Table 4
Toxicity at AUC 8 in dose-escalating phase ($N=6$).

Adverse effect	Grade					
	0	1	2	3	4	Total
Leukopenia	0	0	0	6	0	6
Thrombocytopenia	0	0	1	4	1	6
Neutropenia	0	0	0	0	6	6
Anemia	0	0	4	2	0	6
Cardiovascular	5	0	1	0	0	6
Constitutional	1	2	3	0	0	6
Dermatologic (not alopecia)	4	0	2	0	0	6
Gastrointestinal	0	1	4	1	0	6
Genitourinary/Renal	4	1	0	1	0	6
Hepatic	5	1	0	0	0	6
Infection/Neutropenic	5	0	0	1	0	6
Infection/Not neutropenic	4	0	0	2	0	6
Metabolic	2	3	1	0	0	6
Neuropathy—sensory	0	6	0	0	0	6
Neuropathy—other	5	0	1	0	0	6
Pain (abdominal)	1	3	1	1	0	6

Table 5
Toxicity in expanded phase cohort AUC 7 ($N=20$).

Adverse effect	Grade					
	0	1	2	3	4	Total
Leukopenia	0	1	3	11	5	20
Thrombocytopenia	2	9	2	4	3	20
Neutropenia	0	1	1	2	16	20
Anemia	0	2	13	5	0	20
Cardiovascular	13	4	2	1	0	20
Constitutional	2	3	13	1	1	20
Dermatologic (not alopecia)	12	8	0	0	0	20
Gastrointestinal	0	6	11	2	1	20
Genitourinary/Renal	15	1	2	1	1	20
Hepatic	13	5	2	0	0	20
Infection/Neutropenic	15	0	1	3	1	20
Infection/Not neutropenic	14	1	2	3	0	20
Metabolic	7	5	4	4	0	20
Neuropathy—sensory	8	10	2	0	0	20
Neuropathy—other	7	5	7	1	0	20
Pain (abdominal)	10	6	4	0	0	20

the goal of the study was to determine the tolerability of treatment over multiple cycles, escalation to an AUC of 9 was not felt prudent. The expanded phase was therefore opened at an IP carboplatin AUC of 7 with plans to escalate or de-escalate based on the results. The total number of planned cycles was also reduced to six to be consistent with the standard recommended cycle number for intravenous carboplatin and paclitaxel on other GOG trials.

Expanded phase: toxicity

IP carboplatin AUC 7. Twenty-two patients were entered and two were not eligible for 4-cycle toxicity evaluation due to hypersensitivity reactions to paclitaxel in the first cycle. Of the 20 eligible patients treated, there were nine DLTs within four cycles (Table 5). There was one death due to neutropenic sepsis associated with a *c. difficile* infection after cycle #1. There were four DLTs due to a delay of >2 weeks to recover neutrophil counts, two due to neutropenic fever (including the death), two due to grade 3 or 4 thrombocytopenia, and one due to grade 4 metabolic toxicity. Given that there were greater than eight DLTs, this regimen was not considered feasible for a Phase III trial. In addition, there was only 1 IP port problem (port abscess requiring removal) and 11 patients (55%) completed six cycles.

IP carboplatin AUC 6. Forty-seven patients were entered and seven were not eligible for four-cycle toxicity evaluation (two treated at wrong dose, two hypersensitivity reactions to paclitaxel in first cycle, two progression of disease by cycle 3, and one patient refused IP therapy after the first cycle). Of the 40 eligible patients treated, there were 14 DLTs. There were six DLTs due to grade 3 or 4 thrombocytopenia, four DLTs due to a delay of >2 weeks to recover neutrophil counts, two DLTs due to neutropenic fever, one grade 4 neutropenia >7 days, and one DLT due to grade 3 mental status changes requiring hospitalization. Thirty (75%) patients completed six cycles of IP therapy with dose adjustments after cycle #4 when required by protocol. There were two IP port malfunctions. Both were replaced and both patients completed six cycles. The highest grade of toxicity for each of the 40 evaluable patients is listed in Table 6.

Response rates and progression

Response rates and data regarding progression were evaluated for patients treated at an AUC 6 in the expanded phase. An intent-to-treat analysis revealed that of all 47 patients entered at an AUC 6, 14 (30%, 95% CI 17–45%) had disease progression within 1 year of initiating protocol treatment. Two patients had progression of disease before cycle #4. Of the 35 patients treated at an AUC 6 who completed at least four cycles of protocol therapy, nine (26%, 95% CI, 12–43%) had evidence of disease progression within 1 year of initiating therapy. Four of 35 patients (11%) had suboptimal disease. However, only two of those patients had measurable disease on radiologic imaging and both had a complete clinical response after treatment.

Discussion

The GOG has sought to develop regimens using IP carboplatin for use in a Phase III trial comparing systemic carboplatin and paclitaxel to intraperitoneal chemotherapy. Retrospective evaluation of the experience with IP carboplatin and IV paclitaxel (175 mg/m^2) as primary treatment of ovarian, peritoneal or fallopian tube cancer in Japan confirms that myelotoxicity, especially thrombocytopenia, appears to be dose limiting [15]. In the study reported here, grade 4 neutropenia was seen in 63% of patients treated at an IP carboplatin AUC of 6. Grade 3 or 4 thrombocytopenia was only seen in 15% of patients at this dose but was always considered dose limiting. In GOG-158, 72% grade 4 neutropenia and 39% grade 3 and 4 thrombocytopenia were observed in patients treated with IV paclitaxel (175 mg/m^2) and IV carboplatin (AUC=7.5) [14].

The most recently reported GOG randomized trial of intraperitoneal chemotherapy (GOG-172) demonstrated a relative risk of recurrence of 0.73 and a 15.9-month improvement in overall survival with the IP regimen. This was despite the fact that only 42% of patients completed the planned six cycles IP and 49% in the IP arm received three or fewer IP treatments [3]. IP catheter problems occurred in 34% of patients and were a major reason for discontinuing IP therapy [16]. In the study reported here, only 7/90 (8%) of patients entered had problems related to the IP catheter and five were responsible for discontinuing IP therapy. This low rate may be due to the use of IP carboplatin alone, more common placement of catheters at the time of initial surgery or more experienced surgeons and staff participating in Phase I trials with the GOG. The progression rate at 1 year (30%) for the expanded cohort treated at a carboplatin dose of AUC 6 is comparable to GOG-172 where 25% of patients had disease progression in 1 year [3].

This Phase I trial established that the first-cycle MTD of IP carboplatin was at least an AUC of 8 when given every 3 weeks with paclitaxel at 175 mg/m^2. However, follow-up of patients on the dose-seeking phase treated beyond the first cycle revealed that it was unlikely that multiple cycles would be tolerated at the MTD. In the expanded phase, evaluating four-cycle toxicity, even an AUC 7 was not considered feasible in a Phase III trial. At a carboplatin AUC 6, 13/14 DLTs were due to myelosuppression: six due to thrombocytopenia and seven due to leukopenia or neutropenia.

Table 6
Toxicity in expanded phase cohort AUC 6 ($N=40$).

Adverse effect	Grade					
	0	1	2	3	4	Total
Leukopenia	0	5	16	18	1	40
Thrombocytopenia	13	13	8	2	4	40
Neutropenia	0	0	4	11	25	40
Anemia	1	14	17	7	1	40
Cardiovascular	28	7	5	0	0	40
Constitutional	4	21	14	1	0	40
Dermatologic (not alopecia)	28	11	1	0	0	40
Gastrointestinal	4	20	10	6	0	40
Genitourinary/Renal	39	0	1	0	0	40
Hepatic	16	12	0	2	0	40
Infection/Neutropenic	36	0	0	3	1	40
Infection/Not neutropenic	29	0	8	3	0	40
Metabolic	19	17	1	3	0	40
Neuropathy—sensory	6	21	9	4	0	40
Neuropathy—other	26	7	3	4	0	40
Pain (abdominal)	18	12	5	5	0	40

Although not feasible for incorporation into a Phase III trial based on the criteria of this study, the regimen of IP carboplatin at an AUC 6 with IV paclitaxel at 175 mg/m^2 is well tolerated over multiple cycles with a high six cycle completion rate (75%). Serious outcomes associated with myelosuppression, such as febrile neutropenia or bleeding, were infrequent. The pattern of DLTs suggests that with broadened criteria for dose delay or incorporation of granulocyte colony-stimulating factors, this dose could be feasible in a Phase III trial.

The GOG has recently opened a randomized trial comparing IV and IP chemotherapy (Fig. 1, online only). All regimens will also contain bevacizumab during treatment and for 11 months after chemotherapy. The IP carboplatin dose chosen is an AUC of 6, combined with IV paclitaxel (80 mg/m^2) on days 1, 8, and 15 based on recent trial suggesting improved survival and comparable toxicity with the dose-dense regimen versus the standard 3-week IV regimen [17]. Given the survival advantage of IP therapy in the treatment of women with ovarian, fallopian tube, and primary peritoneal carcinoma, it is hoped that findings from this study which have been incorporated into the ongoing GOG trial will make this therapy equally efficacious and more tolerable.

