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Phase II study of interval debulking surgery followed by intraperitoneal chemotherapy for advanced ovarian cancer: A Kansai Clinical Oncology Group study (KCOG9812)☆

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HIGHLIGHTS

- Phase II multicenter study revealed efficacy of interval debulking surgery followed by intraperitoneal chemotherapy.
- Thirty-six percent of the enrolled patients had no intraperitoneal disease at first recurrence.

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ABSTRACT

Objective. Intraperitoneal chemotherapy (IP) is known to be effective after optimal primary debulking surgery (PDS) for ovarian cancer (OC). Here, we conducted a phase II study to investigate its effectiveness after interval debulking surgery (IDS).

Methods. Thirty-seven patients with FIGO stage IIIB-IV and suboptimal (≥1 cm diameter) residual disease after PDS were enrolled. Carboplatin (AUC 4 IV, Day 1) and cisplatin (50 mg/m^2 IV, Day 3) were given q21d for 3 cycles. After IDS, paclitaxel (175 mg/m^2 IV Day 1 or 60 mg/m^2 IV Days 1, 8, and 15, since 2000) and cisplatin (75 mg/m^2 IP Day 2) were given q21d for 4 cycles. The primary endpoint was progression-free survival (PFS), and secondary endpoints were overall survival (OS) and adverse events (CTCAE ver. 2.0). Clinical manifestations at first recurrence and subsequent treatment were also surveyed.

Results. Of the 37 patients, high-grade, serous adenocarcinoma was found in 33. Stages IIIB, IIIC, and IV were found in 2, 24, and 11 patients, respectively. After IDS, 23 patients had no macroscopic residual tumor. No patients had permanent enterostomy, febrile neutropenia, or platelet transfusion. The treatment protocol was completed in 22 patients, and discontinued in 5 due to IP catheter-related complications. Median PFS and OS were 22 and 57 months, respectively. Among the 28 patients with recurrence, 10 had no intraperitoneal disease at first recurrence. Among the 8 patients who underwent surgical cytoreduction, 6 had no residual tumor, while 2 had a <1-cm-diameter residual tumor.

Conclusion. IP after IDS for patients with initially suboptimally debulked OC was effective.

Introduction

The majority of women with ovarian cancer are diagnosed with advanced stage disease; approximately 70% are diagnosed stage III or IV [1]. Standard, initial management involves surgical staging and maximal cytoreduction, followed by platinum and taxane combination chemotherapy [2]. Multiple retrospective, nonrandomized studies have demonstrated that primary optimal cytoreduction successfully predicts prognosis. Specifically, the amount of residual disease at the end of a cytoreductive surgery is directly correlated with survival [3–5]. However, the subsequent treatment for patients who had a macroscopic residual tumor after primary surgery is still under investigation.

The historical background of the current study is as follows. In 1995, interval debulking surgery (IDS) was first shown to prolong survival when macroscopic residual tumors remained after primary debulking surgery (PDS) [6], while the survival advantage of front-line intraperitoneal (IP) chemotherapy was first reported in 1996 [7]. Therefore, here, we conducted a phase II study to evaluate the efficacy of IDS followed by IP chemotherapy for patients who had residual tumors after primary surgery. In this trial, suboptimally debulked ovarian cancer patients who had undergone primary surgery were enrolled, and the platinum combination of cisplatin and carboplatin was administered intravenously. Chemotherapy after IDS consisted of IP administration of cisplatin and intravenous administration of paclitaxel repeated for 21 days. The dose

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of cisplatin was 75 mg/m^2, while paclitaxel was given at 175 mg/m^2 intravenously over 3 h on day 1 during the early period of this trial. Since 2000, weekly administration of 60 mg/m^2 over 1 h has been conducted.

The primary endpoint of this trial was progression-free survival (PFS), while secondary endpoints were overall survival (OS) and adverse events. Clinical manifestations at recurrence and subsequent treatment were also surveyed.

Patients and methods

Eligibility criteria

Eligible patients had undergone PDS and had a minimal residual tumor larger than 1 cm in diameter, with a histologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. Additional requirements included an Eastern Cooperative Oncology Group performance status of ≤2; adequate bone marrow, renal, and hepatic function; and age >15 and <75 years old. Other exclusion criteria were active infection, uncontrolled diabetes mellitus, severe heart disease, active second malignancy, ileus, or brain metastasis. Stage IV was diagnosed by cytology of pleural effusion or by computed tomography findings completed by independent radiologists.

