemotherapy		
Cisplatin based	48	18
AP	42	16
Others	6	2
Carboplatin based	212	81
TC	192	73
DC	7	3
Others	13	5
Nedaplatin based	2	1
Second-line chemotherapy		
Cisplatin based	68	26
AP	52	20
Others	16	6
Carboplatin based	184	70
TC	147	56
DC	31	12
Others	6	2
Nedaplatin based	10	4

AP: doxorubicin + cisplatin, TC: paclitaxel + carboplatin, DC: docetaxel + carboplatin.

Table 3
Platinum free interval and response at second-line chemotherapy (n = 262).

Response	Platinum free interval (months)			
	PFI < 6	6 ≤ PFI < 12	12 ≤ PFI < 24	24 ≤ PFI
Complete response	7	8	17	24
Partial response	9	17	24	19
Stable disease	11	18	8	8
Progression disease	35	19	14	10
Not evaluable	2	3	4	5
Total	64	65	67	66
Overall response (%)	25	38	61	65

Response

Table 3 presents the relationship between platinum-free interval and response rate. The response rates among patients with platinum-free intervals of <6 months, 6–11 months, 12–23 months, and ≥24 months were 25%, 38%, 61%, and 65%, respectively. The response to second-line platinum-based chemotherapy increased in association with a longer platinum-free interval ($P < 0.0001$, Cochran–Armitage trend test).

Survival

The median follow-up period for OS was 16.9 months ($N = 262$). Fig. 1 displays PFS and OS after second-line platinum-based chemotherapy, estimated by the Kaplan–Meier method, for patients classified according to the duration of the platinum-free interval. PFS and OS tended to be significantly longer when the platinum-free interval was longer ($P < 0.0001$, log-rank test). Fig. 2 displays PFS and OS estimated by the Kaplan–Meier method after second-line platinum-based chemotherapy for patients with platinum-free intervals of <12 months and ≥12 months. The median PFS was 4.4 months (95% CI: 3.7–5.8) and 10.3 months (8.2–12.6), respectively ($P < 0.0001$, log-rank test). In addition, the median OS period was 13.8 months (10.6–18.1) and 40.9 months (25.3–54.2), respectively ($P < 0.0001$, log-rank test).

Multivariate analysis revealed that only platinum-free interval and the presence of a residual tumor at the time of primary surgery were significant predictors of PFS or OS. When patients were matched one-to-one on the basis of the existence of a residual tumor at primary surgery, the median PFS period was 4.9 months (95% CI: 3.7–6.1) in patients with a platinum-free interval of <12 months ($N = 86$) and 9.2 months (7.7–10.6) in patients with a platinum-free interval of ≥12 months ($N = 86$). There was a survival benefit in favor of patients with a platinum-free interval ≥12 months ($P = 0.0024$, log-rank test; Fig. 3A). Moreover, the median OS was 16.1 months (95% CI: 11.5–26.3) in patients with a platinum-free interval of <12 months ($N = 86$), and 27.4 months (19.8–43.0) in patients with a platinum-free interval ≥12 months ($N = 86$). Furthermore, there was a survival benefit in favor of patients with a platinum-free interval of ≥12 months ($P = 0.0494$, log-rank test; Fig. 3B).

Discussion

The results of the present study indicate that the concept of "platinum sensitivity" can be applied to recurrent endometrial cancer. The probability of response to second-line platinum-based chemotherapy tended to be higher with longer platinum-free intervals. In addition, patients with platinum-free intervals longer than 12 months had significantly longer PFS and OS after second-line platinum-based chemotherapy. Thus, the platinum-free interval was a predictor of response to second-line platinum-based chemotherapy and of survival in patients with recurrent endometrial cancer and history of receiving a platinum agent as first-line chemotherapy.