Supplementary materials related to this article can be found online at doi:10.1016/j.ygyno.2010.12.358.

Conflict of interest statement
The authors wish to report that they have no conflicts of interest.

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ORIGINAL ARTICLE

Evaluation of a formula for individual dosage of nedaplatin based on renal function

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Abstract
Purpose Nedaplatin (NDP), a platinum derivative, has been developed to reduce nephrotoxicity and gastrointestinal toxicity of cisplatin. The pharmacokinetic profile of NDP is similar to that of carboplatin (CBDCA). The optimal dosing for CBDCA is determined by the area under the curve (AUC) using Calvert's formula. However, the administration dose of nedaplatin (NDP) is determined based on the body surface area in clinical treatment. Ishibashi et al. reported a formula for predicting NDP clearance based on renal function like Calvert's formula for CBDCA. We conducted the present study to evaluate the Ishibashi's formula.
Methods A total of 22 patients with cervical or ovarian cancer, who underwent chemotherapy consisting of NDP and irinotecan (CPT-11), were examined in this study. Blood samples were collected at 0, 1, 2, 4, and 6 h after the end of infusion of NDP (48–80 mg/m^2), and free platinum concentrations were measured. Observed AUCs were compared with predicted AUCs, which were calculated by the Ishibashi's formula. In addition, the relative reduction in platelets (PLTs) was assessed as a parameter of adverse effects.
Results The observed AUC of NDP ranged from 4 to 14 ($\mu g\,h^{-1}\,ml^{-1}$) with large variation. The predicted AUC based on renal function was correlated with the observed AUC. There was a relationship between observed AUC and the decrease in PLTs.
Conclusions Ishibashi's formula would be predictable and useful for estimating the individual dose of NDP.

Keywords Nedaplatin · AUC · Formula · Renal function

Introduction

Nedaplatin (cis-diammineglycolatoplatinum, NDP), a platinum derivative, has been developed to reduce nephrotoxicity and gastrointestinal toxicity of cisplatin (CDDP) [1]. NDP has higher antitumor activity than carboplatin (CBDCA) [2, 3]. In the literature, high activities against head and neck cancer, non-small-cell lung carcinoma, esophageal cancer, testicular tumor, and cervical cancer have been demonstrated [4–9]. In addition, a high response rate has also been reported for the combination of irinotecan (CPT-11) and platinum for ovarian and cervical cancer [10–12]. Matsumura et al. reported 80.4% response rate for this combination in neoadjuvant chemotherapy for cervical cancer [13].

It is known that the area under the curve (AUC) of platinum correlates with its antitumor efficacy and toxicity [14, 15]. In practice, the optimal dosing of CBDCA has been determined by the AUC using Calvert's formula. The plasma concentration profile of unbound platinum after NDP infusion is similar to that of total platinum, and the protein binding of NDP has been shown to be lower than that of CDDP [16]. Although the pharmacokinetic profile of NDP is similar to that of CBDCA, the administration dose of NDP is determined by the body surface area (BSA), not the AUC [17]. Ishibashi et al. reported a formula for predicting NDP clearance based on pharmacokinetics that

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NDP is eliminated mainly via kidney [18]. To reduce adverse effects, the optimal dosage should be individualized by considering the variability of the renal function of each patient. We conducted the present study to evaluate Ishibashi's formula, comparing predicted AUC with observed AUC. Furthermore, as a parameter of adverse effects, the predictability of thrombocytopenia was examined in this study.

Methods

A total of 22 patients, who underwent chemotherapy consisting of NDP and CPT-11 at the Jichi Medical College and Tottori University Hospital, were enrolled in this study. The eligibility criteria included the following: age older than 19 and younger than 80 years, Eastern Cooperative Oncology Group (ECOG) performance status of less than 2, adequate bone marrow function (granulocytes $\geq$ 2,000/mm^3, platelet (PLT) count $\geq$ 100,000/mm^3, hemoglobin level $\geq$ 9.0 g/dl), adequate liver function (aspartate transaminase [AST] $\leq$ 100 IU/l, alanine transaminase [ALT] $\leq$ 100 IU/l, t-bilirubin $\leq$ 1.5 mg/dl), renal function (serum creatinine $\leq$ 1.2 mg/dl, creatinine clearance (Ccr) by Cockcroft-Gault formula $\geq$ 50 ml/min), and cardiac function (normal electrocardiogram [ECG] or minor change without treatment).

All patients gave written informed consent before enrollment. This protocol was approved by the Institutional Review Board for Research at both Tottori University and Jichi Medical College.

The dose of NDP (Shionogi Pharmaceutical Co., Osaka, Japan) was determined using the BSA (mg/m^2) calculated with formula of Dubois [(Weight$^{0.425}$ $\times$ Height$^{0.725}$) $\times$ 0.007184]. The dosage was 60 mg/m^2 for ovarian cancer and 80 mg/m^2 for cervical cancer. Three recurrent patients, who had needed reduction in dosage at the primary chemotherapy, were given the agent at 48 mg/m^2 as the 80% dosage of 60 mg/m^2.

CPT-11 (Irinotecan HCL; Yakult Honsha Co., Ltd. Tokyo, Japan) was administered at a fixed dose of 60 mg/m^2. Blood samples were collected at 0, 1, 2, 4, and 6 h after the end of intravenous administration of NDP with 1-h infusion duration, and free platinum and total platinum concentrations were measured. Demographic data, including age, body weight, serum creatinine level, and Ccr, were also recorded for each patient.

The plasma unbound fraction was separated by using an ultrafiltration method [19]. The concentrations of total and free platinum in the plasma were measured by a validated atomic absorption spectrometry assay method at the NAC laboratories (Tokyo, Japan). The lower determination limit for this method is 0.2 μg/mL. Measured values in clinical laboratory tests were obtained from each hospital.

To evaluate the predictability of the AUC by using Ishibashi's formula, the predicted AUC was compared with the observed AUC that was calculated by the trapezoidal method. The relationship between the predicted and observed free platinum clearance (CL) was also evaluated because the AUC was calculated according to the CL.

Ishibashi reported a simple formula (Eq. 1) based on a population pharmacokinetic model [20]. Since they proved that only Ccr was found to be a significant covariate of CL, CL was calculated according to this formula on the basis of the individual Ccr.

$$\mathrm{CL} = 0.0738 \times \mathrm{Ccr} + 4.47 \quad (1)$$

Predicted AUC: The predicted AUC was calculated using Eq. 2 on the basis of pharmacokinetics; the individual CL was predicted by Ishibashi's formula on the basis of the individual Ccr.

$$\mathrm{AUC} = \mathrm{dose}/\mathrm{CL} \quad (2)$$

Observed AUC: The observed AUC was calculated and extrapolated to infinity using Eq. 3.

$$\mathrm{AUC} + \mathrm{AUC}_{\mathrm{last}} + (\mathrm{Ct}/\lambda z), \quad (3)$$

where $\mathrm{AUC}_{\mathrm{last}}$ is AUC from 0 to the time point of the last measurable plasma concentration and calculated by the trapezoidal method on the basis of the individual plasma unbound platinum concentrations. Ct is the last measurable plasma concentration, and λz is the magnitude of the slope of the linear regression of the log-transformed concentration versus time during the terminal phase.

Evaluation: The predictability of the CL and AUC was evaluated by two indices, the mean prediction error (ME) as a measure of bias (Eq. 4) and the root mean squared error (RMSE) as a measure of precision (Eq. 5) [21].

$$\mathrm{ME} = 1/N \cdot \Sigma(\mathrm{Pred} - \mathrm{Obs}) \quad (4)$$

$$\mathrm{RMSE} = \sqrt{1/N} \cdot \Sigma(\mathrm{Pred} - \mathrm{Obs})^2 \quad (5)$$

$$\mathrm{ME}(\%) = 1/N \cdot \Sigma(\mathrm{Pred} - \mathrm{Obs})/\mathrm{Pred} \times 100 \quad (6)$$

$$\mathrm{RMSE}(\%) = \sqrt{1/N} \cdot \Sigma\{(\mathrm{Pred} - \mathrm{Obs})/\mathrm{Pred}\}^2 \times 100 \quad (7)$$

In Eqs. 4–7, Pred is the predicted value of CL or AUC, Obs is the observed value of CL or AUC, and N is the number of patients.

NDP dosing, especially the decrease in PLT count, relates to AUC. The relationship between the decrease in PLT count and AUC is shown in Eq. 8.

$$(\mathrm{PLT}_{\mathrm{nadir}} - \mathrm{PLT}_{\mathrm{pre}})/\mathrm{PLT}_{\mathrm{pre}} \times 100(\%) = -3.76 \times \mathrm{AUC}, \quad (8)$$

where PLT_{nadir} is the nadir of the PLT count after NDP administration and PLT_{pre} is the PLT count before NDP administration.

The nadir of the PLT count retrospectively predicted by using the predicted AUC based on Eq. 8 was compared with the observed nadir of the PLT count after NDP administration.