Written, informed consent was obtained prior to study participation. The study was approved by the appropriate ethical review board(s) and was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and applicable laws and regulations. The study was additionally approved by the Kansai Clinical Oncology Group.

Treatment schedule

Eligible patients received primary chemotherapy consisting of carboplatin area under the curve (AUC) of 4 mg/(min mL) intravenously over 60 min on day 1, and cisplatin 50 mg/m^2 as an intravenous drip over 60–90 min on day 3. The carboplatin dose was calculated according to the Jelliffe formula, and the cycles were repeated every 21 days for 3 cycles. All patients underwent IDS for no more than 4 weeks after completion of primary chemotherapy. IDS was performed at a level required to achieve maximal cytoreduction, and an IP catheter of the Bardport system was implanted [8]. Within 6 weeks of IDS, patients were administered 175 mg/m^2 of intravenous paclitaxel over a 3-h period on day 1, followed by 75 mg/m^2 of intraperitoneal cisplatin on day 2. Since the year 2000, paclitaxel has been administered to these patients at levels of 60 mg/m^2 over 1 h on days 1, 8, and 15. The IP chemotherapy was repeated every 3 weeks for 4 cycles. Cisplatin was reconstituted in 1 L of warm, normal saline and infused as rapidly as possible through an implantable peritoneal catheter. The patients were given antiemetics, including a serotonin antagonist and corticosteroid. Standard premedication to prevent hypersensitivity reactions to paclitaxel was given. The patients were hydrated before cisplatin was administered.

Chemotherapy was resumed after recovery from hematologic toxicities (absolute neutrophil count [ANC] ≥ 1.0×10^9/L and platelet count ≥ 100×10^9/L). If neutropenia had decreased to < 0.5×10^9/L after chemotherapy, granulocyte colony-stimulating factors were administered, according to the guidelines of the Japanese Ministry of Health, Labour and Welfare, until ANC counts recovered.

Study evaluations

The analysis was planned in accordance with the intention-to-treat principle. PFS was defined as the time from the date of study enrollment to the date of disease progression, according to an increase in serum CA-125 levels as defined by GCIG criteria [9], radiological recurrence, or progression by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [10]—or the time to death, whichever occurred first, unless the patient was progression-free at the time of last contact. OS was defined as the time from the date of study enrollment to the time of death from any cause. Tumor response during primary chemotherapy was classified based on RECIST 1.0 in patients with measurable disease, though confirmation was not included. Response in serum CA-125 was defined as a decrease in the CA-125 level to a level less than half of the baseline. Adverse events during both primary and IP chemotherapy were graded according to the National Cancer Institute Common Toxicity Criteria, ver. 2.0 [11]. Protocol discontinuation and the associated reason, clinical manifestations at recurrence, and the subsequent treatment were also surveyed.

Statistical analyses

The trial was designed as a phase II study, with PFS as the main endpoint. The investigator-assessed distributions of PFS and OS, using the Kaplan–Meier method, were estimated for the enrolled patients. This one-stage design tested the null hypothesis that the true median PFS for this population was equal to 13 months, a result based on the control arm of the EORTC trial [6]. This would be in contrast to the clinically relevant alternative of 24 months, a result based on the 6-month improvement of the IDS arm of the EORTC trial, using alpha = 0.05 and beta = 0.2. The planned accrual period was 4 years; the follow-up period was 2 years, and 32 qualified patients were required for the phase II portion. The accrual of 37 patients was planned for the trial. Estimates for enrolled patients were made for the investigator-assessed tumor response rate, proportion of cytoreduction, or completion of the treatment protocol, including a 95% two-sided confidence interval (CI). Patient demographics or treatments were compared using the chi-square test, and PFS and OS were calculated using the Kaplan–Meier method and compared between groups by using log-rank statistics.

Results

From September 1998 through December 2006, a total of 37 patients were enrolled in this study. The majority of the patients had high-grade, serous adenocarcinoma (86.5%) with FIGO stage IIIC-IV (94.6%) (Table 1) [12]. Details regarding residual tumor size after primary surgery and after IDS, procedures of primary surgery, total procedures of primary surgery, and IDS are summarized in Table 2.