To the best of our knowledge, this is the first large-scale study to prove that the concept of "platinum sensitivity" is applicable to recurrent endometrial cancer. Several studies have demonstrated that the

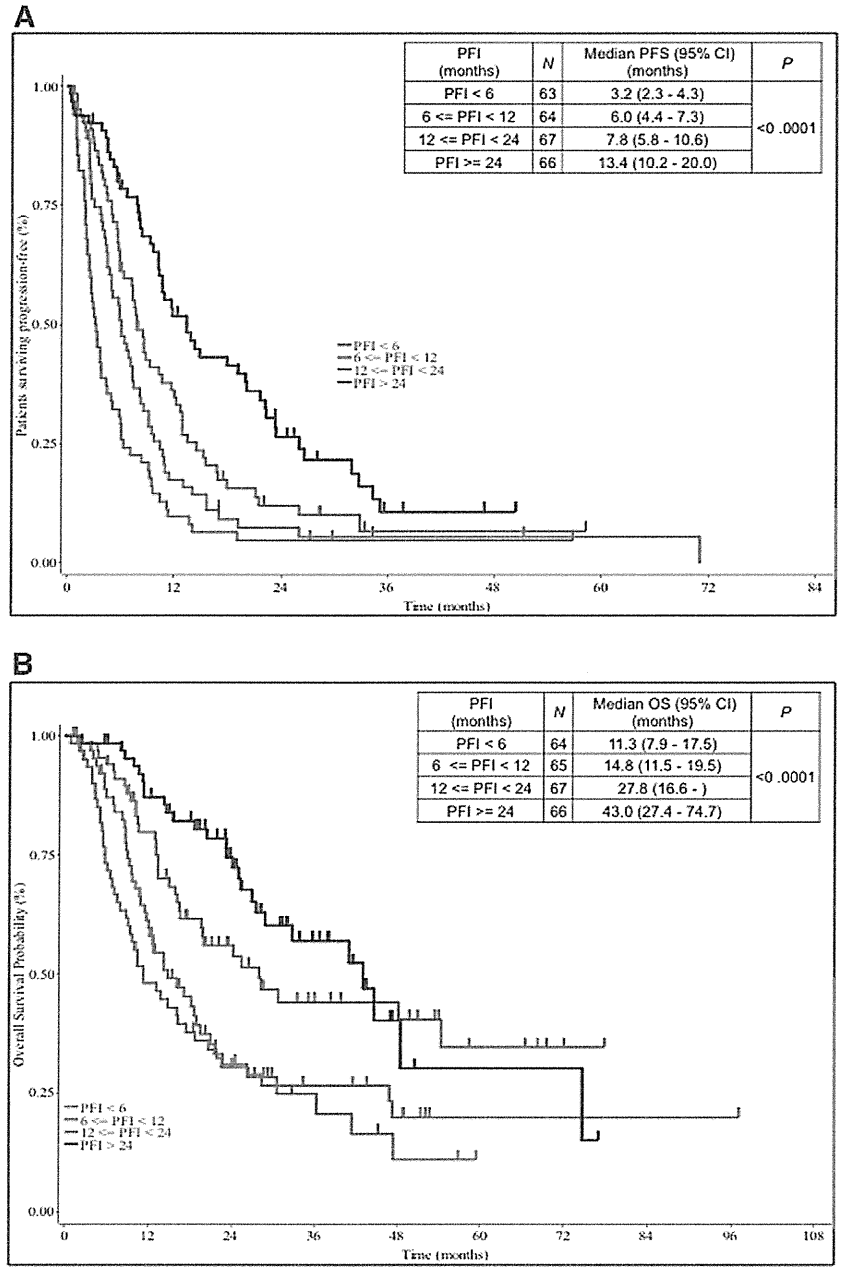

Fig. 1. Estimates of (A) progression-free survival and (B) overall survival after second-line platinum-based chemotherapy for patients classified on the basis of platinum-free interval (all participants). PFI, platinum-free interval; PFS, progression-free survival; CI, confidence interval.

treatment-free interval is the most important factor in predicting the effectiveness of chemotherapy in recurrent endometrial cancer. The Gynecologic Oncology Group conducted a pooled analysis of 586 patients from 5 phase III studies with cancers that recurred after first-line chemotherapy [6]. The progression-free interval was the most significant factor for predicting survival after second-line chemotherapy, with a 30% reduction in the risk of death when PFS was >6 months than when it was <6 months (hazard ratio, 0.70; 95% CI, 0.59–0.84; $P < 0.0001$); in this study, only 75% and 31% of patients received platinum-based chemotherapy as first- and second-line chemotherapy, respectively. Thus, the researchers were not able to evaluate the applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer in this case.

