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ORIGINAL ARTICLE

Intraperitoneal Carboplatin for Ovarian Cancer — A Phase 2/3 Trial

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Abstract

BACKGROUND Intraperitoneal chemotherapy has been shown to be effective at reducing mortality for patients with advanced epithelial ovarian cancer but is not widely used in practice.

METHODS We performed the Intraperitoneal Therapy for Ovarian Cancer with Carboplatin (iPocc) trial as an open-label, international, multi-institutional, randomized phase 2/3 clinical trial in women with newly diagnosed epithelial ovarian cancer who underwent laparotomy or laparoscopy. All patients received intravenous paclitaxel (80 mg/m^2 on days 1, 8, and 15 of a 21-day cycle). In addition, patients in the control group received intravenous carboplatin (dose-dense intravenous paclitaxel plus intravenous carboplatin [dd-TCiv]), whereas patients in the experimental group received dose-dense intravenous paclitaxel plus intraperitoneal carboplatin (dd-TCip). The primary end point was progression-free survival (PFS). Secondary end points included overall survival, tumor response, treatment completion rate, and incidence of adverse events (AEs).

RESULTS Among 655 patients randomized to treatment, median (95% confidence interval [CI]) PFS was 20.7 (18.1 to 22.8) months for dd-TCiv (n=328) and 23.5 (20.5 to 26.9) months for dd-TCip (n=327; hazard ratio, 0.83; 95% CI, 0.69 to 0.99; P=0.04). The PFS benefit with dd-TCip was consistent in patients with different baseline characteristics, stage, size of residual tumor, age, and performance status. The treatment completion rates were 68.3 and 59.9% in the dd-TCiv and dd-TCip groups, respectively. The incidence of intraperitoneal catheter-related AEs in the dd-TCip group was 10.1%; there were no such AEs in the dd-TCiv group.

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CONCLUSIONS In the first-line treatment of advanced epithelial ovarian cancer, intraperitoneal carboplatin resulted in a modest prolongation of PFS when given with dose-dense weekly paclitaxel regardless of residual tumor size, with no impact on noncatheter-related toxicities. (Funded by the Japan Agency for Medical Research and Development, and others; Japan Registry of Clinical Trials number, jRCTs031180141.)

Introduction

Intraperitoneal chemotherapy, which delivers high concentrations of drug directly to tumors, has long been considered an attractive therapeutic approach in advanced ovarian cancer given that it typically involves extensive and early peritoneal dissemination.[1] A meta-analysis of eight randomized controlled trials conducted by the National Cancer Institute (NCI) found that for patients with advanced epithelial ovarian cancer who had undergone optimal surgical resection, intraperitoneal chemotherapy reduced the risk of death by 21.6%; this finding led to a treatment recommendation for this condition of cisplatin, given by both the intravenous and intraperitoneal routes, or intravenous plus intraperitoneal paclitaxel.[2]

Despite this recommendation, intraperitoneal chemotherapy has not been widely used in practice.[3,4] There are several reasons for this, including: uncertainty about intraperitoneal chemotherapy efficacy related to randomized controlled trial design issues, such as imbalances in drug dosage between groups and lack of comparison with standard treatment[4,5]; concerns about cisplatin toxicity and peritoneal irritation caused by intraperitoneal delivery; low completion rates in some trials, such as GOG (Gynecologic Ocology Group)-172, in which there was only a 42% completion rate in the intraperitoneal group[6]; and concerns about the intraperitoneal port, such as difficulties with intraperitoneal administration and port management.[4,5] One reasonable solution is to use carboplatin, a less toxic substitute for cisplatin. However, carboplatin has been considered inferior to cisplatin as an intraperitoneal drug,[5] although several clinical studies have reported its efficacy.[7-9]

Several study groups initiated new clinical studies to reassess intraperitoneal chemotherapy in ovarian cancer using improved randomized controlled trial designs, and three large randomized controlled trials (GOG-0252, OV21, and Intraperitoneal Therapy for Ovarian Cancer with Carboplatin [iPocc]) were planned.[10-12] Although the GOG-0252 trial was completed, the null hypothesis between the two intraperitoneal groups and the control group (with bevacizumab 15 mg/kg intravenously every 3 weeks in cycles 2 to 22) could not be rejected with the data obtained. OV21 was ultimately found to be underpowered to detect differences and was not clinically directive.[11,12]

A related issue that also remains unanswered is the impact of tumor volume on the efficacy of intraperitoneal therapy. Traditionally, patients with small-volume residual disease were considered the best candidates for intraperitoneal therapy based on the idea that intraperitoneal therapy worked by direct contact of high concentrations of the anticancer drug with the tumor; as a consequence, it was assumed that the depth of drug penetration from the surface would be limited in large tumors compared with small tumors. Despite this conceptual concern, retrospective, phase 1, and pharmacokinetic studies have shown that intraperitoneal carboplatin has excellent efficacy even in large tumors greater than or equal to 2 cm in diameter, suggesting that intraperitoneal carboplatin may be effective in patients with larger residual tumors.[5,8,9,13]