Among the 37 enrolled patients, 13 did not have reliable or valid lesions as shown by repeated measurements on CT. Among the remaining 24 evaluable patients, as determined by RECIST 1.0, we found that 1 patient had a complete response, 13 had partial responses, and 10 had stable disease before IDS. The response rate of primary chemotherapy was 58.3% (95% CI: 38.6–78.1), whereas response in serum CA-125 level was achieved in 32 patients, with a rate of 86.5% (95% CI: 75.5–97.5). After primary surgery, 67% patients had a residual tumor >5 cm in diameter. After IDS, 62.2% had no macroscopic residual tumor and no radiological findings of metastasis, while 86.5% had a residual tumor <1 cm in diameter. There was a tendency for more aggressive treatment to be conducted during the later period. LAR was conducted in 4 of 11 (36.3%) patients and 13 of 19 patients (68.4%) before and after 2000, respectively ($p = 0.016$).

Hematological toxicity ≥grade 3 and non-hematological toxicity ≥grade 2 during treatment are summarized in Table 3. No patient had grade 4 non-hematological toxicities. The nadir of platelets among enrolled patients was $\geq25\times10^9$/L, and no patients had fibril neutropenia or platelet transfusion during the protocol treatment. We found that protocol treatment was completed among 22 patients (59.5%), as shown in Fig. 1. Among 34 patients who underwent IP chemotherapy, 15 were administered paclitaxel intravenously on a tri-weekly schedule, whereas 19 followed a weekly schedule. The incidence of grade 2 and 3 sensory neuropathy was similar between those treated tri-weekly and weekly (46.7% and 52.6%, respectively). Among the reasons for discontinuing the protocol, cisplatin-related toxicities were suspected in 3 patients. One patient had grade 3 sensory neuropathy after 3 cycles of IP chemotherapy. Two patients with renal toxicity had transient

Table 1
Pretreatment characteristics of eligible patients ($N=37$). *duplicate; ECOG, Eastern Cooperative Group; PS, performance status.

	n (%)
Enrolled patients	: 37
Age (year old)	: 19–70 (median 55)
Histology	
Serous	:33
Low-grade	: 1
High-grade	:32 (86.5)
Endometioid	: 1
Mixed	: 1
Adenosquamous	: 1
Undifferentiated	: 1
FIGO stage	
Stage IIIB	: 2
Stage IIIC	: 25 (67.6)
Stage IV	: 10 (27.0)
Liver	: 8*
Pleural	: 2
Lung	: 1*
Performance status (ECOG)	
PS 0	: 11 (29.7)
PS 1	: 13 (35.1)
PS 2	: 13 (35.1)

elevation of serum creatinine of grade ≤2. One patient discontinued treatment because of transient rash (grade 1). Five patients (14.7%) discontinued the treatment protocol because of IP catheter-related complications.

Current patient status is as follows: 8 with no evidence of disease, 5 alive with disease, 23 dead due to disease, and 1 dead due to intercurrent disease. Median PFS was 21.8 months (95% CI: 5.6–38.0) and median OS was 56.6 months (95% CI: 38.6–74.6), as shown in Fig. 2. Among the 28 patients who experienced recurrence, 10 (35.7%) had no IP disease at first recurrence (Table 4). One patient with isolated brain metastasis underwent stereotactic radiosurgery.

Among the 14 patients who had no extraperitoneal disease at first recurrence, 4 had complete surgery without residual tumor. Among the 8 patients who underwent surgical cytoreduction, 6 had no residual tumor and 2 had a residual tumor <1 cm in diameter.

Table 2
Characteristics of primary and interval debulking surgery (IDS). n, number of conducted procedures during primary surgery or after IDS among 37 enrolled patients. n, the number of patients in each residual volume at maximum diameter; BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy; TAH, total abdominal hysterectomy; OMT, omentectomy; LND, pelvic and paraaortic lymphadenectomy; LAR, low anterior resection of rectum with pelvic peritoneum.

Primary surgery	*n*	Primary + IDS	*n*
Tissue sampling alone	: 15	TAH, BSO, OMT	: 33
BSO or USO	: 20	LND	: 29
OMT	: 7	LAR	: 17
TAH	: 5	Appendectomy	: 11
Appendectomy	: 2	Resection of intestine	: 8
LND	: 1	Resection of liver	: 4
Transient enterostomy	: 1	Resection of diaphragma	: 3
		Splenectomy	: 2
		Partial resection of stomach	: 1
		Permanent enterostomy	: 0
Residual tumor			
After primary surgery	*n* (%)	After IDS	*n* (%)
Maximum 1–2 cm	4 (10.8)	None	: 23 (62.2)
Maximum 2–5 cm	: 8 (21.6)	Maximum < 1 cm	: 9 (24.3)
Maximum >5 cm	: 25 (67.6)	Maximum 1–2 cm	: 2 (5.4)
		Maximum >2 cm	: 3 (8.1)

