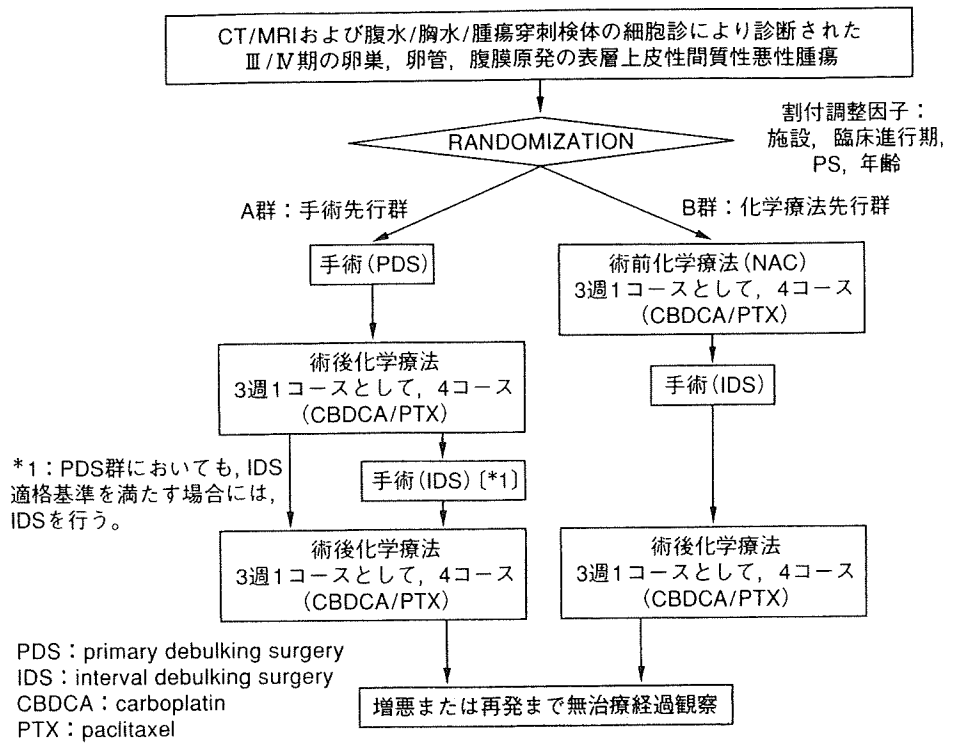

図2　JCOG0602 シェーマ

CT，MRI などの画像診断，腹水，胸水や腫瘍穿刺液の細胞診，および腫瘍マーカーにより，NAC 療法の対象となる症例を正確に診断できることを確認し，将来の第Ⅲ相試験において診断確認のための手術を省略することを検討することであった。

JCOG 0206 試験のプロトコール治療の概要を図1に示す。この試験では，画像診断，細胞診および腫瘍マーカーにて卵巣癌，卵管癌，腹膜癌のⅢ/Ⅳ期と診断されて登録された全症例に対して，診断的腹腔鏡により臨床的診断の確認を行った。診断が確認された症例には，4コースの NAC，IDS，4コースの術後化学療法よりなる治療が行われた。化学療法は，卵巣癌に対する標準化学療法である TC 療法とし，PTX は 175 mg/m^2，CBDCA は AUC6 を初回投与量とした。

Primary endpoint は，試験治療完了時点での完全腫瘍消失割合，secondary endpoint は臨床診断の正診割合，無増悪生存割合，全生存割合など（endpoint の正確な定義は文献を参照）であった。登録期間1年，観察期間3年，予定登録数 56 症例の予定で開始された試験は，ほぼ予定どおり終了し，現在最終結果公表の準備中である。結果の詳細をお示しすることはできないが，この試験により NAC 療法の有効性，安全性が再確認され，また第Ⅲ相試験において診断確認のための手術を省略することが許容されると判断された。

2）NAC 療法と標準治療の第Ⅲ相無作為比較試験

JCOG0206 試験の結果を受け，JCOG の婦人科腫瘍グループでは，第Ⅲ相比較試験「Ⅲ期/Ⅳ期卵巣癌，卵管癌，腹膜癌に対する手術先行治療 vs. 化学療法先行治療のランダム化比較試験」(JCOG0602)[17]を，2006 年 11 月より行っている。

JCOG0602 試験の治療の概要を図2示す。対象は，Ⅲ期/Ⅳ期卵巣癌，卵管癌，腹膜癌で，適格規準の詳細は JCOG0206 とほぼ同じである。化学療法は TC 療法である。