On the basis of these questions, we performed the international, open-label, randomized iPocc trial to evaluate the efficacy and safety of intraperitoneal carboplatin compared with those of intravenous carboplatin, both in combination with dose-dense weekly intravenous paclitaxel as a standard therapy. This trial also sought to verify the efficacy of intraperitoneal carboplatin in patients with large residual tumors.[14]

Methods

STUDY DESIGN AND PATIENTS

GOTIC (Gynecologic Oncology Trial and Investigation Consortium)-001/JGOG (Japanese Gynecologic Oncology Group)-3019/GCIG (Gynecologic Cancer InterGroup) (the iPocc trial) was an open-label, international, multi-institutional, randomized phase 2/3 clinical trial conducted in two parts. Part A (phase 2) confirmed the feasibility in terms of completion rates, side effect and adverse event (AE) profiles, and response rates of dose-dense weekly intravenous paclitaxel (80 mg/m^2 on days 1, 8, and 15 of a 21-day cycle) plus concurrent intraperitoneal carboplatin

administered once every 3 weeks (dose-dense intravenous paclitaxel plus intraperitoneal carboplatin [dd-TCip] therapy) compared with dose-dense intravenous paclitaxel plus intravenous carboplatin (dd-TCiv) therapy. In part B (phase 3), patients who transitioned from part A, as well as newly enrolled patients, received dose-dense weekly intravenous paclitaxel; the studied comparison was the efficacy and safety of dd-TCip therapy and dd-TCiv therapy as first-line chemotherapy in women with epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Eligible patients were women 20 years of age or older with newly diagnosed, untreated International Federation of Gynecology and Obstetrics (FIGO) stages II to IV (II, pelvic spread; III, intra-abdominal spread or lymph node metastasis; IV, positive for cancer in pleural effusion [IVA] or parenchymal metastasis to the liver or spleen or distant metastases [IVB]) epithelial ovarian, fallopian tube, or primary peritoneal cancer who planned to undergo laparotomy or laparoscopy. Patients were permitted to undergo an exploratory laparotomy followed by neoadjuvant chemotherapy as determined by each physician–patient treatment plan before study enrollment. Patients with both optimal (residual tumor <2 cm in diameter) and suboptimal (residual tumor ≥ 2 cm in diameter) residual disease after primary surgery were included. The main exclusion criteria were borderline malignancy of the ovary, previous chemotherapy or radiation therapy to treat the current disease, synchronous malignancy, or a progression-free interval less than 5 years for a metachronous malignancy. Full inclusion and exclusion criteria are included in Table S1 in the Supplementary Appendix. Representativeness of this trial population to the general population of women with ovarian cancer is detailed in Table S2.

Registration and randomization involved procedures before, during, and following surgery. After the patients gave written informed consent to participate in the trial but before surgery, eligible patients were tentatively registered through the Web Registration System of the Kitasato University Clinical Trial Coordinating Center. To minimize surgeon bias at the time of surgery, when tumor removal was judged to be as complete as possible but before abdominal wall closure, patients were randomly assigned and formally registered into the Web Registration System. The 1:1 randomization allocation used a minimization technique built into Medidata RAVE[15] based on the following stratification factors: institution, initial FIGO stage (II, III, or IV), and size of residual disease (0 [no noted residual disease], <1, 1 to 2, or >2 cm). At that time, patients randomized to receive dd-TCip underwent placement of a Bard Titanium Implanted Port (14.3F). After surgery, patient eligibility was confirmed by pathologic examination of removed specimens, at which time patients could receive protocol treatment. In all patients, radiographic tumor measurements were performed every two cycles and at the time of discontinuation of the protocol treatment. CA-125 and other tumor markers were measured at every treatment cycle.

After completion of the assigned treatment, imaging, measurement of CA-125 and other tumor markers, and physical examination were repeated in 3-month intervals for the first 2 years, 6-month intervals for the following 2 years, and once a year thereafter.

TREATMENT

All patients received intravenous paclitaxel in addition to their assigned experimental treatment of dd-TCip or dd-TCiv (Table S3). Protocol treatment was repeated for six cycles for patients who received primary debulking surgery, with the need for interval debulking surgery as determined by the local physician. Interval debulking surgery could be performed after three to five cycles of protocol therapy, and a patient could then subsequently receive up to three additional cycles of chemotherapy.

OUTCOMES

For the phase 3 part of this trial, the primary end point was progression-free survival (PFS) as determined locally; the secondary end points included overall survival (OS), tumor response, treatment completion rate, and the type and incidence of all AEs, regardless of whether they were believed to be treatment related by investigators. Tumor response was evaluated only in patients with measurable residual disease using the Response Evaluation Criteria in Solid Tumors version 1.1. AEs were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0 issued by the NCI of the National Institutes of Health. The final AE evaluation was conducted 3 weeks after the final administration of the protocol treatment. Adverse reactions of grade 2 or higher required that evaluations be conducted at each follow-up until all noted AEs had resolved.