Table 3
Chemotherapy-related toxicities during protocol treatment (CATCAE ver. 2.0). Hematological toxicity ≥grade 3 and non-hematological toxicity ≥grade 2 among enrolled patients were summarized.

n (%)	Grade 3	Grade 4	Grade 3/4
Leukocytes	13	1	14 (38)
Neutrophils	3	12	15 (41)
Febrile neutropenia	0	0	0
Platelets	6	0	6 (16)
n (%)	Grade 2	Grade 3	Grade 2/3
Neuropathy-sensory	10	1	11 (30)
Renal (elevation of serum creatinine)	1	0	1
Allergic reaction	1	0	1
Cognitive disturbance	1	0	1

Discussion

The standard treatment of ovarian cancer is PDS meant to achieve complete resection with no macroscopic, residual tumor. We agree with the perspective that IDS after neoadjuvant chemotherapy should not be used in cases of poor surgical skills [13–15]. However, further study is called for to determine the proper use of this alternative treatment.

The recent EORTC-NCIC randomized trial comparing PDS to neoadjuvant chemotherapy in advanced epithelial ovarian carcinoma reported a median PFS of 12 months and OS of 30 months for both arms [16]. Patients who underwent biopsy without gross tumor resection were enrolled in that trial. In our trial, enrolled patients had undergone primary surgery and were found to have disseminated tumors in the peritoneal cavity, especially on the small intestine. In these patients, bowel resection was shown to pose a high risk of post-anastomotic leakage; alternatively, achievement of primary, complete resection demanded permanent stoma, which the patients refused. During the period of this trial, cytoreduction of the upper abdominal disease – including resection of diaphragm, liver, or spleen – was conducted in a limited number of patients who had undergone IDS. Furthermore, 63% patients had no macroscopic residual tumor, while 86% had a residual tumor <1 cm in diameter. Thirty-two patients (86%) underwent subsequent IP chemotherapy. In intention-to-treat analysis, the median PFS and OS were 24 and 56 months, respectively. The median PFS was 6 months longer in comparison with the IDS group from van der Burg's report [6].

Primary chemotherapy was conducted with a non-taxane platinum combination regimen. The results of GOG-132, presented at the annual meeting of the American Society of Conical Oncology (ASCO) in 1997 and published in January 2000, showed that a single agent, cisplatin (100 mg/m^2), obtained better response and longer survival than did a combination regimen of paclitaxel and cisplatin for patients who had a macroscopic residual tumor after primary surgery. However, the differences were not statistically significant [17]. A trial of ICON4 failed to show a survival advantage for paclitaxel and cisplatin compared with other non-taxane, platinum-based chemotherapies [18]. To increase the dose of platinum agents, a combination therapy of carboplatin and cisplatin has been studied [19]. Because the 2 drugs have different dose-limiting toxicities, the combination regimen showed fewer adverse events in terms of thrombocytopenia, ototoxicity, or nephrotoxicity compared with single-therapy of cisplatin or carboplatin. The combination therapy also showed favorable clinical and pathological responses [20,21]. Therefore, the non-taxane, platinum combination regimen was used in this trial, with the aim of achieving chemical debulking before IDS. Nevertheless, the conventional tri-weekly paclitaxel and carboplatin regimen has been conducted in daily clinics since the statement of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG-OCCC) at Baden in 2004 [2].

The dose of cisplatin was reduced to 75 mg/m^2 because drug-related toxicity, particularly emesis, was often not controlled for Japanese