In contrast to Western countries, Japanese institutions prefer adjuvant chemotherapy over adjuvant radiation therapy for endometrial cancer. A survey by the Japanese Gynecologic Oncology Group regarding postoperative management of endometrial cancer demonstrated that adjuvant chemotherapy (79.9%) was significantly ($P < 0.01$) preferred over adjuvant radiotherapy (13.0%) [7]. A majority of the regimens were contained a platinum agent in combination with another drug. Therefore, in Japan, most patients with recurrent endometrial cancer have a history of platinum-based chemotherapy. Thus, we have an advantageous environment for assessing platinum sensitivity of recurrent endometrial cancer. An earlier Japanese retrospective study investigated the effectiveness of second-line chemotherapy for recurrent endometrial cancer, which was previously treated with a taxane- and

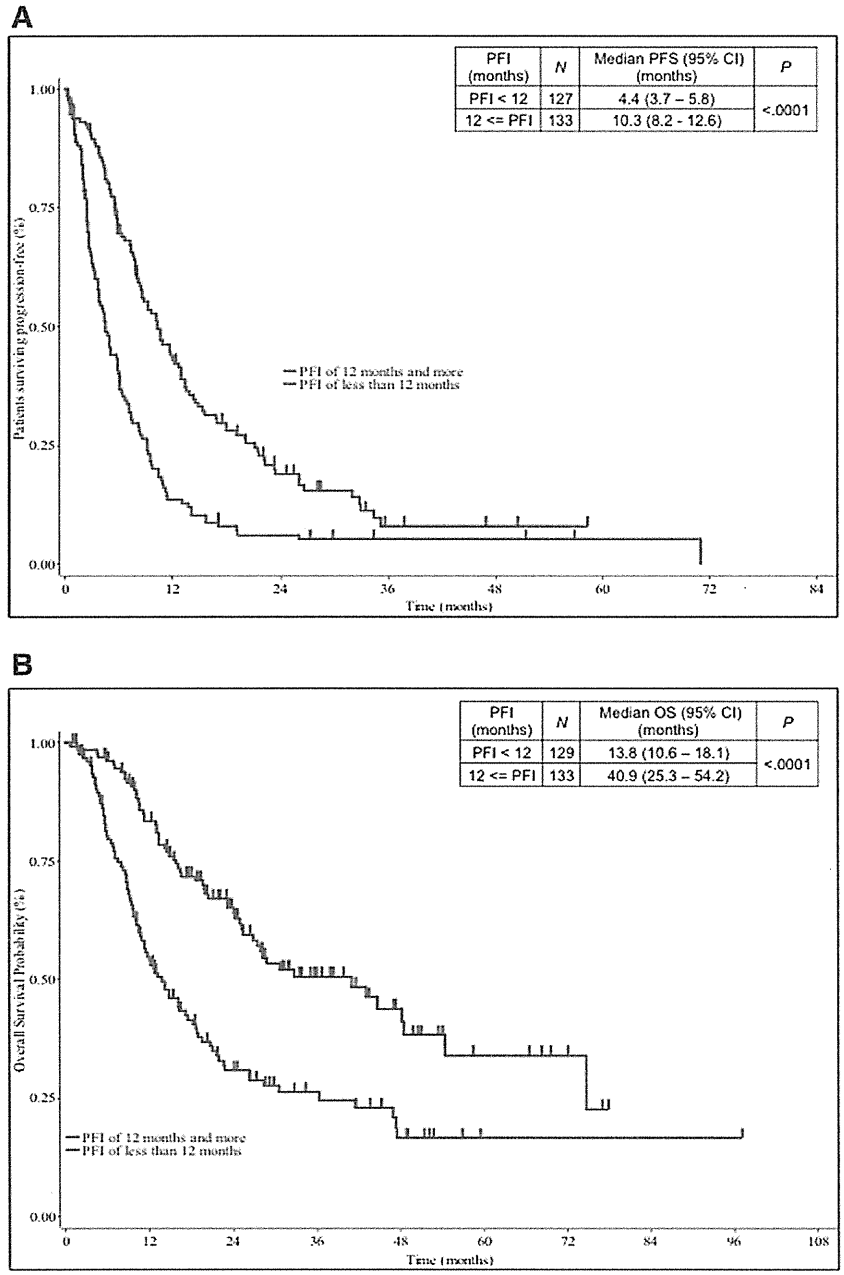

Fig. 2. Estimates of (A) progression-free survival and (B) overall survival after second-line platinum-based chemotherapy for patients with platinum-free intervals of <12 months and ≥12 months (matched patients). PFI, platinum-free interval; PFS, progression-free survival; CI, confidence interval.

platinum-containing chemotherapy [8]. A treatment-free interval of <6 months was demonstrated to be significantly associated with response to second-line chemotherapy ($P = 0.0026$), PFS ($P = 0.0003$), and OS ($P = 0.025$). However, this study was too small to draw any definitive conclusions, and thus, to date, there has been no definitive evidence indicating the applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer.

The present study included patients from 30 institutions, primarily cancer centers or Japanese University hospitals nationwide. Thus, these participants are representative of the current clinical conditions in Japan. Although the recommended first-line regimen for advanced or recurrent endometrial cancer in the Japanese treatment guidelines is AP therapy, a significant proportion of the community has adopted TC therapy for endometrial cancer [9]. Most patients in this study received TC/DC first-line (76%) or second-line (68%) chemotherapy regimen; this distribution of regimens reflects the current clinical practice scenario.

There were a few limitations to the present study because of lack of research funding. First, we could not perform a central pathological review; hence, the accuracy of the pathologic sub-classification may be questionable. Second, we could not perform a central radiological review. In addition, both RECIST and WHO criteria ware used to assess response to second-line chemotherapy. Nevertheless, only 9 patients (3%) were assessed according to the WHO criteria, whereas the remaining 256 patients (97%) were assessed according to the RECIST 1.1 criteria. Thus, it is assumed that the impact of the use of these different criteria on the main analysis findings could be minimal.