この試験では，適格規準を満たし，Ⅲ期/Ⅳ期

卵巣癌，卵管癌，腹膜癌と診断され，登録された症例は，診断的腹腔鏡による診断確認を行うことなく手術先行の標準治療群，あるいは化学療法先行のNAC群に割り振られ治療を開始する。NAC群ではNAC4コース，IDS，術後化学療法4コースからなる治療を行う。手術先行群では，PDSの後，8コースの化学療法であるが，規準を満たせば化学療法4コース後にIDSを行う場合もある。PDS後のIDSの有用性に関しては統一した見解が得られていないことから，PDSにてsuboptimal surgeryの場合もIDSを必須とはしていない。

Primary endpointは，全生存割合，secondary endpointは，手術に関連した侵襲（手術回数，輸血必要量など），試験治療完了時点での完全腫瘍消失割合，無増悪生存割合など（endpointの正確な定義は文献を参照）である。登録期間3年，観察期間5年，予定登録数300症例の予定で開始され，現在症例登録中である。

この試験は，EORTCの第Ⅲ相試験同様，NAC療法が標準治療に対して，効果の点で劣らないことを検証する非劣性試験である。NAC療法では手術に関連した侵襲（手術回数，出血量，輸血必要量など）の軽減が期待されるため，効果の非劣性が証明され治療侵襲の軽減も示されれば，NAC療法が進行卵巣癌の新しい標準治療になると考えられる。

おわりに

Retrospective studyの結果から，進行卵巣癌に対するNAC療法は，治療成績およびQOL（quality of life）の改善が期待される治療ではあるが，診断が不正確となる可能性，手術の機会を逸する可能性，薬剤耐性の出現を助長する可能性，根治性を損なう可能性などのriskをも有している。現時点ではあくまでも全身状態により初回手術不能あるいは切除不能な症例に対する代替的な治療と考えられる。現在，EORTCやJCOGで行われている，標準治療との比較試験により，手術可能な症例も含めた進行卵巣癌におけるNAC療法の役割が明らかとなることが期待される。

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Is randomized trial of neoadjuvant chemotherapy of ovarian cancer necessary?

To the Editor,

I have read the interesting paper of Onda et al. [1] in the January issue. There is a well concerted effort to see the efficacy of neoadjuvant chemotherapy in advanced ovarian cancer by large randomized trials. Two of them are EORTC protocol 55971 and Japan Clinical Oncology Group Study JCOG0602. With the high response rate of carboplatin-paclitaxel, benefit of neoadjuvant chemotherapy must be reaching a higher number of sufferers now. I have noticed an interesting finding of Schwartz (2008) [2] which I think is very correct. If 23% of stage III and 8% of stage IV are amenable to satisfactory cytoreduction (Schwartz 2008) and anecdotal about 70% ovarian cancer is in the advanced stage how come primary cytoreduction can compete with neoadjuvant chemotherapy as is done in RCTs. This is because a number of patients get fully treated in the neoadjuvant arm and is clearly much above those in the primary cytoreduction arm in practice. How can they be compared? Universality of neoadjuvant arm due to 90% response rate of carbo-pacli should negate any such competition and comparison. A much greater number of such ovarian cancers must be treated now. At least my experience is like this. Many more women must be living for many more years. The total sum of life year saved by neoadjuvant is important now and need be calculated.

Conflict of interest statement
Author has no conflict of interest to declare.

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A phase III randomized trial comparing neoadjuvant chemotherapy and upfront debulking surgery is indispensable as a basis for changing the standard treatment of advanced Müllerian cancer

To the Editor,

We appreciate the question raised by Dr. Chinmoy K. Bose regarding our ongoing phase III study [1], which follows on from a feasibility study of neoadjuvant chemotherapy (NAC) published in a recent issue of this journal [2]. We would like to reply by stating our opinion for the necessity of randomized trials that compare NAC-setting treatment (NACT) and primary debulking surgery followed by chemotherapy (PDS-CT).

As Dr. Bose mentioned, considering the high response rate to TC chemotherapy (paclitaxel and carboplatin) and the disappointingly low rate of successful cytoreduction in primary debulking surgery, NACT is expected to improve the dismal prognosis of advanced Müllerian cancer patients. We had also expected a favorable treatment outcome using NACT, and thus conducted the Japan Clinical Oncology Group (JCOG) 0206 study. In this study, we confirmed the promising treatment outcome and the safety of NACT. However, these results were insufficient to prove the superiority of NACT compared to PDS-CT. To date, several studies have compared the results of treatment with either NACT or PDS-CT for advanced ovarian cancer (Table 1). With the exception of the studies by Jacob et al. [3], Kuhn et al. [4], and Vrščaj and Rakar [5], NACT was administered to elderly patients, patients who had more advanced disease or had a lower performance status. Although the selection of treatment in these studies was highly biased, and as such was unfavorable to NACT, most of the studies yielded comparable results using NACT that were not significantly different to those obtained using PDS-CT. Moreover, in a non-randomized phase II study, Kuhn et al. reported a better outcome for the patients receiving NACT compared to those receiving PDS-CT. We thus consider that NACT is potentially promising, although on the basis of the currently available data we are as yet unable to conclude that NACT is superior to PDS-CT. Indeed, the possibility remains that NACT is rather inferior compared to PDS-CT.