STATISTICAL ANALYSIS

Based on evidence from the JGOG-3016 trial and the meta-analysis by the NCI, the median PFS in the dd-TCiv group of this trial was expected to be 28 months, with the hazard ratio for PFS being 0.78 in the dd-TCip group

versus the dd-TCiv group. Based on an initial registration period of 3 years and a follow-up period of 3 years, the required sample size and the number of events were 746 patients (373 patients per group) and 510 events (239 events in the dd-TCip group), respectively. However, the protocol was formally revised because of the recalculation of patient numbers secondary to two instances of enrollment delay (January 20, 2013; December 16, 2014) and a 1-year extension in the follow-up period (July 10, 2019) secondary to a delay in the occurrence of events. Because of the instances of delayed recruitment, the registration period was modified to 6.5 years with a follow-up period of 3 years. Under these conditions, the required sample size and the number of events became 654 patients (327 patients per group) and 510 events to detect a PFS hazard ratio of 0.78 with a two-sided 5% significance level and 80% power using the log-rank test.

For the primary end point, the Kaplan–Meier method was used to predict PFS, with the difference compared by using the log-rank test. For secondary outcomes, the Kaplan–Meier method was used to predict OS, which was compared by using the log-rank test. Exact 95% CIs for the response rates and the treatment completion rates in each group were calculated with differences compared by using Fisher's exact test and a 95% CI for the odds ratio on the basis of normal approximation.

No adjustments were made for multiple comparisons in the analysis of secondary end points. There was potential for type I errors because of multiple comparisons, and findings for analyses of secondary end points are therefore reported without P values as point estimates and 95% CI only. Any differences should be considered exploratory and not clinically directive.

Results

PATIENT CHARACTERISTICS

A total of 655 patients from Japan, Singapore, South Korea, New Zealand, the United States, and Hong Kong were randomly assigned during the enrollment period (May 2010 to August 2016) and comprised the intention-to-treat (ITT) population (dd-TCiv, n=328; dd-TCip, n=327); the modified ITT (mITT) population of 602 patients was composed of the ITT population minus excluded patients (Fig. 1).

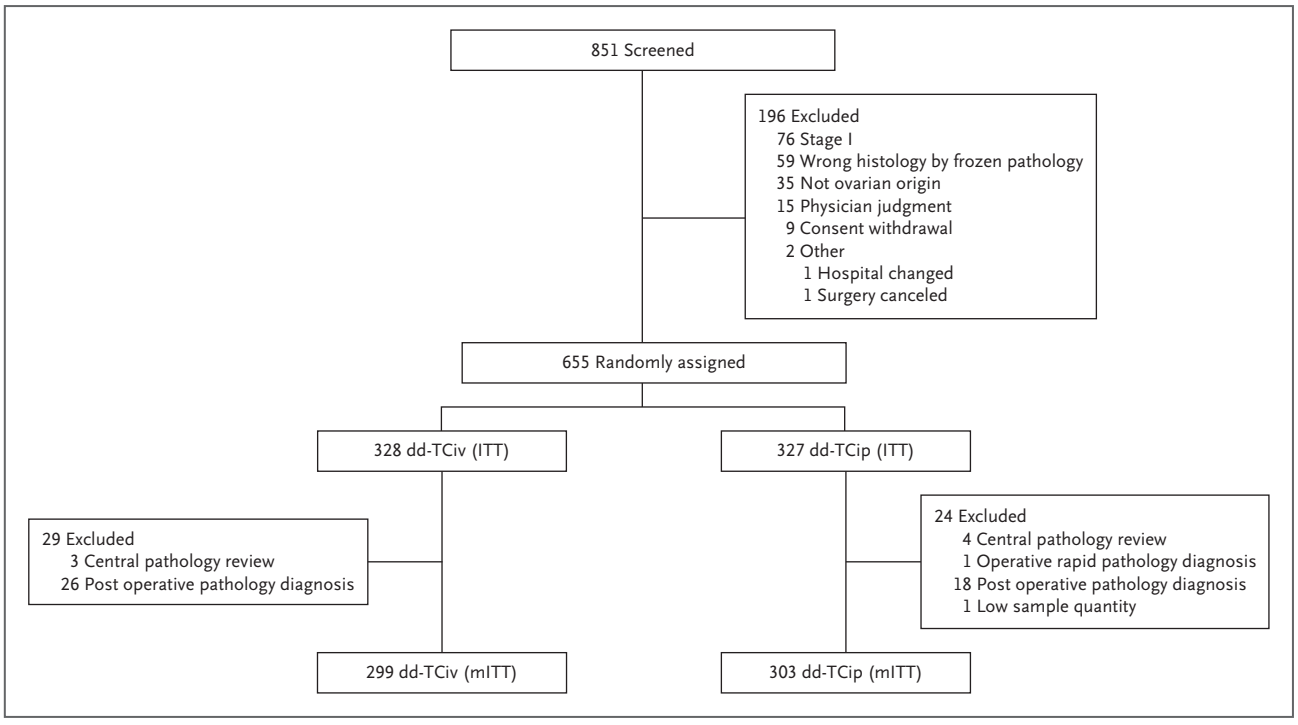

Figure 1. Patient Disposition.

dd-TCip denotes dose-dense intravenous paclitaxel plus intraperitoneal carboplatin; dd-TCiv, dose-dense intravenous paclitaxel plus intravenous carboplatin; ITT, intention-to-treat; and mITT, modified intention-to-treat.