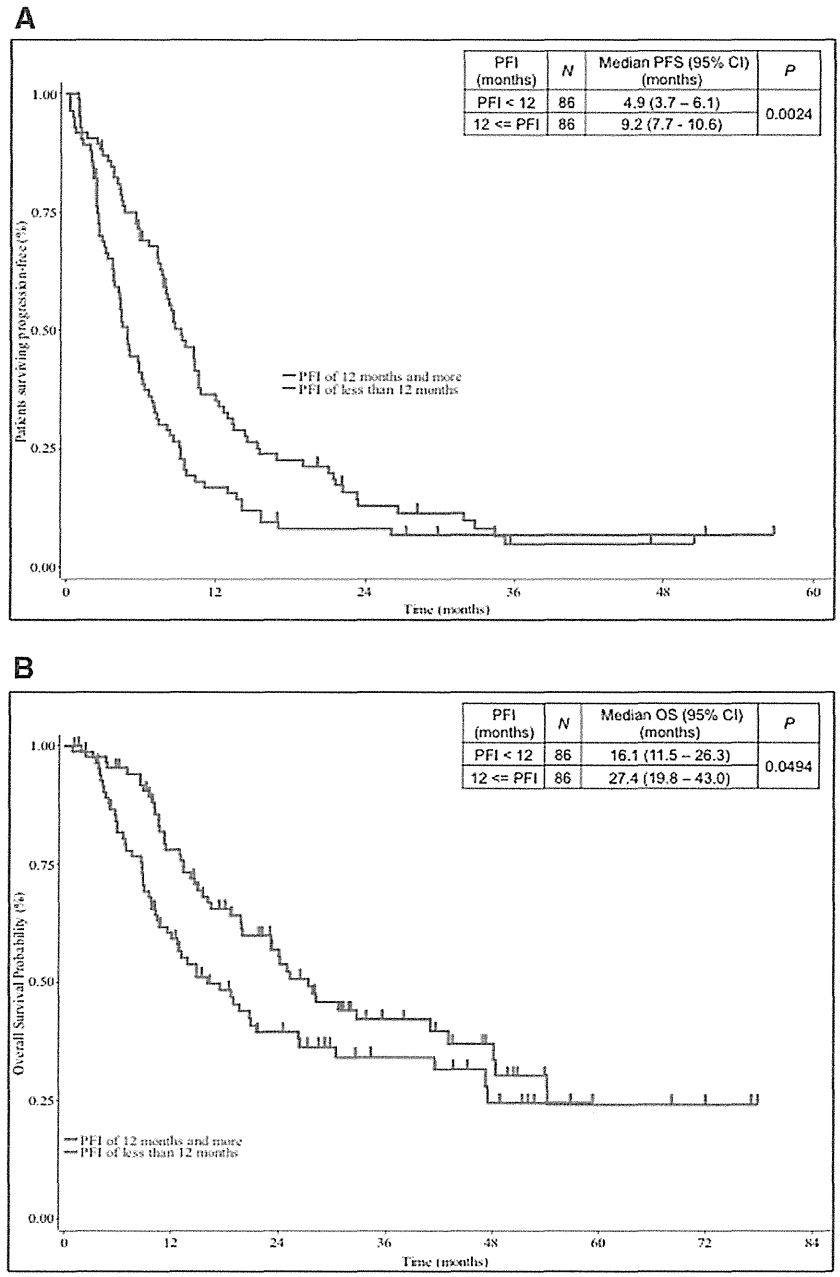

Fig. 3. Estimates of (A) progression-free survival and (B) overall survival after second-line platinum-based chemotherapy for patients with platinum free intervals of <12 months and ≥12 months (matched patients). One-to-one matching was performed on the basis of the presence of a residual tumor for groups with platinum-free intervals of <12 months and ≥12 months in order to adjust for background factors (histology, grade, and site of recurrence). PFI, platinum-free interval; PFS, progression-free survival; CI, confidence interval.

Although further validation by a prospective study is required, this is not a realistic objective. Therefore, it is recommended that patients with recurrent endometrial cancer, who have long platinum-free intervals, should receive a platinum-containing second-line chemotherapy regimen. In addition, the results of the present study may also influence the design of other clinical research studies, such as clinical trials of patients with long platinum free intervals, who receive platinum-containing chemotherapy in combination with new molecularly targeted agents.

In summary, platinum-free interval was a predictor of response to second-line platinum-based chemotherapy and also of survival in patients with recurrent endometrial cancer, who had history of receiving a platinum agent during first-line chemotherapy. Thus the concept of "platinum sensitivity" is applicable to recurrent endometrial cancer.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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References