Results

The age of the study participants ranged from 35 to 71 years (average 53.9). Their height, body weight, and BSA ranged from 135 to 166 cm (153), from 40.0 to 62.0 kg (50.7), from 1.29 to 1.61 m^2 (1.46), respectively. The averages of serum creatinine and creatinine clearance were 0.64 mg/dl (0.48–1.17) and 86.4 ml/min (51–126). There were 15 cervical carcinomas and 7 ovarian carcinomas. Fourteen patients with cervical cancer previously received concurrent chemoradiotherapy (CCRT). The doses of NDP were 48 mg/m^2 in three patients, 60 mg/m^2 in 8 patients, and 80 mg/m^2 in 11 patients. The actual dosage of NDP distributed from 73.4 to 125.6 mg.

The range of the observed AUC of NDP was wide (4–14 $\mu g\ h^{-1}\ ml^{-1}$). There was no relationship between the observed AUC and dose based on the BSA (Fig. 1). The AUC showed a more than threefold inter-patient variation. On the other hand, there was a favorable correlation between observed AUC and dose normalized by Ccr (Fig. 2). The predicted AUC was correlated with the observed AUC (Fig. 3). The ME and RMSE were 0.92 (8.0%) and 2.72 (27.8%).

There was a relationship between the observed AUC and the relative reduction ratio of PLTs (Fig. 4). The dose of NDP based on BSA did not relate to the relative reduction ratio of PLTs. Five patients showed unexpectedly grade 4 thrombocytopenia, and the predicted PLT did not follow the regression line. These 5 patients received CCRT.

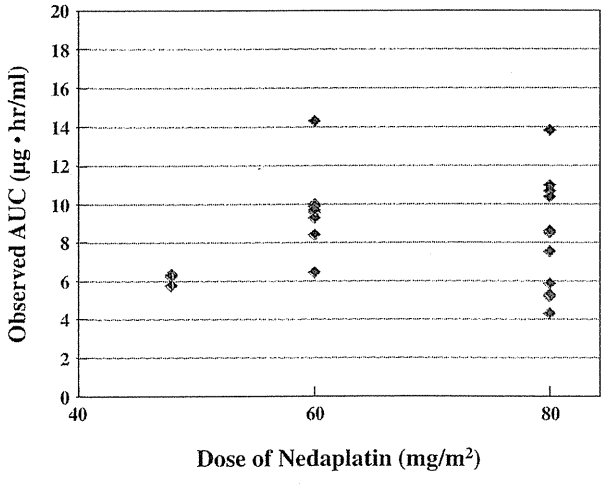

Fig. 1 Observed AUC and dose of nedaplatin (mg/m^2)

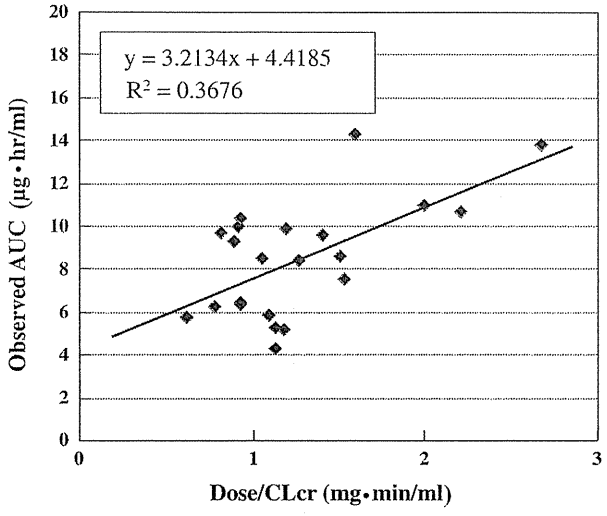

Fig. 2 Observed AUC and clearance

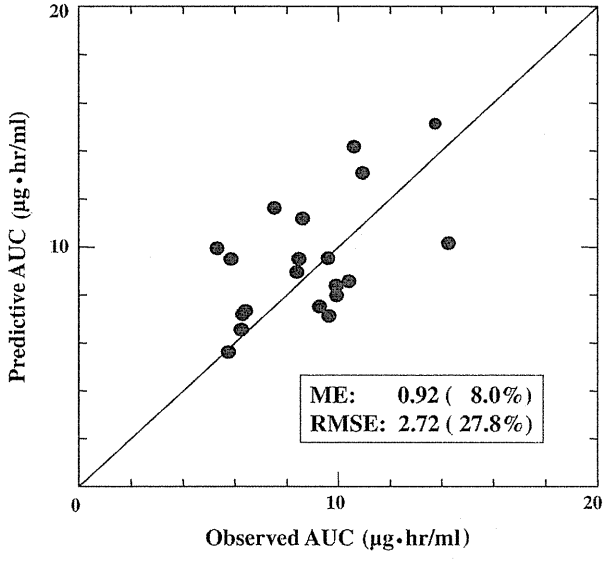

Fig. 3 Predictive and observed AUC

Discussion

The dose-limiting factor (DLT) for NDP as well as CBDCA is their hematological toxicity. The relationship between the AUC of platinum and its antitumor efficacy or toxicity has been demonstrated in previous reports. In general, the dose of CBDCA was calculated by using a targeted AUC [22]. The Calvert's formula is most frequently used for CBDCA dosing. Since the pharmacokinetic profile of NDP is similar to

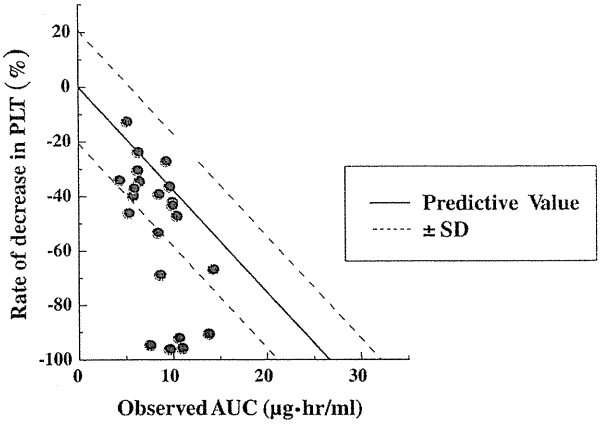

Fig. 4 Observed AUC and relative reduction rate of platelet

that of CBDCA, such a formula for NDP is necessary to use this drug more effectively. However, the dose of NDP has been determined by using the BSA, and the therapeutic dose of NDP is recommended to be between 80 and 100 mg/m^2. In the current study, we demonstrated that the AUC of NDP varies after administration of NDP based on the BSA. The range of the observed AUC of NDP was wide, and there was no relationship between the observed AUC and dose based on the BSA. Those findings suggest that dosage of NDP based on BSA involves the uncertainty of the effect as well as various risks. We found a favorable correlation between AUC and Ccr. Therefore, the renal function should be considered when NDP is administered.

Ishibashi et al. reported a formula for predicting NDP clearance on the basis of pharmacokinetics. In their study, ME and RMSE were 0.629 (−32.0%) and 3.469 (24.2%) [18]. The current study showed that ME and RMSE were 0.92 (8.0%) and 2.72 (27.8%), indicating that the bias and precision were similar to the previous data. Therefore, we could confirm good prediction accuracy of the platinum AUC with Ishibashi's formula, and Ishibashi's formula might be reliable to predict the AUC of NDP.

Ishibashi et al. also showed a linear relationship between thrombocytopenia measured by the extent of PLT decrease with the AUC of unbound platinum after NDP infusion [23]. In addition, the nadir of the PLT count was predicted by using the AUC. However, the decrease in the PLT count could not be predicted in 5 out of 22 patients. Those patients received concurrent chemoradiotherapy for cervical cancer. They had potential bone marrow suppression because they already received irradiation for whole pelvis and weekly administration of cisplatin (40 mg/m^2) concomitantly.

This study showed that Ishibashi's formula for estimating CL was useful for the treatment with NDP. Therefore, NDP might be safely administered on the basis of an adequate dose calculation using this formula. Based on the results of this study, we planned a Phase I study in which the dose of NDP was determined by AUC.

Conflict of interest None of the authors has any former or present conflict of interest related to this study.

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ORIGINAL ARTICLE

Questionnaire survey of the current status of radical trachelectomy in Japan

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Abstract
Background The number of young patients with cervical cancer has been increasing recently in Japan. Radical trachelectomy is a potential option for patients who wish to preserve their fertility, but its status is not clear. The present survey was conducted to clarify the status of radical trachelectomy in Japan.
Methods Questionnaires were mailed to 164 selected institutions based on tumor registration with the Japanese Obstetrics Gynecology Society. The subjects were patients undergoing radical trachelectomy between 2000 and 2008.
Results The response rate to the questionnaire was 88.4% (145/164). Radical trachelectomy was performed on 269 patients in 26 institutions (17.9%) . Most cases (74.7%, 201/269) underwent an abdominal approach. Three institutions had performed more than 21 cases (max. 61 cases), whereas 8 institutions had performed only one case. Twenty pregnancies and 13 deliveries were achieved and the frequency of delivery later than the 29th gestational week was 62% (8/13). "Tumor size ≤2 cm (81%)" and "stage ≤Ib1 (96%)" were commonly regarded as indications for radical trachelectomy. On the other hand, 46% of the centers did not consider the histological type as an indication.
Conclusion This survey is the first report on the current status of radical trachelectomy in Japan. It reveals a difference in the criteria for surgery applied in each institution.