In general, in order to change the standard treatment for advanced Müllerian cancer, it is necessary to demonstrate the superiority of NACT in treatment outcome or to show the non-inferiority of NACT in terms of treatment outcome and lower toxicity compared to PDS-CT. The most reliable and quickest way to demonstrate the superiority or non-inferiority of NACT is, we believe, to conduct a randomized phase III study comparing NACT and PDS-CT. Until we are able to obtain conclusive evidence that NACT is superior to PDS-CT as a standard treatment for advanced Müllerian cancer, we should refrain from selecting an easy way to administer NACT for all cases of advanced Müllerian cancer.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

Table 1
Comparison of treatment outcomes between NACT and PDS-CT.

Author	Treatment	Number	Median survival		5-year survival	
			Time (months)	Statistical difference	Rate	Statistical difference
Jacob et al. [3]	PDS-CT	18	18			
	NACT	22	16	NS		
Onnis et al. [6]	PDS-CT	284			21%	
	NACT	88			19%	NS
Schwartz et al. [7]	PDS-CT	206	26			
	NACT	59	13	NS		
Kayikçioğlu et al. [8]	PDS-CT	158	38		24%	
	NACT	45	34	NS	30%	NS
Kuhn et al. [4]	PDS-CT	32	23			
	NACT	31	42	$p = 0.007$		
Vrščaj and Rakar [5]	PDS-CT	55	26			
	NACT	20	25	NS		
Loizzi et al. [9]	PDS-CT	30	40			
	NACT	30	32	NS		
Hegazy et al. [10]	PDS-CT	32	28			
	NACT	27	25	NS		
Lee et al. [11]	PDS-CT	22	55			
	NACT	18	53	NS		
Everett et al. [12]	PDS-CT	102	42			
	NACT	98	33	NS		
Inciura et al. [13]	PDS-CT	361	25			
	NACT	213	24	NS		
Hou et al. [14]	PDS-CT	109	47			
	NACT	63	46	NS		

PDS-CT: primary debulking surgery followed by chemotherapy, NACT: neoadjuvant chemotherapy-setting treatment, NS: not significant.

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Feasibility study of neoadjuvant chemotherapy followed by interval debulking surgery for stage III/IV ovarian, tubal, and peritoneal cancers: Japan Clinical Oncology Group Study JCOG0206☆,☆☆

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ABSTRACT

Background. To assess the safety and efficacy of neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) for müllerian carcinomas, such as ovarian, tubal, and peritoneal cancers, and to determine whether we can omit diagnostic laparoscopy before treatment initiation, a feasibility study was performed.

Methods. Eligible patients had presumed stage III/IV müllerian carcinomas clinically diagnosed by imaging studies, cytology, and tumor markers. All patients underwent diagnostic laparoscopy to confirm the clinical diagnosis. Four cycles of paclitaxel and carboplatin were administered as NAC, followed by interval debulking surgery and an additional 4 cycles of chemotherapy. The primary end point was the proportion of patients achieving clinical complete remission (cCR) among all stage III/IV müllerian carcinomas confirmed by diagnostic laparoscopy. The major secondary end point was the positive predictive value (PPV) of clinical diagnosis.

Results. Fifty-six patients were enrolled into the study. The PPV of overall clinical diagnosis for the tumor origin, histology, and stage was 95% (53/56). Fifty-three patients received the protocol treatment starting with NAC. IDS was performed in 89% (47/53) of patients. Complete resection without residual tumors was achieved in 55% (29/53) and residual tumors became <1 cm in 17% (9/53) of patients. Twenty-two patients (42%) achieved cCR after completion of the treatment. The median overall and progression-free survival was 45 and 14 months, respectively.

Conclusion. NAC without diagnostic laparoscopy for advanced müllerian carcinomas holds sufficient promise to be compared with direct surgery in a phase III trial.