[1] Blackledge G, Lawton F, Redman C. Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and the design of phase II trials. Br J Cancer 1989;59:650–3.

[2] Markman M, Rothman R, Hakes T, Rechman B, Hoskins W, Rubin S, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol 1991;9:389–93.

[3] Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2006;24:36–44.

[4] Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecol Oncol 2008;108:226–33.

[5] Vandenvbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 2007;4(10):e297.

[6] Moore KN, Tian C, McMeekin DS, Tigpen JT, Randall ME, Gallion HH, et al. Does the progression-free interval after primary chemotherapy predict survival after salvage chemotherapy in advanced and recurrent endometrial cancer? Cancer 2010;116:5407–14.

[7] Watanabe Y, Kitagawa R, Aoki D, Takeuchi S, Sagae S, Sakuragi N, et al. Practice pattern for postoperative management of endometrial cancer in Japan: a survey of the Japanese Gynecologic Oncology Group. Gynecol Oncol 2009;115:456–9.

[8] Ueda Y, Miyake T, Egawa-Takata T, Matsuzaki S, Yokoyama T, Miyoshi Y, et al. Second-line chemotherapy for advanced or recurrent endometrial carcinoma previously treated with paclitaxel and carboplatin, with or without epirubicin. Cancer Chemother Pharmacol 2011;67:829–35.

[9] Nagase S, Katabuchi H, Hiura M, Sakuragi N, Aoki Y, Kigawa J, et al. Evidence-based guidelines for treatment of uterine body neoplasm in Japan: Japan Society of Gynecologic Oncology (JSGO) 2009 edition. Int J Clin Oncol 2010;15:531–42.