Keywords Cervical cancer · Radical trachelectomy · Fertility-sparing

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Introduction

Cervical cancer is the second most common female cancer [1]. Radical hysterectomy is generally considered a therapeutic option for patients with stage Ib cervical cancer; in Japan, most patients with stage Ib are treated with radical hysterectomy. Approximately 15% of all cervical cancers and 45% of surgically treated stage Ib cancers occur in women under the age of 40 [2]. Recently, the incidence of young patients with cervical cancer has increased, and many women are diagnosed with this cancer during their reproductive years [3]. Accordingly, fertility preservation is an important issue for gynecological oncologists.

Radical trachelectomy was introduced as an alternative to radical hysterectomy for the treatment of young patients with cervical cancer wishing to preserve their fertility [4]. There are many reports on radical trachelectomy [5–8]; however, its status is not clear in Japan. We therefore conducted a questionnaire survey to clarify the current status of radical trachelectomy in Japan.

Material and methods

One hundred and sixty-four institutions were selected based on tumor registration with the Japanese Obstetrics Gynecology Society. These included all of the main institutions in Japan, and were sent a questionnaire asking about subjects undergoing radical trachelectomy between 2000 and 2008, including the number of radical trachelectomies and pregnancies after surgery, and eligibility. Data were collected from the patients' medical records.

Results

Responses to questionnaire were obtained from 145 institutions (response rate 88.4%). Of 145 institutions, 26 (17.9%) performed radical trachelectomy, and 269 patients had undergone radical trachelectomy (abdominal approach 201, laparoscopic approach 40, vaginal approach 28). The number of surgeries ranged from 1 to 61 (Table 1). Three institutions had treated over 20 cases, whereas 8 institutions had treated only one case. Among the 269 patients who had undergone radical trachelectomy, 20 women became pregnant, and 13 delivered. There were only 3 term deliveries (Table 2).

The indications for radical trachelectomy were widely distributed (Fig. 1). "Tumor size ≤2 cm (81%)" and "stage ≤Ib1 (96%)" were commonly regarded as indications. On the other hand, 46% of the institutions did not consider the histological type as an indication.

Table 1 Distribution of patients undergoing radical trachelectomy

Number	Institutions
≤5	17
6–10	2
11–20	4
≥21	3

The number of surgeries ranged from 1 to 61. Three institutions had performed more than 21 cases, whereas 8 institutions had performed only one case

Table 2 Obstetric outcomes

Gestational week	Number
≤21 weeks	7
21–28 weeks	5
29–32 weeks	2
33–36 weeks	3
≥37 weeks	3
Total	20

Twenty pregnancies and 13 deliveries were achieved and the frequency of delivery later than the 29th gestational week was 62% (8/13)

Discussion

The recommended surgical treatment for women with stage Ib2–Ib1 cervical cancer is a radical hysterectomy and bilateral pelvic lymphadenectomy [9]; however, many women diagnosed with cervical cancer have not completed their childbearing. There is increasing evidence in the literature that radical trachelectomy is a viable option for young women with cervical cancer who wish to preserve their fertility [10, 11]; however, the eligibility for this procedure is controversial. Additionally, the status of radical trachelectomy is not clear [3, 4, 12]. This is the first report concerning its status in Japan.

Because the response rate was extremely high (88.4%) in this survey, our results should be reliable and describe the actual situation in Japan. Although 26 institutions had performed radical trachelectomy, over half of the patients (55.3%) had received the surgery in only 3 institutions. On the other hand, 8 institutions had treated only one case. In our series, 74.7% patients had undergone radical trachelectomy with an abdominal approach. Additionally, total laparoscopic surgery was performed in only one institution. In the literature, the vaginal approach has been slow to be adopted, mainly because most gynecological oncologists are not trained in radical vaginal surgery [3].

As regards the obstetric outcomes, 20 women became pregnant, resulting in 7 abortions before 22 gestational

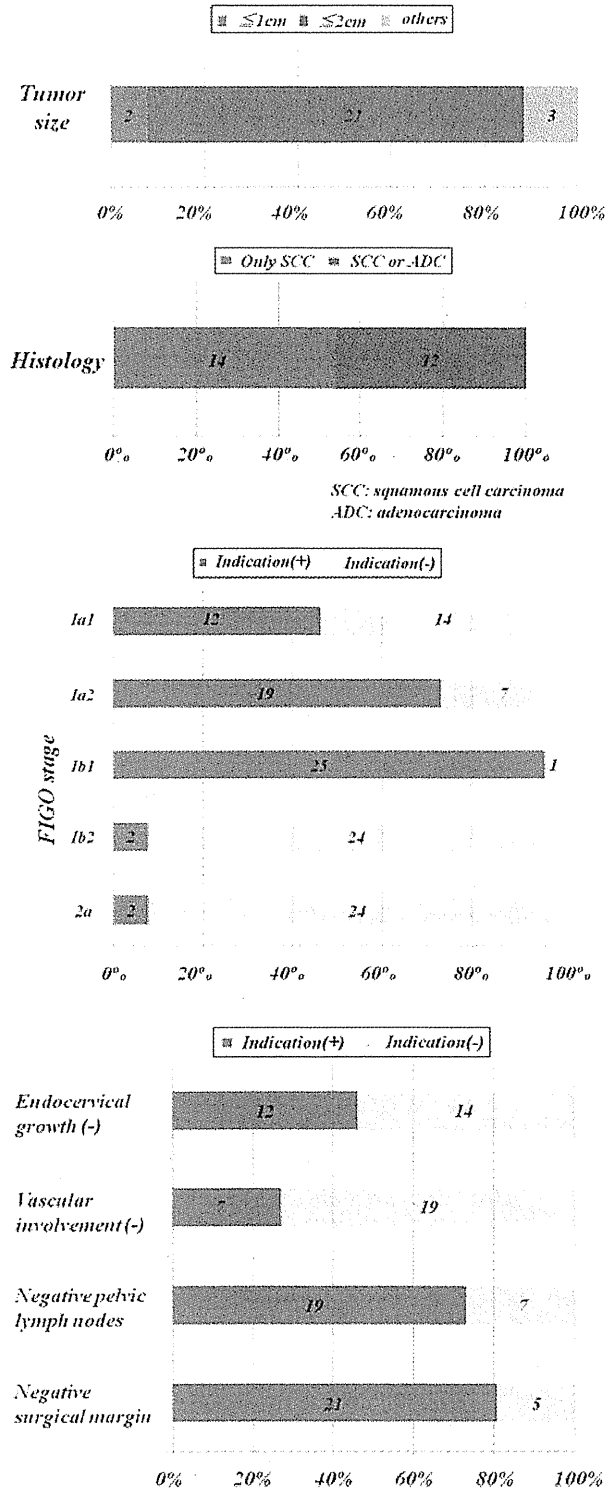

Fig. 1 Surgical indications for radical trachelectomy. Different criteria for radical trachelectomy were applied in each institution. "Tumor size ≤2 cm (81%)" and "stage ≤Ib1 (96%)" were commonly regarded as indications for radical trachelectomy. On the other hand, 46% of the centers did not consider the histological type as an indication

weeks and 13 deliveries. The frequency of delivery later than the 29th gestational week was 62% (8/13). Few obstetric outcomes with radical trachelectomy have been reported in Japan. Those results suggested that the management after radical trachelectomy, including high risk pregnancy, is important.

The criteria for performing radical trachelectomy have been reported by several authors [3–6]. The suggested criteria were, in principle, as follows: "A desire for future fertility", "FIGO stage Ia1 with lymphovascular invasion, stage Ia2, or Ib1", "Tumor size ≤2 cm", "Tumor limited to the cervix", and "No evidence of pelvic lymph node metastasis and/or other distant metastasis". Indications such as "Tumor size ≤2 cm" and "Stage Ia1–Ib1" were commonly acceptable in our series. On the other hand, this survey revealed a difference in the surgical criteria applied in each institution. Radical trachelectomy for patients with tumor size >2 cm or over stage Ib2 was carried out in only a few institutions, and the outcome of patients was not good (data not shown).

The present study suggests that a consensus on radical trachelectomy is necessary in Japan. Further experience of radical trachelectomy in Japan will help to delineate the indications for surgery and the prognosis.

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Conflict of interest No author has any conflict of interest.

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EXPERT REVIEWS

Neoadjuvant chemotherapy for advanced ovarian cancer: overview of outcomes and unanswered questions

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Neoadjuvant chemotherapy for advanced ovarian cancer was initially administered as an alternative treatment for patients not suitable for primary debulking surgery (PDS) because of unresectable tumor or poor performance status. Accumulation of favorable outcomes of this treatment compared with standard treatment starting with PDS made this strategy a candidate for prospective, randomized Phase III studies without limiting the subjects to patients who were unsuitable for PDS. Among the four Phase III studies to date, the earliest study from the European Organization for Research and Treatment of Cancer (EORTC) has revealed noninferior survival with less-serious morbidity in the neoadjuvant chemotherapy arm. These data suggest that neoadjuvant chemotherapy followed by surgical cytoreduction is an acceptable management strategy for patients with advanced ovarian cancer. In this article, we review the treatment outcomes and discuss some unanswered questions, as well as possible future research in this area.