Among the total patients reported in this report, 120 patients were from part A (62 patients treated with dd-TCip and 58 patients treated with dd-TCiv). Because the protocol did not change between part A and part B, those patients are included in this report. Baseline characteristics of the ITT population are presented in Table 1 and Table S4. Both treatment groups were well matched, with no statistically significant differences noted.

Reasons for discontinuation are presented in Table 2. Thirty-four patients (10.4%) in the intraperitoneal group converted to intravenous therapy for the reasons shown

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	dd-TCiv (n=328)	dd-TCip (n=327)	P Value
Age, median (range), yr	59.0 (30–82)	59.0 (32–84)	0.92
PS			
0	243 (74.1)	249 (76.1)	0.53
1	78 (23.8)	68 (20.8)	
2	7 (2.1)	10 (3.1)	
Race			
Asian, Japanese	303 (92.4)	297 (90.8)	0.65
All other	25 (7.6)	30 (9.2)	
Primary site			
Fallopian tube	12 (3.7)	21 (6.4)	0.34
Ovary	255 (77.7)	241 (73.7)	
Peritoneum	45 (13.7)	51 (15.6)	
Other	16 (4.9)	14 (4.3)	
FIGO stage			
II	46 (14.0)	42 (12.8)	0.91
III	223 (68.0)	225 (68.8)	
IV	59 (18.0)	60 (18.3)	
Histologic type†			
Adenocarcinoma NOS	15 (4.6)	16 (4.9)	0.52
Clear cell adenocarcinoma	37 (11.3)	37 (11.3)	
Endometrioid adenocarcinoma	28 (8.5)	33 (10.1)	
Mixed epithelial carcinoma	8 (2.4)	5 (1.5)	
Mucinous adenocarcinoma	7 (2.1)	8 (2.4)	
Serous adenocarcinoma	206 (62.8)	214 (65.4)	
Transitional cell	0 (0.0)	0 (0.0)	
Undifferentiated carcinoma	3 (0.9)	3 (0.9)	
Other	24 (7.3)	11 (3.4)	
Size of residual disease (cm)			
0 (no residual)	82 (25.0)	81 (24.8)	0.99
$0 <$ residual <1	47 (14.3)	50 (15.3)	
$1 \leq$ residual ≤ 2	17 (5.2)	16 (4.9)	
>2	182 (55.5)	180 (55.0)	
Interval debulking surgery			
Yes	88 (26.8)	78 (23.9)	0.43
No	240 (74.2)	249 (76.1)	

* Values are presented as no. (%) unless indicated otherwise. dd-TCip denotes dose-dense intravenous paclitaxel plus intraperitoneal carboplatin; dd-TCiv, dose-dense intravenous paclitaxel plus intravenous carboplatin; FIGO, International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; and PS, performance status. Levels are: 0=Can do all normal activities; 1=Unable to do strenuous activities, but able to carry out light housework and sedentary activities; 2=Able to walk and manage self-care, but unable to work.

† Low-grade serous cancer was considered borderline tumor at the time of this study.

Table 2. Reasons for Discontinuation.

Reason for Discontinuation	dd-TCiv	dd-TCip	Total
Disease progression, relapse during active treatment, n	20	14	34
Adverse events, n	35	56	91
Patient withdrawal or refusal for toxicity reason, n	8	8	16
Patient withdrawal or refusal for reason other than toxicity, n	8	13	21
Death, n	3	1	4
Other, n	32	40	72
Total, n	106	132	238

in Table 3. Transition from part A to part B was decided by an Independent Data Monitoring Committee on the basis of a review of feasibility in part A.

EFFICACY

For the primary end point, median PFS was 20.7 months (95% CI, 18.1 to 22.8) in the dd-TCiv group and 23.5 months (95% CI, 20.5 to 26.9) in the dd-TCip group (Fig. 2A). This equated to a hazard ratio of 0.83 (95% CI, 0.69 to 0.99; P=0.04). Median PFS in the mITT population was 20.0 months (95% CI, 18.0 to 22.2) in the dd-TCiv group and 22.9 months (95% CI, 19.6 to 26.9) in the dd-TCip group (Fig. 2B). This equated to a hazard ratio of 0.78 (95% CI, 0.65 to 0.94).