Introduction

The standard treatment for advanced müllerian cancer (MC), such as ovarian, tubal, and peritoneal cancer, is primary debulking surgery (PDS) and postoperative chemotherapy. Previous studies have demonstrated that optimal debulking at the time of primary surgery improves patient survival [1–3]. Though optimal resection rates of experienced centers on gynecologic oncology reach up to 90%, optimal debulking can be achieved in only 30–60% of stage III/IV ovarian cancers in average institutions [1,2].

Retrospective analyses [4–7] have revealed that survival of the patients who received neoadjuvant chemotherapy (NAC) is comparable to that of patients who underwent direct PDS, even though the former group was older with more advanced disease and had a poorer performance status (PS). Thus, NAC appears to be useful at least for patients with far advanced ovarian cancer. However, NAC is allowed as an alternative to the standard treatment only in MC

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☆☆ This study is registered with Clinicaltrials.gov (identification number: NCT00112086) and with UMIN-CTR [www.umin.ac.jp/ctr/] (identification number: C000000005).

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patients with apparently unresectable bulky tumors or poor PS (NCCN guidelines).

European Organization for Research and Treatment of Cancer (EORTC) started a phase III study comparing NAC with the standard treatment for advanced MC [8] and thereafter, Medical Research Council Clinical Trials Unit (CTU-MRC) started similar phase III study in 2004 [identification number in Clinicaltrials.gov: NCT00075712]. In 2002, we also planned to conduct a phase III trial to compare NAC and direct PDS. At that time, we had little experience with NAC for treatment of advanced MC, including the possibly resectable cases. Thus, we planned to conduct a feasibility study of NAC before a phase III trial. The main purpose of the study was to assess the safety and efficacy of NAC with paclitaxel and carboplatin for advanced MC. The other purpose was to determine whether omission of the diagnostic laparoscopy (DLS) before NAC for advanced MC is possible by the use of imaging studies, cytological findings, and tumor markers. According to the current treatment guidelines, DLS or laparotomy to confirm the diagnosis and stage before NAC is mandatory. However, these procedures lead to a delay in the initiation of treatment and nullify the advantage of less invasiveness of NAC. Therefore, if ethically and medically acceptable, it seems desirable to omit the diagnostic procedure in the phase III trial.

The study protocol was designed by the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG) and was approved by the Clinical Trial Review Committee of JCOG on 6 December 2002 and activated on 14 January 2003 [9].

Patients and methods

Patient selection

The study subjects were patients with presumed stage III/IV MC clinically diagnosed by imaging studies (CT [computed tomography] or MRI [magnetic resonance imaging]) and cytological examination of ascites, pleural effusions, or fluids obtained by tumor centesis. Stage IV disease was diagnosed according to the routine FIGO staging. Diagnosis of stage III disease based on retroperitoneal lymph node metastasis was allowed only when swollen nodes were suspicious for metastasis by imaging studies and >2 cm in diameter. Malignancies of other origins, such as the breast and the digestive tract, when suspected from symptoms, physical examinations, or imaging studies, were ruled out by ultrasonography, endoscopy, or opaque enema. To efficiently rule out malignancies originating from the digestive tract, the criteria for the tumor markers were set as CA125 >200 U/ml and CEA <20 ng/ml. The further inclusion criteria were as follows: clinically deemed to be a candidate for debulking surgery without evidence of brain, bone, bone marrow, or multiple lung or liver metastases; presence of at least one measurable lesion; previously untreated for these malignancies and no history of treatment with chemotherapy or radiotherapy even for other diseases; aged between 20 and 75 years; Eastern Cooperative Oncology Group (ECOG) PS of 0 to 3; adequate organ functions; and written informed consent.

The exclusion criteria include intestinal occlusion necessary for surgical treatment; hypersensitivity to alcohol; and severe medical complications. More details of eligibility criteria were described previously [9].

Treatment plan

After enrollment, DLS was performed. Inspection of peritoneal cavity and biopsy from the main tumor or metastatic tumors was performed to confirm the clinical diagnosis of the origin, histology, and stage.

Four cycles of a combination of intravenous paclitaxel [over 3 h; day 1] and carboplatin [day 1], i.e., TC, were administered every 3 weeks as NAC. Before paclitaxel was administered, standard short premedication was used to avoid anaphylactic reactions. The dose of carboplatin was calculated from the formula of Calvert [10]. The creatinine clearance by the Cockcroft–Gault [11] equation was used as the glomerular filtration rate (GFR) in the formula. The creatinine clearance, body weight, and body surface area on entry into the study were used during all 4 cycles of NAC.