KEYWORDS: interval debulking surgery • neoadjuvant chemotherapy • optimal surgery • ovarian cancer • primary debulking surgery • prognosis • standard treatment

Primary debulking surgery (PDS) followed by chemotherapy (PDS-CT) has been considered a standard treatment procedure for patients with advanced ovarian cancer. Griffiths first demonstrated that survival time was inversely proportional to residual mass size after PDS, and the observation was reproduced and confirmed by many succeeding studies [1]. The goal of debulking surgery is to remove as much of the bulky tumor as possible. According to a recent definition, an optimal surgery achieves a maximum residual tumor size of <1 cm in diameter, which leads to much better survival compared with suboptimal debulking (i.e., nonoptimal debulking). Disappointingly, optimal debulking can be achieved in only 30–60% of stage III/IV ovarian cancers at average institutions [2,3], and physicians often hesitate to perform aggressive debulking surgery in patients with impaired performance status (PS) owing to highly advanced disease.

Another treatment strategy, consisting of neoadjuvant chemotherapy (NAC) and interval debulking surgery (IDS) followed by postsurgical chemotherapy (NAC-setting treatment or NACT), emerged as an alternative approach to PDS-CT in patients with apparently unresectable, bulky tumors or poor PS. The strategy arose from an adoption of IDS as secondary debulking after suboptimal PDS and later an omission of PDS in patients who supposedly would have little benefit from PDS.

Many retrospective studies revealed that survival of patients treated by NACT was comparable with that of patients treated by PDS-CT, although the NACT group had more advanced disease and/or poorer PS. Based on these favorable results for NACT, several prospective studies to assess the efficacy of NACT were conducted. Furthermore, prospective Phase III randomized studies have been conducted without limiting the subjects to patients with apparently unresectable tumors and/or poor PS, and extended target diseases to not only ovarian cancer but also tubal and peritoneal cancers.

The results of the first Phase III NAC trial by the European Organization for Research and Treatment of Cancer (EORTC) have been

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recently published [4]. Results from other Phase III studies conducted in the UK, India and Japan are expected in the next few years. In this article, we review the outcomes of NACT, focusing on a comparison with that of PDS setting treatment, and discuss some of the questions concerning NACT.

Outcome of NACT

Comparable outcomes & reduced morbidity of NACT compared with PDS-CT in retrospective & prospective, nonrandomized comparative studies

To date, numerous retrospective studies reporting treatment results and complications of NACT have been published. Among these, studies comparing treatment outcomes (Table 1) [5–16] and complications related to debulking surgery (Table 2) [5,7,8,10,12,14–17] between PDS-CT and NACT are summarized. In most of the studies, NACT was administered to patients who had older age, more advanced disease or a lower PS, whereas characteristics of subjects for NACT and PDS-CT were not statistically different in studies by Jacob *et al.* [5], Vrščaj *et al.* [9] and Morice *et al.* [10]. In these highly biased settings unfavorable to NACT, all of the studies showed a similar or higher proportion of optimal debulking surgery in NACT, and all but one study by Steed *et al.* yielded noninferior outcomes of NACT compared with those of PDS-CT (Table 1) [14]. After controlling for age, the International Federation of Gynecology and Obstetrics stage, histologic grade and pleural effusions, even the study by Steed *et al.*, demonstrated no statistical difference in overall survival (OS; p = 0.95) between NACT and PDS-CT. As for the invasiveness of debulking surgery,

Table 1. Comparison of outcomes between primary debulking surgery followed by chemotherapy and neoadjuvant chemotherapy-setting treatment in retrospective studies.

Study (year)	Treatment	Patients (n)	Survival: MST	Survival: p-value	Interval debulking surgery: Residual tumor ≥ 1 cm	Interval debulking surgery: Optimal debulking	Ref.
Jacob *et al.* (1991)	PDS-CT	18	18 months		<2	39 (7/18)	[5]
	NACT	22	16 months	NS	<2	77 (17/22)	p = 0.02
Onnis *et al.* (1996)	PDS-CT	284	21%†		<2	29 (83/284)	[6]
	NACT	88	19%†	NS	<2 cm	42 (37/88)	p = 0.027§
Schwartz *et al.* (1999)	PDS-CT	206	2.18 years		NA	NA	[7]
	NACT	59	1.07 years	NS	NA	NA	
Kayikçioğlu *et al.* (2001)	PDS-CT	158	38 months		0	14 (22/158)	[8]
	NACT	45	34 months	NS	0	49 (22/45)	p < 0.001
Vrščaj *et al.* (2002)	PDS-CT	55	26 months		<1	22 (12/55)	[9]
	NACT	20	25 months	NS	<1	60 (12/20)	p = 0.001
Morice *et al.* (2003)	PDS-CT	34	22 months		<2	94 (32/34)	[10]
	NACT	34	26 months	NS	<2	94 (32/34)	NS
Loizzi *et al.* (2005)	PDS-CT	30	40 months		<1	60 (18/30)	[11]
	NACT	30	32 months	NS	<1	63 (19/30)‡	NS§
Everett *et al.* (2006)	PDS-CT	102	42 months		<1	54 (55/102)	[12]
	NACT	98	33 months	NS	<1	86 (84/98)	p < 0.001
Inciura *et al.* (2006)	PDS-CT	361	25 months		<2	67 (242/361)	[13]
	NACT	213	24 months	NS	<2	63 (134/213)	NS
Steed *et al.* (2006)	PDS-CT	66	3.7 years		<2	50 (33/66)	[14]
	NACT	50	2.4 years	p = 0.03	<2	52 (26/50)‡	NS§
Hou *et al.* (2007)	PDS-CT	109	47 months		<1	71 (77/109)	[15]
	NACT	63	46 months	NS	<1	95 (60/63)	<0.001
Colombo *et al.* (2009)	PDS-CT	142	38 months		<1	63 (89/142)	[16]
	NACT	61	26 months	NA	<1	84 (51/61)	p = 0.003§

†Shows 5-year survival rates.
‡Recalculated as to include all patients into denominators.
§Calculated using Fisher's exact test because the values are not available.
MST: Median survival time; NA: Not available; NACT: Neoadjuvant chemotherapy-setting treatment; NS: Not significant; PDS-CT: Primary debulking surgery followed by chemotherapy.

Table 2. Comparison of surgical invasiveness between primary debulking surgery and interval debulking surgery in retrospective studies.

Author	Treatment	Cases	Blood loss	Ascites	Bowel resection	Stoma therapy	Surgical complications	Stay in ICU	Postoperative stay	Ref.
Jacob *et al.* (1991)	PDS-CT	18	44% (>2000 ml)							[5]
	NACT	22	31% (>2000 ml)							
			NA							
Schwartz *et al.* (1999)	PDS-CT	206	1000 ml					1.26 days	11 days	[7]
	NACT	59	600 ml					1.03 days	7 days	
			p = 0.001					p = 0.01	p < 0.001	
Kayikçioğlu *et al.* (2001)	PDS-CT	158			16% (colon)	11%				[8]
	NACT	45			2% (colon)	0%				
					p = 0.01	p = 0.02				
Morice *et al.* (2003)	PDS-CT	28		39%	61%	7%	36% (severe)			[17]
	NACT	57		21%	19%	5%	7% (severe)			
				NS	p = 0.01	NS	p = 0.01			
Morice *et al.* (2003)	PDS-CT	34		56%	73%		53%	36%	20 days	[10]
	NACT	34		18%	18%		12%	12%	12 days	
				p < 0.001	p < 0.001		p < 0.001	p = 0.02	p < 0.001	
Everett *et al.* (2006)	PDS-CT	102		2.47 U	11%		15%	1.8 days	6 days	[12]
	NACT	98		3.02 U	16%		17%	1.5 days	6 days	
				NS	NS		NS	NS	NS	
Steed *et al.* (2006)	PDS-CT	66			5% (colon)					[14]
	NACT	50			2%† (colon)					
					NS					
Hou *et al.* (2007)	PDS-CT	109	1033 ml	2.4 U	22% (colon)	3%	34%	1.6 days	8.5 days	[15]
	NACT	63	546 ml	1.2 U	5%† (colon)	0%	28%†	2 days	5.7 days	
			p < 0.0001	p = 0.03	p = 0.004‡	NA	NS	NS	p < 0.0001	
Colombo *et al.* (2009)	PDS-CT	142			51%	4%	12% (major)		14 days	[16]
	NACT	61			51%	8%	13% (major)		14 days	
					NA	NS‡	NS		NS	

†Patients who did not underwent interval debulking surgery are not included in denominators.
‡Calculated using Fisher's exact test.
NA: Not available; NACT: Neoadjuvant chemotherapy-setting treatment; NS: Not significant; PDS-CT: Primary debulking surgery followed by chemotherapy.

several studies revealed significantly less invasiveness in the NACT group. For example, compared with the PDS group, the NACT group had a smaller amount of blood loss, lower rate or amount of blood transfusion, lower rate of bowel resection, lower rate of splenectomy, lower rate of surgical morbidities, shorter and less frequent stay in an intensive care unit (ICU) and shorter duration of hospitalization (Table 2). In addition to the benefits for the NACT group compared with the PDS-CT group described in Table 2, a significantly lower frequency of tumor invasion to the appendix (22 vs 80%; $p < 0.001$) [8], a lower rate of permanent colostomy (6 vs 24%; $p = 0.04$) [10], a lower rate of complications requiring surgery (3 vs 21%; $p = 0.03$) [10], and a shorter duration of surgery (211 vs 276 min; $p < 0.0001$) [15] were also reported.