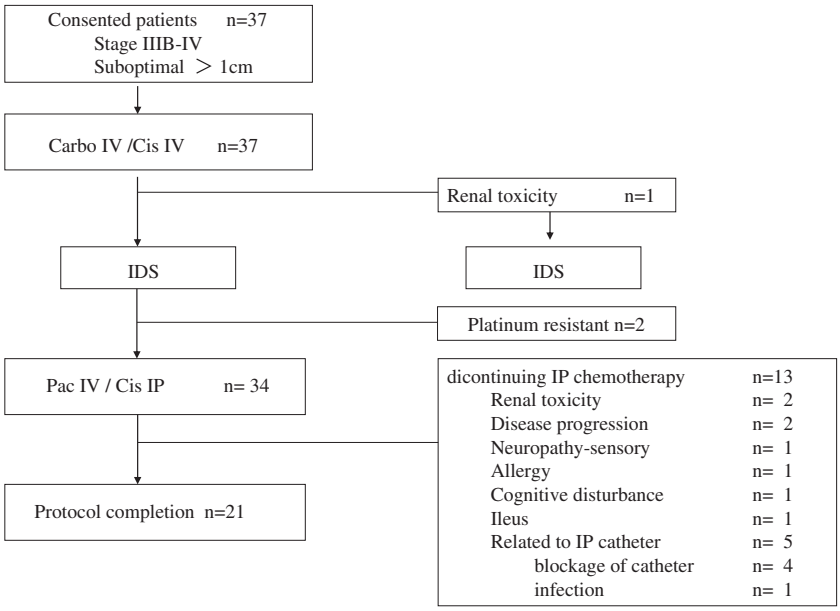

Fig. 1. Consort diagram showing the flow of participants throughout the duration of the study. Abbreviations: Carbo IV/Cis IV, intravenous administration of carboplatin and cisplatin; IDS, interval debulking surgery; IP, intraperitoneal; Pac IV/Cis IP, intravenous administration of paclitaxel and intraperitoneal administration of cisplatin; *n*, number.

patients during the study period, while aprepitant or palonosetron hydrochloride was not available in Japan [7,22].

Administration of paclitaxel has been altered from a tri-weekly to weekly schedule since 2000, because longer exposure to paclitaxel is postulated to increase efficacy as well as cause fewer toxicities [23–25]. In 2003, at the annual meeting of ASCO, a phase III study for patients with non-small cell lung cancer showed a weekly schedule of paclitaxel with carboplatin carried fewer toxicities, especially of sensory neuropathy, compared with a tri-weekly schedule at the same dose intensity [26]. This was confirmed later in another phase III trial [27]. Dose-dense, weekly paclitaxel administration with carboplatin for patients with ovarian cancer was found to improve overall survival, with similar adverse events, as compared to a conventional, tri-weekly regimen [28].

In a questionnaire survey, IP chemotherapy after IDS was chosen by 2.6% of the responding ESGO members vs. 42% of responding SGO members [13,29]. In our institutes, IP chemotherapy has also been conducted in other trials since the 1990s. Protocol completion of IP chemotherapy in clinical trials was low; in GOG-172, it was 42% [30]. The incidences of IP-related complications dropped after the introduction of the Bardport system [31]; after this, the management of IP-related adverse events as well as obtaining informed consent was not difficult for physicians and medical staff. Recently, the GOG-172 regimen or its modified version has been introduced to patients as an alternative treatment option in daily practice. To decrease cisplatin-related toxicity, carboplatin-based IP chemotherapy is a potential option [32]; thus, patients were recruited into a phase II clinical trial of JGOG-3019, which investigated the efficacy of IP carboplatin.

Two Canadian studies have reported shorter PFS after IP chemotherapy following IDS compared with PDS. Nelson et al. compared patients with FIGO stages II–IV in an IDS group to those with FIGO stages II–III in a PDS group [33]. Patients in the PDS group had no bowel resections, but had optimal cytoreduction (residual tumor, <1 cm in diameter). Le et al. did not show the baseline FIGO stage in their study, however [34]. Both studies were retrospective analyses, and median PFS time was 11 months in the former IDS group and 14.1 months in the latter

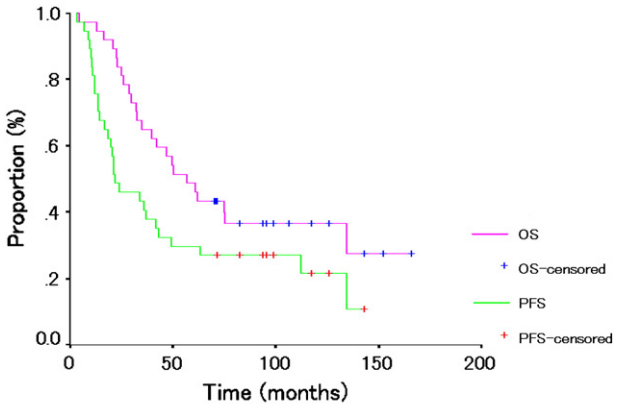

Fig. 2. Kaplan–Meier analysis of PFS and OS. Median PFS was 21.8 months (95% CI: 5.6–38.0), with 21.6% censoring, and median OS was 56.6 months (95% CI: 38.6–74.6), with 35.1% censoring.