FULL PAPER

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Surgery for endometrial cancers with suspected cervical involvement: is radical hysterectomy needed (a GOTIC study)?

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Background: Radical hysterectomy is recommended for endometrial adenocarcinoma patients with suspected gross cervical involvement. However, the efficacy of operative procedure has not been confirmed.

Methods: The patients with endometrial adenocarcinoma who had suspected gross cervical involvement and underwent hysterectomy between 1995 and 2009 at seven institutions were retrospectively analysed (Gynecologic Oncology Trial and Investigation Consortium of North Kanto: GOTIC-005). Primary endpoint was overall survival, and secondary endpoints were progression-free survival and adverse effects.

Results: A total of 300 patients who underwent primary surgery were identified: 74 cases with radical hysterectomy (RH), 112 patients with modified radical hysterectomy (mRH), and 114 cases with simple hysterectomy (SH). Median age was 47 years, and median duration of follow-up was 47 months. There were no significant differences of age, performance status, body mass index, stage distribution, and adjuvant therapy among three groups. Multi-regression analysis revealed that age, grade, peritoneal cytology status, and lymph node involvement were identified as prognostic factors for OS; however, type of hysterectomy was not selected as independent prognostic factor for local recurrence-free survival, PFS, and OS. Additionally, patients treated with RH had longer operative time, higher rates of blood transfusion and severe urinary tract dysfunction.

Conclusion: Type of hysterectomy was not identified as a prognostic factor in endometrial cancer patients with suspected gross cervical involvement. Perioperative and late adverse events were more frequent in patients treated with RH. The present study could not find any survival benefit from RH for endometrial cancer patients with suspected gross cervical involvement. Surgical treatment in these patients should be further evaluated in prospective clinical studies.

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Endometrial cancer is the most frequently occurring gynaecologic cancer in the United States and Europe (Evans *et al*, 2011; Siegel *et al*, 2012). The most common histology is endometrioid-type and the majority of the tumours are confined to the uterine corpus. The 1988 International Federation of Gynecology and Obstetrics (FIGO) staging defined stage II disease as pathological involvement of the uterine cervix. At the time, stage II disease was subclassified as glandular involvement alone (IIA) or stromal invasion (IIB). Estimated 5-year overall survival (OS) rate of surgical stage II disease was ~85% (Cornelison *et al*, 1999; Ayhan *et al*, 2004; Cohn *et al*, 2007). However, there have been several factors affecting the prognosis of stage II patients, such as cervical stromal invasion, lymph-vascular invasion, and high grade histology.

Recently, the presence of glandular involvement only was not included in stage II disease (Creasman, 2009), as the prognosis of stage IIA patients was not relatively worse. Radical hysterectomy was recommended for patients with suspected gross cervical involvement (Nagase *et al*, 2010; NCCN Guidelines, 2013). However, it is still undetermined which type of hysterectomy should be undertaken for the patients with stage II endometrial cancers. The objective of the present study was to evaluate the efficacy of operative procedure for endometrial cancers within the largest series of the cases using multivariate analyses.

MATERIALS AND METHODS

Patients and tumours. Institutional review board approval was obtained at seven academic institutions belonging to Gynecologic Oncology Trial and Investigation Consortium of North Kanto (GOTIC): National defense medical college, the University of Tsukuba, the Jichi medical University, Saitama cancer centre, Saitama Shakaihoken hospital, the Gunma University, Saitama medical University International Medical centre.

Medical charts of the patients who met the criteria as shown below were retrospectively analysed: (a) endometrial cancer patients that were treated during the period of 1995–2009, (b) patients that had suspected pathological cervical involvement by MR images or cervical biopsy, (c) extra-uterine disease was not detected by preoperative CT or MRI images. Only patients who received primary surgical therapy were included. Clinical data abstracted included type of surgery, complication related with surgery, adjuvant therapy, and follow-up data including recurrent site and patient status at the last visit.