Kuhn *et al.* [18], Hegazy *et al.* [19] and Lee *et al.* [20] conducted similar comparisons by nonrandomized, prospective studies (Table 3). Kuhn *et al.* offered a NACT protocol to patients with stage IIIC ovarian cancer with an estimated >500 ml of ascites [18]. Patients who agreed with the proposal received NACT, and the other patients who refused the proposal received conventional PDS-CT treatment. The characteristics of these two groups were not statistically different. Compared with the PDS-CT group, there was a higher proportion of optimal surgeries in the NACT group and an improved median survival time (MST) in the NACT group.

Hegazy *et al.* chose NACT or PDS-CT for the patients with stage III/IV ovarian cancer according to tumor resectability estimated by diagnostic laparotomy or laparoscopy. Patients who received NACT because of tumor unresectability were older than the patients who received PDS-CT (average age: 58.7 vs 53.6 years, respectively; $p = 0.04$) [19]. They reported no difference in proportion of optimal surgery and OS.

Lee *et al.* selected patients who received NACT for stage IIIC/IV ovarian cancer according to diagnoses based on imaging studies, such as computed tomography (CT) or MRI [20]. Patients who refused NACT received PDS-CT. The characteristics of these two groups were not statistically different. Compared with the PDS-CT group, there was a higher proportion of optimal surgery in the NACT group, but the improvement did not impact survival.

As for surgical invasiveness of NACT compared with PDS-CT, two studies [19,20] showed statistically significant reductions of blood loss, and one study showed a reduction in the duration of ICU stay and hospitalization [19].

Giannopoulos *et al.* compared the parameters of surgical invasiveness between PDS-CT (n = 29) and NACT (n = 35) in the treatment of stage IIIC/IV ovarian cancer [21]. Patients treated with NACT were nonrandomly selected according to the unresectability of tumors evaluated by laparoscopy or CT imaging. They demonstrated that median, intraoperative blood loss (500 vs 1000 ml; $p = 0.043$), median hospital stay (7 vs 8 days; $p = 0.005$), and possibility of admission to the ICU (5.7 vs 48.3%; $p < 0.001$) were significantly less in the NACT group than in the PDS-CT group.

From these retrospective or nonrandomized, prospective, comparative studies, NACT did not seem to compromise the survival of patients with advanced-stage ovarian, tubal or peritoneal cancer and seemed to greatly reduce surgical invasiveness.

Increased possibility of optimal surgery by NACT but rather poor survival in meta-analyses

Bristow *et al.* selected 22 cohorts from 21 studies and performed a meta-analysis in order to determine the OS and relative effect of multiple, prognostic variables in cohorts of patients with advanced-stage ovarian cancer treated with NACT (Table 4) [22]. The main selection criteria for the study were:

- Subjects were predominantly (>90%) patients with stage III/IV epithelial ovarian cancer;
- Subjects underwent NAC that included cisplatin (CDDP) or carboplatin (CBDCA);
- Subjects underwent NAC prior to cytoreductive surgery.

The target period for the Medline search was from 1 January 1989 to 30 September 2005. Using linear regression models, the effects of six variables (i.e., the proportion of maximal interval cytoreduction, stage IV disease, taxane use, median number of NAC cycles, median age and year of publication) on MST were assessed. The weighted mean MST was 24.5 months, and the weighted mean proportion of maximum cytoreduction was 65.0%. All variables other than median age were significantly correlated to MST. Each 10% increase in maximum cytoreduction was associated with a 1.9-month increase in MST, and each incremental increase in NAC cycles was associated with a 4.1-month decrease in MST. The authors reported that the survival outcome of NAC was equivalent to that of suboptimal PDS (>1 cm) followed by six cycles of CDDP and cyclophosphamide in the Gynecologic Oncology Group (GOG) 111 trial (24.5 vs 24 months). They concluded that NACT is associated with inferior OS compared with PDS-CT. However, this conclusion was not surprising because NACT was initially predominantly administered to older patients, with more advanced-stage disease, or patients with low PS, as mentioned earlier.

Recently, Kang *et al.* published the results of a similar meta-analysis (Table 4) [23]. The main selection criteria for this study were identical with the preceding study. The target period for the Medline search was extended until 30 June 2008. Although the number of selected studies were the same, seven studies were excluded and seven newer studies were included. To produce more reliable results, they chose a random-effects model instead of a simple linear regression model. The weighted mean MST was 27.5 months, and the weighted mean proportion of maximum cytoreduction was 70.0%. Again, the proportion of maximal interval cytoreduction, taxane use and year of publication were significantly associated with MST. However, the proportion of stage IV disease and median number of NAC cycles did not have a statistically significant association with MST. Furthermore, they examined ten comparative studies between NACT and PDS-CT, and analyzed the proportion of optimal cytoreduction. They found that the risk of suboptimal cytoreduction in the NACT group was reduced to 0.5 (95% CI: 0.29–0.86; $p = 0.012$) compared with the PDS-CT group, and concluded that NACT helped gynecologic oncologists to achieve an increased rate of optimal cytoreduction.

Table 3. Comparison between primary debulking surgery followed by chemotherapy and neoadjuvant chemotherapy-setting treatment in nonrandomized prospective studies.

Variables compared	Kuhn et al. [41]			Hegazy et al. [42]			Lee et al. [43]		
	PDS-CT (n = 32)	NACT (n = 31)	p-value	PDS-CT (n = 32)	NACT (n = 27)	p-value	PDS-CT (n = 22)	NACT (n = 18)	p-value
Patient factors									
Age (years)	66 (median)	61 (median)	NS	53.6	58.7	p = 0.04	46.8	45.0	NS
Performance status 2 (%)							32	28	NS
Stage IV (%)				56	59	NS	9	11	NS
Debulking surgery									
Performance of IDS		97% (30/31)			67% (18/27)			100% (18/18)	
Definition of optimal surgery	<2 cm	<2 cm		<1 cm	<1 cm		<2 cm	<2 cm	
Proportion of optimal surgery	63% (20/32)	84% (26/31)	p = 0.04	62% (20/32)	48% (13/27)	NS	46% (10/22)	78% (14/18)	p = 0.04
Blood loss				735 ml	420 ml	p = 0.02	1061 ml	620 ml	p = 0.04
Blood transfusion (median)	2 U	2 U	NS						
Duration of surgery	270 min	260 min	NS	190 min	150 min	NS			
Duration of ICU stay				4.4 days	1.7 days	p = 0.03			
Duration of hospitalization				15.9 days	10.5 days	p < 0.05	10.4 days	9.7 days	NS
Organ resection (n)									
Intestinal resection	11	9	NS				3	1	NA
Other organ resection				11 in total	4 in total	NS	2	0	NA
Complications (n)									
Ileus	3	0	NS						
Wound infection				2	2	NS			
Wound dehiscence	1	3	NS						
Fever >3 days	7	2	NS	7	1	NS			
Cystitis	2	1	NS						
Atelectasis	1	1	NS	1	1	NS			
Pleural effusion				2	0	NS			
Thromboembolism	1	1	NS	3	1	NS			
Outcome									
MST	23 months	42 months	p = 0.007	28 months	25 months	NS	55 months	53 months	NS
PFS				19 months	21 months	NS	17 months	15 months	NS

IDS: Interval debulking surgery; MST: Median survival time; NA: Not available; NACT: Neoadjuvant chemotherapy-setting treatment; NS: Not significant; PDS-CT: Primary debulking surgery followed by chemotherapy; PFI: Progression-free interval; PFS: Progression-free survival.

Final comparisons by prospective, randomized Phase III trials

Although NACT seems to be a promising approach for the treatment of patients with advanced-stage ovarian cancer, to become a standard treatment, it is necessary to demonstrate the superiority of NACT in treatment outcome or to show the noninferiority of NACT in treatment outcome and lower toxicity compared with PDS-CT. The most reliable and quickest way to demonstrate superiority or noninferiority of NACT is to conduct a randomized Phase III study comparing NACT and PDS-CT. Until now, at least four Phase III studies have begun in Europe [4,24], India (ClinicalTrials.gov identifier: NCT00715286 [101]) and Japan (Table 5) [25]. Subjects were patients with stage III/IV or IIIC/IV disease. In all studies, patients who were not suitable for PDS because of medical contraindication or poor PS were excluded. Target diseases included not only ovarian cancer but also tubal and peritoneal cancers in three European or Japanese studies.