In relation to the secondary efficacy end points, median OS was 67.0 months (95% CI, 55.4 to 78.2) in the dd-TCiv group and 64.9 months (95% CI, 56.4 to 84.9) in the dd-TCip group (Fig. 2C); for the ITT population as a whole, this equated to a hazard ratio of 0.95 (95% CI, 0.77 to 1.17). Results for OS in the mITT population are shown in Figure 2D. In terms of tumor response, the best overall response and response rate in the 52.0% of enrolled patients with measurable residual disease (171 in the dd-TCip group and 168 in the dd-TCiv group) are presented in Table S5. Response rate (complete response + partial response) in the dd-TCiv group (72.6%) was not different from that in the dd-TCip group (70.2%). The proportions of patients who completed six cycles in the dd-TCiv and dd-TCip groups were 68.3 and 59.9%, respectively (Table S6). Dose reduction status for paclitaxel and carboplatin is shown in Tables S7 and S8.

Table 3. Reasons for Switching to Intravenous Therapy in the Intraperitoneal Group.

Reason for Therapy Switch	No.
Port leak	10
Port obstruction	4
Port destruction	1
Skin around port problem	3
Catheter infection	2
Needle did not reach	3
Vaginal leak	10
Abdominal pain	1
Abdominal distention	1
Patient refusal	1
Total	36

SUBGROUP ANALYSIS

Figure 3 displays the forest plot for the various prespecified subgroups analyzed. PFS was consistent in prespecified subgroups, including patients with different baseline characteristics, stage, size of residual tumor, age, and performance status. In addition to these prespecified groups, post hoc data are presented for histologic type and patients with or without interval debulking surgery.

SAFETY

Vaginal anastomotic leak occurred in 17 patients in the dd-TCip group and 1 patient in the dd-TCiv group. The duration of noted leakage varied from one to six cycles; four patients in the dd-TCip group required hospitalization to undergo resuturing. In the one patient with a vaginal anastomotic leak in the dd-TCiv group, the leak healed without specific intervention (Tables 2 and 3).

Other than the AEs noted earlier, AEs excluding those related to the peritoneal port and catheter (including abdominal pain) were similar in the dd-TCiv and dd-TCip groups (Table 4 and Table S9). No deaths were believed to be directly related to treatment side effects. Specific catheter-related complications consisted of catheter obstruction in 8 patients (2.7%), intraperitoneal site leakage in 17 patients (5.7%), and other complications in 10 patients (3.4%). Grade 3 or higher AEs occurred in 93.2% of patients in the dd-TCip group and 96.0% of patients in the dd-TCiv group. The most common AEs noted in both treatment groups were anemia, decreased neutrophil count, decreased platelet count, abdominal pain, nausea, vomiting, fatigue, malaise, peripheral motor neuropathy, peripheral sensory neuropathy, arthralgia, and myalgia (Table 4).

The six-cycle completion rate was 68.3% in the dd-TCiv group and 59.9% in the dd-TCip group (Table S6).