Pathologic data such as FIGO stage, histologic type, tumour grade, depth of myometrial invasion, cervical stromal invasion, lymph-vascular invasion, and retroperitoneal lymph node involvement were also analysed. A formal review of the pathologic material was performed by at least one pathologist in each institution. Confirmation of cervical invasion and staging was made by the review of these pathologic reports. Patients with carcinosarcoma, or endometrial stromal sarcoma were not included in the present analysis.

Procedures of hysterectomy. All surgeries were performed or supervised by board-certified gynaecologic oncologists. Type of hysterectomy was based on the definition made by Japan Society of Gynecologic Oncology (JSGO) as shown below (Nagase *et al*, 2010).

Simple hysterectomy (SH): uterine support structures and vaginal canals are severed near the uterine attachment site. This is an extrafascial technique that removes some vaginal wall so that there is no residual cervical area.

Modified radical hysterectomy (mRH): The anterior layer of the vesicouterine ligament is separated and resected. The ureters are avoided and displaced laterally, and the uterus is resected by dividing as much as possible the anterior support and vaginal wall from the cervix. However, the posterior layer of the vesiocouterine ligament is not separated or severed. An extra 1.5–2 cm of vaginal wall can therefore be removed. Another characteristic of this technique is that more of the cardinal ligament is resected than in a SH. Extended total hysterectomy is used synonymously with mRH.

Radical hysterectomy (RH): the paravesical space and pararectal space are extended, and each of the anterior, middle, and podterio uterine supports is separated and severed. Portions of the vaginal wall and pelvic connective tissue are widely excised, and a regional pelvic node dissection is performed. That is, the cardinal ligament is severed near the pelvic wall, and the anterior layer of the vesicouterine ligament is separated and severed. The ureters are detached and displaced laterally, and the posterior layer is separated and severed. The rectovaginal ligament and ligament in the rectal space are severed. The paravaginal connective tissue and a portion of the vaginal wall (at least 3 cm) are then excised.

Grading of adverse events was judged by Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Statistical methods. Progression-free survival (PFS) was measured from the date of primary surgery to the date of subsequent radiologic relapse, progression, or to the date of last contact for disease-free patients. Overall survival was defined as the period from the date of primary surgery to death or the date of last contact. Local recurrence-free time was the duration between the date of surgery and the development of local recurrence including vaginal cuf, paravaginal tissues, and pelvic lymph nodes, or to the date of last contact for local recurrence-free patients.

Kaplan–Meier method was used for calculation of patient survival distribution. The significance of the survival distribution in each group was tested by the log-rank test. The χ^2 test and Student's *t*-test for unpaired data were used for statistical analysis. Cox proportional hazards model was used for multivariate analysis of the survival. A *P*-value of <0.05 was considered statistically significant. The Stat View software ver.5.0 (SAS Institution Inc., Cary, NC, USA) was used to analyse the data.

RESULTS

A total of 300 patients were identified: 74 cases with RH, 112 patients with mRH, and 114 cases with SH. Characteristics of the patients were summarised in Table 1. Median age was 47 years, and median duration of follow-up was 47 months. There were no significant differences of age, performance status, body mass index, and stage distribution among three groups. In the patients who underwent RH, more cases were suspected to have cervical stromal involvement, and underwent lymphadenectomy. As a postoperative therapy, chemotherapy was administered in 46 cases (62%) of RH, 50 cases (45%) of mRH, and 58 patients (51%) of SH group, indicating that there was no significant difference of the rate. Also, there were no significant differences among rates that received adjuvant radiation: 14 cases (19%) of RH, 12 cases (11%) of mRH, and 17 cases (15%) of SH groups (Table 1).

Pathologic findings of the patients were shown in Table 2. There were no significant differences of histological subtype, degree of cervical involvement, and peritoneal implantation beyond pelvis among three groups. Additionally, pathological parametrial invasion was observed in 10.8% in RH, 4.4% in mRH, and 5.3% in SH; however, there was no significant difference among three groups. Significantly, more cases in patients that underwent RH had myometrial invasion more than one half of the thickness. Additionally, the involvement of lymph node was more frequently observed in the patients with RH ($P<0.01$).

Local recurrence-free survival curves showed there were no significant differences among three groups, not only in all cases but also in patients with cervical stromal involvement