The results of the earliest study by Vergote *et al.* in the EORTC trial (EORTC55971) have recently been published [4]. They compared NACT, which consisted of three cycles of NAC followed by IDS, and three cycles of postsurgical chemotherapy with PDS-CT, consisting of PDS followed by six cycles of postsurgical chemotherapy. The chemotherapy regimen was a combination of platinum and taxane chosen by each institution. Patients with biopsy- or cytology-proven stage IIIC/IV ovarian, tubal or peritoneal cancer were enrolled in the study. The study was open from September 1999 to December 2006 and 718 patients were enrolled. The outcome of 670 patients randomized into two treatment arms was analyzed. The largest residual tumor was ≤1 cm in diameter in 41.6% of patients after PDS and in 80.6% of patients after IDS. Although statistical analyses were not performed, postoperative infections, venous complications, fistula, hemorrhage and postoperative mortality tended to be lower after IDS in the NACT group than after PDS. The MST was 29 months in the PDS-CT group and 30 months in the NACT group, and the median progression-free survival (PFS) in both groups was 12 months in the intent-to-treat analysis. The hazard ratio for death in the NACT group compared with that in the PDS-CT group was 0.98 (90% CI: 0.84–1.13; p = 0.01 for noninferiority). They concluded that NACT was not inferior to PDS-CT as a treatment option for patients with bulky stage IIIC/IV ovarian carcinoma.

In March 2004, Kehoe *et al.* at the Medical Research Council Clinical Trials Unit (MRC-CTU) had started a Phase III part of a Phase II/III study named Chemotherapy or Upfront Surgery (CHORUS) [24]. The planned accrual number was 150 individuals in the Phase II part and 400 in Phase III part. The Phase III part of the study closed in August 2010. One of the distinct characteristics of the study was that patients were enrolled into the study based only on imaging diagnosis without cytological or histological confirmation. Other characteristics included that the chemotherapy regimen was a single-agent CBDCA or a combination with other agents chosen for each patient, and that the study was designed to demonstrate the noninferiority of NACT in OS by combining the data with that from the EORTC 55971 trial. The follow-up data are still accumulating, thus the results of the study have not yet been published.

The Japan Clinical Oncology Group (JCOG) conducted a similar Phase III study (JCOG0602) [25] after successfully completing a feasibility study (JCOG0206) [26,27]. Patients were enrolled into the study with a clinical diagnosis of stage III/IV ovarian, tubal or peritoneal cancer based on imaging studies, cytological diagnoses, serum CA125 (>200 U/ml) and carcinoembryonic antigen (CEA) titer (<20 ng/ml). Histological diagnosis, instead of cytology, was allowed in patients with available lesions without laparoscopy or laparotomy. Diagnostic laparoscopy or laparotomy after enrollment was not performed because their preceding feasibility study showed that target disease (i.e., stage III/IV ovarian, tubal and peritoneal cancer) can be diagnosed reliably using the same criteria adopted in this study. This means eliminating an extra surgical procedure for the purpose of the clinical trial in both treatment arms, and it has the advantage of allowing NACT to start earlier. Other special characteristics of the study were that the regimen of chemotherapy was restricted to a combination of paclitaxel (PTX) and CBDCA, the number of cycles of NAC was four, and the number of cycles of chemotherapy was eight in total, considering the advanced stage of the subjects.

Kumar *et al.* from the All India Institute of Medical Sciences are conducting a Phase III study. They set the target disease as stage IIIC/IV ovarian cancer [28,29]. Stage IV disease was restricted to disease upstaged owing to pleural effusion. Cytological or histological diagnosis was necessary before enrollment. The study started in November 2001 and is open according to information last updated on 14 July 2008 (ClinicalTrials.gov identifier: NCT00715286 [101]).

From the favorable results of the EORTC study, NACT may be one of treatment options available for patients with bulky stage IIIC or IV ovarian, tubal and peritoneal cancer. Furthermore, NACT would be expected to become a standard treatment for unselected patients with advanced ovarian cancer when favorable results are confirmed and several problems are resolved by the following studies.

Problems & questions about NACT

As NACT becomes more widely used, several problems that should be solved or questions that should be answered will arise. We will discuss some of these important issues next.

How should target diseases be diagnosed before NACT?

In the PDS-CT treatment setting, the aims of surgery are to confirm the diagnosis of ovarian, tubal or peritoneal cancer; determine an accurate stage of the disease; and reduce bulky tumors.

We understand that it is necessary in principle to perform diagnostic laparoscopy or laparotomy in order to confirm diagnosis and stage of the disease before chemotherapy also in the setting of NACT. However, the procedure may spoil the merits of NACT, such as less-invasiveness and immediate initiation of treatment. How to quickly and accurately confirm the diagnosis of the disease before NACT is a major problem.

The MRC-CTU study allowed patients to enroll on the basis of diagnoses using imaging studies without cytological or histological confirmation [24]. To exclude gastrointestinal cancer,

Table 4. Results of meta-analyses for neoadjuvant chemotherapy-setting treatment.

	Bristow *et al.* (2009)	Kumar *et al.* (2009)
Major selection criteria:	– Stage III/IV>90%	
	– NAC regimen included CDDP or CBDCA	
	– NAC was administered before cytoreductive surgery	
Target period for Medline search	1 January 1989–30 September 2005	1 January 1989–30 June 2008
Studies (n)	21	21
Weighted mean values		
MST	24.5 months	27.5 months
Taxane use (%)	47.7	48.2
Optimal cytoreduction (%)	65.0	70.0
Stage IV (%)	27.4	28.9
Age (years)	61.1	60.4
Univariate analysis		
Year of publication	p = 0.004 (1.1 months/year)	p = 0.002
Rate of taxane use	p < 0.0005 (1.6 months/10%)	p = 0.007
Rate of optimal cytoreduction	p = 0.012 (1.9 months/10%)	p = 0.012
Rate of stage IV patients	p = 0.002 (-2.3 months/10%)	p = 0.101 (NS)
NAC cycles (n)	p = 0.046 (-4.1 months/cycle)	p = 0.701 (NS)
Age	p = 0.448 (NS)	NA
Statistical method	Simple linear regression model	Random-effects model

CBDCA: Carboplatin; CDDP: Cisplatin; MST: Median survival time; NA: Not assessed; NAC: Neoadjuvant chemotherapy; NS: Not significant.

the tumor marker criterion (CA125/CEA ratio >25) could be used. After enrollment, patients assigned to NACT required laparoscopic biopsy, image-guided biopsy or fine-needle biopsy. Although the rate of benign disease or the rate of other malignancy may be revealed by the study, at present we cannot recommend starting NACT by using only diagnoses based on imaging tests and serum tumor marker results.

Schwartz *et al.* evaluated the role of cytology in the pretreatment diagnosis of advanced-stage ovarian cancer [30]. They performed NACT for patients with advanced-stage ovarian cancer diagnosed based on clinical findings. Pretreatment cytology slides of ascitic fluid were reviewed and categorized as consistent with ovarian cancer, not consistent with ovarian cancer, or insufficient. Pathological diagnosis at IDS and cytological diagnosis were compared in 47 patients. In total, 42 out of 43 patients with cytology consistent with ovarian cancer had ovarian cancer and one had no pathologic evidence of disease. Two out of three patients with cytology not consistent with ovarian cancer had ovarian cancer, and one had a mesonephric adenocarcinoma. The authors conclude that cytology has proven to be extremely helpful in supporting clinical impressions of apparently advanced-stage ovarian cancer.

Freedman *et al.* compared diagnostic strategies for predicting final pathology of ovarian cancer among 149 patients who underwent NACT [31]. The initial diagnosis was based on cytology in 108 patients, histology in 26 patients and only clinical factors (imaging studies and CA125) in 15 patients. Pathological diagnoses of disease in four patients who obtained complete pathological responses were determined to be consistent with ovarian cancer. The diagnostic accuracy of the cytology, histology and clinical factors alone was 98, 96 and 87%, respectively (p = 0.04). The authors conclude that diagnosis of epithelial ovarian cancer based on cytology and histology are superior to clinical factors alone.

The JCOG0206 study assessed the accuracy of clinical diagnosis based on imaging tests, cytology from ascites, pleural effusion or tumor, and tumor markers (CA125 >200 U/ml and CEA <20 ng/ml) [27]. All enrolled patients underwent diagnostic laparoscopy in order to determine accurate diagnoses. The disease was ovarian, tubal or peritoneal cancer in 100% (56 out of 56 patients), and stage III/IV in 95% (53 out of 56 patients). As for the stage of the disease, laparotomy performed immediately after the diagnostic laparoscopy revealed stage IIIb disease in one out of the aforementioned three patients. The results suggest that appropriate target diseases for NACT can be diagnosed with >90% accuracy by clinical diagnoses based on findings including cytology, according to the Bayesian statistical methods.