Table 4
Primary recurrent sites among 28 patients who experienced recurrence. The primary sites were detected during or after routine follow-up by physical examination, serum CA125, vaginal ultrasonography, and computed tomography (CT). Further examination included 67-Ga citrate or 99 m-Tc bone scintigraphy, magnetic resonance imaging, or 18F-FDG-positron emission tomography.

Primary recurrent site	*n* (%)	Without other sites
Peritoneal cavity	18 (64.3)	14 (50.0)
Pelvis	13 (46.4)	5 (17.9)
Extra-pelvis only	3 (10.7)	2 (7.1)
Ascites only	2 (7.1)	
Extra-peritoneal cavity	15 (53.6)	10 (35.7)
Distant metastases	9 (32.1)	7 (25.0)
Liver	5 (17.9)	3 (10.7)
Skin	2 (7.1)	2 (7.1)
Pleural effusion	2 (7.1)	1 (3.6)
Brain	1 (3.6)	1 (3.6)
Bone	1 (3.6)	0
Spleen	1 (3.6)	0
Lymphnodes	5 (17.9)	2 (7.1)
Retroperitoneum	2 (7.1)	0
Extra-retroperitoneum	3 (10.7)	2 (7.1)

IDS group. The baseline characteristics or surgical procedures for those studies might differ from those in our study.

Patterns of recurrence after IP chemotherapy both in the adjuvant setting or after IDS were reported to differ from those after IV chemotherapy [35,36]. The majority of primary, recurrent sites after IV chemotherapy were shown to be located inside the abdominal cavity, especially in the pelvis. On other hand, more patients experienced recurrence outside the abdominal cavity after IP chemotherapy than at other sites. In our study, 35.7% of patients had no IP disease at first recurrence, a pattern consistent with previous articles.

Cytoreductive surgery at recurrence was conducted in 9 patients, in 8 of whom complete resection was achieved without macroscopic disease. Stereotactic radiosurgery for brain tumor as the primary recurrent site was conducted in 1 patient. Complete cytoreduction with no residual tumor was the predictor of improved survival for IDS, and defined as "optimal surgery" [16]. Several reports have shown that complete resection at recurrence leads to improved survival [37], and Harter et al., verified that primary optimal surgery was a predictive factor for successful surgery at recurrence [38]. We treated patients who had microscopic residual tumors in the pelvic peritoneum obtained during IDS. Once the tumor recurred around the Douglas pouch, secondary debulking surgery often demanded colostomy. Therefore, we put in maximum surgical efforts to reduce tumor occurrence by low anterior resection of rectum with pelvic peritoneum during IDS. In addition, IP chemotherapy demands optimal surgery to improve its efficacy. Although the relationship between optimal IDS and successful surgery at recurrence is not known, 63% of optimal IDS as well as IP chemotherapy shown in our trial might demonstrate the benefit of surgery at recurrence.

Chi et al. reported the outcome of a similar population who had PDS, with a median PFS of 17 months and OS of 50 months after radical surgery. In this study, 33% underwent extensive upper abdominal surgical procedures. Our surgical procedure during the trial period was less radical. The similar survival outcome might be due to IP chemotherapy after IDS.

Accrual of all results was delayed because results from the GOG-152 trial were presented at the annual meeting of ASCO in 2002 [39], and paclitaxel and carboplatin had been considered as standard first-line treatments since the statement made by GCIG-OCCC in 2004. These facts made us reluctant to conduct IDS or a first-line, non-taxane regimen. The long accrual period resulted in changes to treatment schedules as well as extent of surgery; however, adverse events, PFS, and OS were similar before and after 2000. To the best of our knowledge, this is the first report to show the efficacy of IP after IDS in a prospective study. We think upfront surgery with macroscopic, complete resection should remain the standard therapeutic approach in advanced ovarian cancer. Nevertheless, for some populations with poor PS or for cases in which patients refuse radical surgery before primary surgery, IDS followed by IP chemotherapy could be an efficient treatment option. As in the case with clinical trials on IP chemotherapy, many patients discontinued this treatment protocol. IP administration of carboplatin instead of cisplatin could be a favored option, as well as upfront chemotherapy consisting of carboplatin, with or without paclitaxel, instead of a combination of carboplatin and cisplatin.

Conflict of interest statement

Hiroshi Tsubamoto and co-authors have no conflicts to disclose.

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