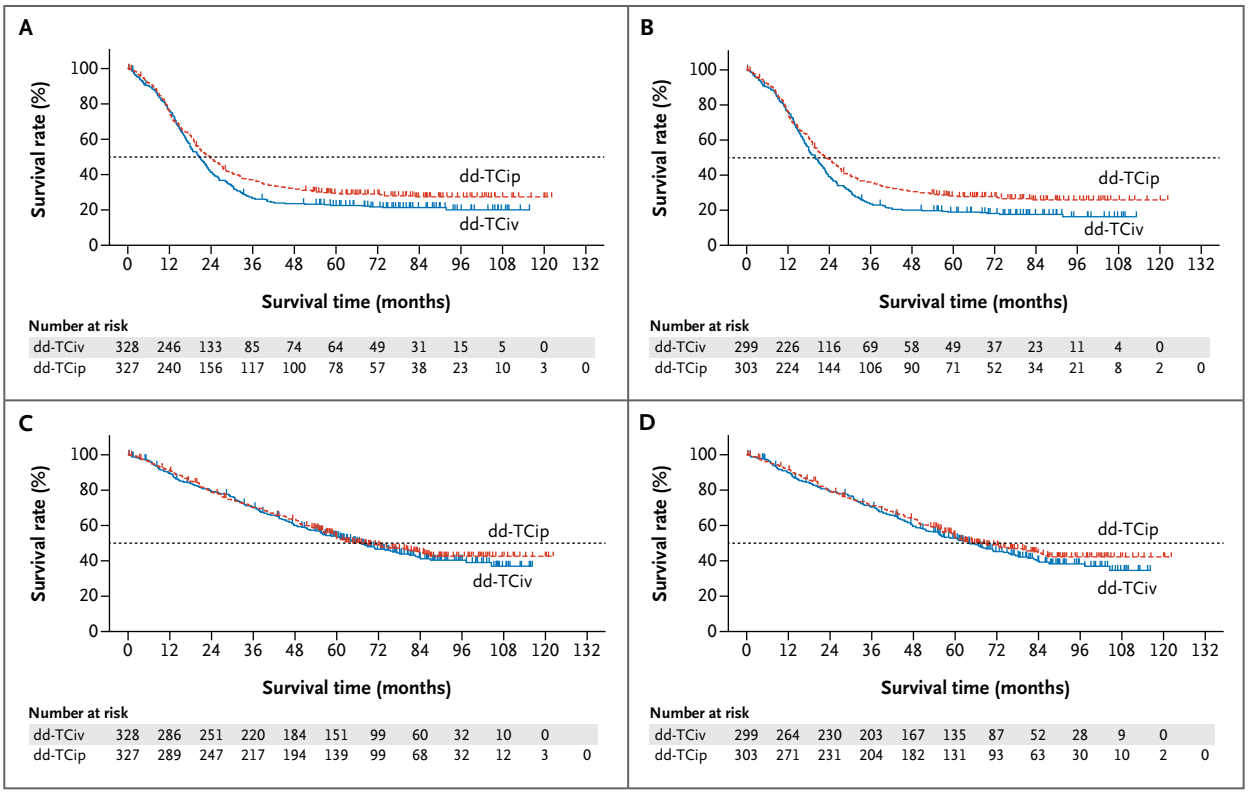

Figure 2. Kaplan–Meier Analysis.

Progression-free survival in the ITT population (Panel A), progression-free survival in the modified ITT population (Panel B), overall survival in the ITT population (Panel C), and overall survival in the modified ITT population (Panel D). dd-TCip denotes dose-dense intravenous paclitaxel plus intraperitoneal carboplatin; dd-TCiv, dose-dense intravenous paclitaxel plus intravenous carboplatin; and ITT, intention-to-treat.

Discussion

The results of this open-label, randomized trial of first-line treatment of advanced epithelial ovarian cancer showed that, in the overall population, the intraperitoneal carboplatin group had a statistically significant longer PFS compared with the intravenous carboplatin group, regardless of residual tumor size after surgery. However, no difference in OS was observed between the intravenous and intraperitoneal carboplatin treatment groups. In terms of safety, there was a difference in vaginal anastomotic leak, but there were no differences in the incidence of grade 3/4 AEs or the percentage of patients requiring dose reduction to remain in the protocol between the intraperitoneal carboplatin and intravenous carboplatin groups. Furthermore, the six-cycle completion rate with intraperitoneal carboplatin was similar to — albeit slightly lower than — that with intravenous carboplatin.

Our study adopted a design similar to that of the GOG-252 study, except the current study did not include bevacizumab combination or maintenance therapy. Unlike the current study, however, the results for GOG-252 showed no benefit for women with intraperitoneal chemotherapy.[12] Another key difference between the two studies is that although the GOG-252 study included patients with residual tumors, only 6.9% of patients had residual tumors greater than 1 cm. In contrast, approximately 60% of patients in this study had residual tumors greater than 1 cm in diameter, and approximately 55% had residual tumors greater than 2 cm in diameter. Both factors could account for the distinct outcomes observed in the current study.

Both carboplatin and cisplatin are water-soluble small molecules, which may allow them to be absorbed through the peritoneum into the systemic circulation before eventually reaching the inner core of malignant peritoneal lesions through the tumor vasculature, regardless of size.[13]

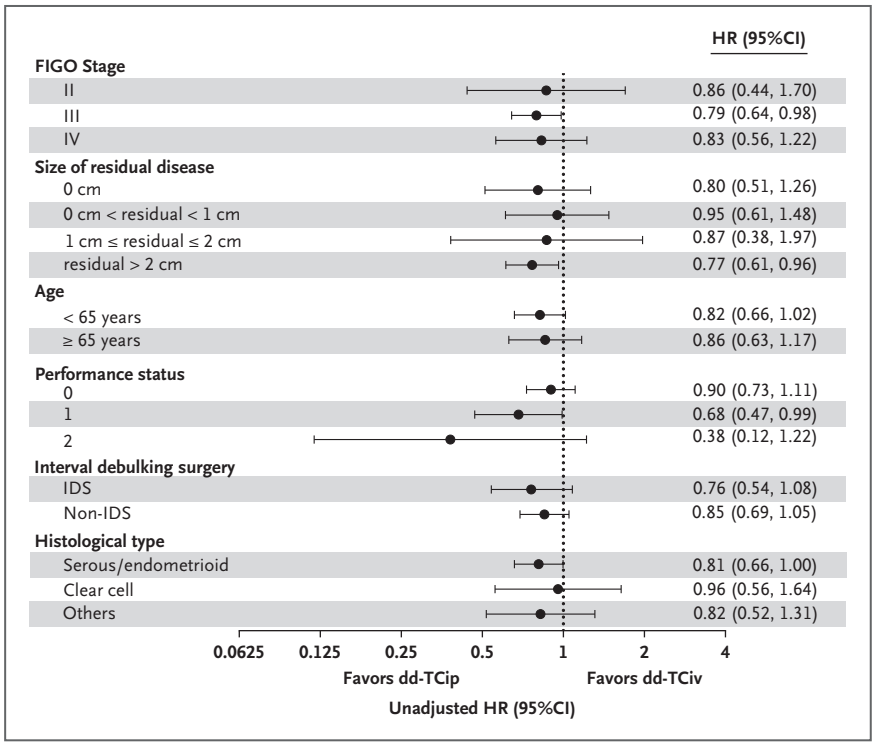

Figure 3. Subset Analysis of PFS in the ITT Population.