From these studies, it can be concluded that cytological examination of ascites, pleural effusion or tumor in addition to imaging diagnosis and tumor markers may be necessary before NACT for accurate diagnosis of advanced-stage ovarian, tubal or peritoneal cancer, unless we select diagnostic laparotomy or laparoscopy.

Table 5. Phase III randomized studies comparing neoadjuvant chemotherapy-setting treatment and primary debulking surgery followed by chemotherapy.

Study group	EORTC	CTU-MRC	JCOG	All India Institute of Medical Sciences
Study name or ID	EORTC55971	CHORUS	JCOG0602	ID I473
Principal Investigator	Vergote IB	Kehoe S	Yoshikawa H	Kumar L
Country or area	Europe	UK	Japan	India
Target disease origin	Ovary, tube and peritoneum	Ovary, tube and peritoneum	Ovary, tube and peritoneum	Ovary
Stage	Stage IIIC/IV	Stage III/IV	Stage III/IV	Stage IIIC + IV (pleural effusion)
Phase of the study	III	II/III	III	III
Eligibility				
Necessity for biopsy/ cytology	Biopsy is preferentially necessary FNA cytology is allowed	Neither biopsy nor cytology is necessary	Cytology is necessary biopsy is allowed	Either biopsy or cytology is allowed
Tumor marker	CA125/CEA ratio >25†	CA125/CEA ratio >25‡	CA125 >200 U/ml; CEA <20 ng/ml	Normal CEA
Regimen	Platinum (CDDP or CBDCA) + taxane (PTX or DTX)	CBDCA or CBDCA based	PTX + CBDCA	PTX + CBDCA
Chemotherapy cycles (n)	NAC: 3/total: 6	NAC: 3/total: 6	NAC: 4/total: 8	NAC: 3/total: 6
Planned number of patients	704	150 (Phase II) + 400 (Phase III)	300	180
Start date	21 September 1998	March 2004 (Phase III part)	17 November 2006	November 2001
Accrual period	4 years	4 years	3 years	5 years
Status of the study	Closed on 6 December 2006	Closed on 31 August 2010	Open	Open
Design of the study	Noninferiority	Noninferiority (combined with EORTC patients)	Noninferiority	Noninferiority (probably)
Database registration ID	NCT00003636	NCT00075712	UMIN000000523	NCT00715286
Registered day	1 November 1999	9 January 2004	17 November 2006	14 July 2008

†Supplementary criterion to omit investigations for gastrointestinal or colon cancer in whom cytology was used for the confirmation of malignancy.
‡Supplementary criterion to omit investigations for gastrointestinal cancer.
CBDCA: Carboplatin; CDDP: Cisplatin; CEA: Carcinoembryonic antigen; CHORUS: Chemotherapy or Upfront Surgery; CTU-MRC: Medical Research Council Clinical Trials Unit; DTX: Docetaxel; EORTC: European Organization for Research and Treatment of Cancer; FNA: Fine-needle aspiration; JCOG: Japan Clinical Oncology Group; NAC: Neoadjuvant chemotherapy; PTX: Paclitaxel.

When should we perform IDS?

In earlier studies of NACT, the number of cycles of NAC was sometimes based on the response to NAC. Occasionally, the number of cycles of NAC reached more than six cycles in each patient base [7,32,33], while in more recent studies, the number of cycles of NAC usually settled at three or four cycles. However, the optimal number of cycles of NAC has not yet been determined. Some reports paid attention to the number of NAC cycles.

Lim and Green administered NAC to 30 patients with stage III/IV ovarian cancer [34]. The NAC regimen consisted of CBDCA, ifosfamide, and mesna for a median of three cycles. Objective responses were observed in 13 patients, including five patients who achieved a complete response after three cycles. This study showed that more than three cycles of NAC did not increase the number of complete responses, but were associated with greater toxicity. The use of three cycles was optimal in terms of the response rate, feasibility of beneficial surgery, and so on.

In a retrospective study by Loizzi *et al.*, 30 women were treated with NACT [11]. The mean number of NAC cycles was 4.1, and the NAC regimen consisted of CDDP and cyclophosphamide in 12 patients and PTX and CBDCA in 18 patients. In this study, the outcome of patients who underwent ≤three cycles of NAC were compared with those who received >three cycles. No statistically significant difference between the two groups was observed

Table 6. Summary of interval debulking surgery outcomes following neoadjuvant chemotherapy composed of platinum and taxane combination.

Study (year)	Patients (n)	NAC: Median cycles (n)	NAC: Regimen	Performance rate and results of IDS: Performance rate %	RD <2 cm %	RD <1 cm %	RD = 0 %	Type of study	Ref.
Kuhn *et al.* (2001)	31	3	CBDCA + PTX	97 (30/31)	84 (26/31)†	NR	32 (10/31)†	Prospective	[18]
Chan *et al.* (2003)	17	3	Platinum + PTX	76 (13/17)	59 (10/17)†	NR	29 (5/17)†	Retrospective	[52]
Morice *et al.* (2003)	57	3	Platinum + PTX	100 (57/57)	84 (48/57)	NR	51 (29/57)	Retrospective	[17]
Le *et al.* (2005)	61	3	CBDCA + PTX	100 (61/61)	80 (49/61)	54 (33/61)	26 (16/61)	Retrospective	[50]
Le *et al.* (2006)	58	3	CBDCA + PTX	100 (58/58)	79 (46/58)	55 (32/58)	28 (16/58)	Retrospective	[51]
Lee *et al.* (2006)	18	3	CDDP + PTX	100 (18/18)	78 (14/18)	NR	NR	Prospective	[20]
Tiersten *et al.* (2009)	58	3	CBDCA + PTX	62 (36/58)	NR	45 (26/58)†	NR	Prospective	[53]
Pölcher *et al.* (2009)	44	2	CBDCA + DTX	98 (43/44)	NR	73 (32/44)†	43 (19/44)†	Prospective	[35]
Pölcher *et al.* (2009)	44	3	CBDCA + DTX	91 (40/44)	NR	68 (30/44)†	27 (12/44)†	Prospective	[35]
Onda *et al.* (2009)	53	4	CBDCA + PTX	89 (47/53)	NR	72 (38/53)	55 (29/53)	Prospective	[27]
Vergote *et al.* (2010)	322	3	Platinum + taxane	91 (292/322)‡	NR	74 (239/322)‡	47 (152/322)‡	Prospective	[4]
Total Number	763			91 (695/763)	80 (193/242)	67 (430/640)	42 (288/687)		
Range	17–322	NAC 2–4 cycles		62–100	59–84	45–74	26–55%		

†Frequencies are recalculated to include all patients into denominators.
‡Frequencies are calculated from the number of patients in per-protocol analysis.
CBDCA: Carboplatin; CDDP: Cisplatin; DTX: Docetaxel; IDS: Interval debulking surgery; NAC: Neoadjuvant chemotherapy; NR: Not recorded, PTX: Paclitaxel; RD: Residual disease.

with respect to the response to NAC (p = 0.82) and median survival (p = 0.74). The issue of whether women who received ≤three cycles of NACT benefited more than those who had >three cycles could not be answered in their study.

Colombo *et al.* analyzed prognostic factors in 61 patients treated with NACT in a retrospective study [16]. IDS was performed after three to six cycles of NAC consisting of platinum and PTX in 39 patients, and platinum and another agent in 22 patients. In addition to the response to NAC (p = 0.04), the range of mesenteric involvement (p = 0.025), performance of digestive resection (p = 0.01), residual tumor after IDS (p = 0.014) and number of NAC cycles (three or four vs >four; p = 0.04) were identified as statistically significant prognostic factors in univariate analysis. Median survival of patients treated with three or four cycles of NAC was much better than that of patients treated with >four cycles of NAC (31 vs 20 months, respectively).

Pölcher *et al.* prospectively compared two and three cycles of NAC in NACT, consisting of IDS and six cycles of combination regimen of CBDCA and docetaxel in total [35]. A total of 44 patients were each allocated to two or three cycles of the NAC arm. There were no significant differences in PFS (12.5 vs 12.2 months; p = 0.77) and OS (28.4 vs 24.1 months; p = 0.87). The authors concluded that a treatment schedule with two preoperative cycles is a reasonable option for NACT.

Bristow *et al.* demonstrated in their meta-analysis that each incremental increase in NAC cycles was associated with a 4.1-month decrease in MST (p = 0.046), and one of their important conclusions was that definitive operative intervention should be undertaken as early as possible in the treatment program [22]. On the contrary, Kang *et al.* demonstrated in their meta-analysis that the between-study variation of the number of NAC cycles did not influence survival (p = 0.701) [23]. The difference between the two studies probably results from differences in both selection of studies and statistical methods. In any case, we cannot draw a definitive conclusion from these meta-analyses.

From these aforementioned studies, it seems that three or four cycles may be the most likely optimal amount, and two cycles may be a reasonable option for the optimal number of NAC cycles. To decide the number of NAC cycles, individual evaluation of tumor resectability discussing in the following section may be of use. However, further evaluation is still necessary.