CI denotes confidence interval; dd-TCip, dose-dense intravenous paclitaxel plus intraperitoneal carboplatin; dd-TCiv, dose-dense intravenous paclitaxel plus intravenous carboplatin; FIGO, International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery; ITT, intention to treat; and PFS, progression-free survival.

We therefore speculate that intraperitoneal carboplatin or cisplatin permits equivalent systemic absorption of the drug through the peritoneal vasculature while also allowing higher concentrations of the drug in the peritoneal cavity, which could result in better efficacy against larger peritoneal lesions. In the GOG-104 study (which compared intraperitoneal cisplatin with intravenous cisplatin in patients with residual disease of up to 2 cm), the hazard ratio for the overall population was 0.76 but was 0.80 in patients with minimal residual disease (defined as residual disease $\leq$0.5 cm),[16-18] suggesting that intraperitoneal cisplatin had similar efficacy in patients with residual tumors greater than 0.5 cm in diameter. Previous clinical studies have also detailed the efficacy of intraperitoneal carboplatin in larger tumors.[7,9] Notably, our subgroup analysis showed that patients with larger or smaller amounts of residual disease did not display a substantial difference in response between the intraperitoneal and intravenous treatments with carboplatin (Fig. 3).

We found a statistically significant longer PFS but no differences in OS in this study. We currently have no evidence to explain this discrepancy. It is possible that poststudy treatment may have affected the OS. However, an important finding is that the PFS survival curves in the ITT population are approximately 7% better for the intraperitoneal group at 5 years, and they then plateau and do not cross after 9 to 10 years. We speculate that the intraperitoneal group may have led to prolonged periods of remission in more cases than intravenous treatment.

The key limitation of the current study is that it mainly included Japanese patients in addition to a small population of non-Japanese patients, and generalizability is, therefore, somewhat limited. Furthermore, this study was initiated before the advent of homologous recombination deficiency (HRD) testing in ovarian cancer, and the lack of molecular stratification presents a challenge in further interpretation of these results compared with recently completed first-line poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor maintenance trials.

Nonetheless, given the PFS benefit observed in the current study, it is possible that intraperitoneal carboplatin with

Table 4. Adverse Events Occurring in More Than 5% of Patients in Either Treatment Group.*

	dd-TCiv (n=297)		dd-TCip (n=296)	
MedDRA System Organ Class Lowest-Level Term	**Total**	**Grade ≥3**	**Total**	**Grade ≥3**
Blood and lymphatic system disorders	296 (99.7)	200 (67.3)	293 (99.0)	192 (64.9)
Anemia	296 (99.7)	199 (67.0)	293 (99.0)	190 (64.2)
Febrile neutropenia	11 (3.7)	11 (3.7)	15 (5.1)	15 (5.1)
Gastrointestinal disorders	246 (82.8)	29 (9.8)	259 (87.5)	35 (11.8)
Abdominal pain	103 (34.7)	0 (0.0)	153 (51.7)	4 (1.4)
Constipation	118 (39.7)	1 (0.3)	121 (40.9)	5 (1.7)
Diarrhea	106 (35.7)	4 (1.3)	92 (31.1)	3 (1.0)
Ileus	19 (6.4)	9 (3.0)	31 (10.5)	12 (4.1)
Mucositis oral	77 (25.9)	0 (0.0)	68 (23.0)	0 (0.0)
Nausea	187 (63.0)	8 (2.7)	206 (69.6)	3 (1.0)
Vomiting	95 (32.0)	7 (2.4)	83 (28.0)	1 (0.3)
General disorders and administration site conditions	237 (79.8)	5 (1.7)	249 (84.1)	6 (2.0)
Fatigue	153 (51.5)	4 (1.3)	160 (54.1)	5 (1.7)
Fever	19 (6.4)	1 (0.3)	23 (7.8)	0 (0.0)
Malaise	68 (22.9)	0 (0.0)	75 (25.3)	0 (0.0)
Edema limbs	107 (36.0)	0 (0.0)	95 (32.1)	0 (0.0)
Infusion site extravasation	9 (3.0)	0 (0.0)	15 (5.1)	1 (0.3)
Immune system disorders	37 (12.5)	5 (1.7)	28 (9.5)	1 (0.3)
Allergic reaction	30 (10.1)	3 (1.0)	22 (7.4)	0 (0.0)
Infections and infestations	61 (20.5)	22 (7.4)	80 (27.0)	43 (14.5)
Catheter-related infection	2 (0.7)	1 (0.3)	30 (10.1)	25 (8.4)
Urinary tract infection	13 (4.4)	4 (1.3)	15 (5.1)	5 (1.7)
Injury, poisoning, and procedural complications	12 (4.0)	3 (1.0)	31 (10.5)	6 (2.0)
Vaginal anastomotic leak	1 (0.3)	0 (0.0)	17 (5.7)	3 (1.0)
Investigations	291 (98.0)	255 (85.9)	292 (98.6)	243 (82.1)
Alanine aminotransferase increased	34 (11.4)	6 (2.0)	25 (8.4)	2 (0.7)
Alkaline phosphatase increased	14 (4.7)	2 (0.7)	23 (7.8)	2 (0.7)
Aspartate aminotransferase increased	29 (9.8)	6 (2.0)	26 (8.8)	2 (0.7)
Neutrophil count decreased	283 (95.3)	245 (82.5)	282 (95.3)	237 (80.1)
Platelet count decreased	257 (86.5)	78 (26.3)	238 (80.4)	82 (27.7)
Weight gain	41 (13.8)	0 (0.0)	30 (10.1)	0 (0.0)
Weight loss	77 (25.9)	3 (1.0)	89 (30.1)	2 (0.7)
White blood cell count decreased	282 (94.9)	195 (65.7)	280 (94.6)	191 (64.5)
GGT increased	14 (4.7)	7 (2.4)	17 (5.7)	6 (2.0)
Metabolism and nutrition disorders	171 (57.6)	26 (8.8)	174 (58.8)	16 (5.4)
Anorexia	135 (45.5)	7 (2.4)	136 (45.9)	6 (2.0)
Hyperkalemia	6 (2.0)	1 (0.3)	18 (6.1)	2 (0.7)
Hypokalemia	17 (5.7)	13 (4.4)	9 (3.0)	4 (1.4)
Hyperlipidemia	18 (6.1)	0 (0.0)	19 (6.4)	0 (0.0)
Musculoskeletal and connective tissue disorders	129 (43.4)	1 (0.3)	145 (49.0)	2 (0.7)
Arthralgia	95 (32.0)	1 (0.3)	101 (34.1)	0 (0.0)
Myalgia	98 (33.0)	0 (0.0)	113 (38.2)	0 (0.0)
Nervous system disorders	259 (87.2)	16 (5.4)	267 (90.2)	7 (2.4)
Dysgeusia	68 (22.9)	0 (0.0)	76 (25.7)	0 (0.0)
Peripheral motor neuropathy	108 (36.4)	3 (1.0)	87 (29.4)	2 (0.7)

(continued)

Table 4. (cont.)

MedDRA System Organ Class Lowest-Level Term	dd-TCiv (n=297)		dd-TCip (n=296)	
	Total	Grade ≥3	Total	Grade ≥3
Peripheral sensory neuropathy	254 (85.5)	13 (4.4)	258 (87.2)	5 (1.7)
Psychiatric disorders	22 (7.4)	2 (0.7)	24 (8.1)	1 (0.3)
Insomnia	15 (5.1)	0 (0.0)	17 (5.7)	0 (0.0)
Epistaxis	16 (5.4)	0 (0.0)	8 (2.7)	0 (0.0)
Skin and subcutaneous tissue disorders	265 (89.2)	0 (0.0)	269 (90.9)	1 (0.3)
Alopecia	260 (87.5)	0 (0.0)	267 (90.2)	0 (0.0)
Nail discoloration	20 (6.7)	0 (0.0)	6 (2.0)	0 (0.0)
Pruritus	55 (18.5)	0 (0.0)	52 (17.6)	0 (0.0)
Rash	49 (16.5)	0 (0.0)	47 (15.9)	0 (0.0)
Vascular disorders	85 (28.6)	18 (6.1)	82 (27.7)	13 (4.4)
Hypertension	40 (13.5)	5 (1.7)	49 (16.6)	3 (1.0)
Thromboembolic event	28 (9.4)	10 (3.4)	25 (8.4)	8 (2.7)

* Values are presented as no. (%). dd-TCip denotes dose-dense intravenous paclitaxel plus intraperitoneal carboplatin; dd-TCiv, dose-dense intravenous paclitaxel plus intravenous carboplatin; GGT, gamma-glutamyl transferase; and MedDRA, Medical Dictionary for Regulatory Activities.

dose-dense paclitaxel could represent the optimal first-line regimen before the commencement of poly(adenosine diphosphate–ribose) polymerase inhibitor maintenance therapy.[19-21] In an ancillary analysis in the GOG-172 study, intraperitoneal therapy was shown to be more effective in patients with aberrant *BRCA* expression,[21,22] although it should be noted that *BRCA1* immunohistochemical expression has not been validated as a surrogate marker for HRD. Translational research (the iPocc Translational Research study [TriPocc]) is in progress to evaluate the effect of *BRCA* mutation and HRD status regarding intraperitoneal effectiveness.[23]

In conclusion, this open-label, randomized trial found that, in the first-line treatment of advanced epithelial ovarian cancer over the full range of treated tumor sizes, intraperitoneal carboplatin modestly prolonged PFS when given in combination with weekly paclitaxel. There were more intraperitoneal catheter-related AEs and treatment discontinuations, but differences in noncatheter-related toxicities were not noted.

Disclosures

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