Interval debulking surgery (IDS) was performed after the fourth cycle of NAC, unless there was evidence of disease progression. The standard procedures in IDS comprised total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and maximal debulking of the metastatic tumors. Systematic pelvic and/or paraaortic lymphadenectomies were allowed, but not included in the standard procedure.

After IDS, an additional 4 cycles of chemotherapy was administered as postoperative chemotherapy (8 cycles in all). The creatinine clearance, body weight, and body surface area between IDS and the first cycle of postoperative chemotherapy were used during all 4 cycles of postoperative chemotherapy.

Modification of the treatment

Four dose levels were set for both paclitaxel and carboplatin. The initial dose of paclitaxel was 175 mg/m^2 (level 0), and the dose was reduced to 130 mg/m^2 (level −3) in decrements of 15 mg/m^2. The dose of carboplatin was reduced from the starting targeted area under the curve (AUC) of 6 (level 0) to 5, 4.5, and 4 (level −3) in a step-by-step manner. Even when the toxicities disappeared, the dose level was not restored to the previous dose level. The level during NAC was carried forward to postoperative chemotherapy.

Hematological toxicities that required a dose reduction of 1 level of both agents were grade 4 neutropenia observed in an interval of >3 days in the same cycle, neutropenic fever observed in an interval of >1 day in the same cycle, and grade 3 thrombocytopenia. Neurotoxicity that required a dose reduction of 1 level of paclitaxel alone was grade 2 sensory-neuropathy.

When the toxicities that required dose reduction were observed at the lowest level, or grade 3 sensory-neuropathy was observed at any dose level, the treatment protocol was discontinued. The other discontinuation criteria were progression of the disease, delay of chemotherapy for >2 weeks, delay of surgery from the planned time period, grade 3 allergic-reaction/hypersensitivity, grade 4 non-hematological toxicities, and misdiagnosis confirmed by DLS.

End points

The primary end point was the proportion of clinical complete remission (%cCR) among all patients with stage III/IV MC, whose diagnosis was confirmed by DLS. Clinical complete remission was defined as the disappearance of all lesions on CT or MRI, no pleural effusion on chest radiography, and a serum CA125 level of <20 U/ml upon completion of the treatment.

The secondary end points were positive predictive value (PPV) of the clinical diagnosis with regard to the origin and histology, FIGO stage, and overall clinical diagnosis among all the participants. The PPV of overall clinical diagnosis was the end point to decide whether we could omit DLS in the subsequent phase III study. Because laparoscopy was performed only in patients diagnosed as stage III/IV MC by clinical findings, it was not possible to use sensitivity or specificity to evaluate the accuracy of clinical diagnoses, therefore we adopted PPV. With regard to the histology, the histological diagnosis compatible with any of the epithelial ovarian carcinomas was considered as correct diagnosis. Concerning the diagnosis of stage, surgical stage III was considered as correct even if substage was different from prelaparoscopic stage III substage. Regarding prelaparoscopic stage IV disease, the diagnosis of the stage was correct irrespective of the peritoneal findings on DLS.

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The other secondary end points were the response rate to NAC, the proportion of patients who underwent IDS, progression-free survival (PFS) among patients whose clinical diagnosis was confirmed by laparoscopy, the operative morbidity, the adverse events, and the overall survival (OS) among all the enrolled patients. The response to NAC was assessed according to the RECIST (Response Evaluation Criteria In Solid Tumor) [12]. Grading of the adverse events was performed based on NCI-CTC (National Cancer Institute-common toxicity criteria) ver. 2.0.

Study design and statistical methods

The study was planned as a single-stage safety and efficacy study. Sample size calculation was primarily based on the binominal test for the primary end point. Forty-four patients were required when expected %cCR of 40% and an acceptable lowest %cCR of 20% with a one-sided alpha error of 0.05 and a beta error of 0.1. Additionally, the PPV of overall prelaparoscopic diagnoses was to be sufficiently confident to enable the omission of laparoscopy in the subsequent phase III study. Thus, Bayesian monitoring of PPV was planned, and it required 56 patients to have a 10% or lower Bayesian posterior probability that PPV is less than 90% in case of 3 false-positive patients assuming the prior distribution of Beta (9,1). The target sample size was determined to be 56, which is also sufficient for the primary end point. The planned accrual period was 1 year, and the follow-up period was 3 years. All analyses were performed using the SAS software release 9.1 (SAS Institute, Cary, NC).

Results

Patient characteristics

Fifty-six women were entered between January 2003 and February 2004. All but one patient were eligible for the study. The ineligible patient once fulfilled the eligibility 1 week before enrollment. However, the blood examination just before enrollment showed a slightly lower WBC and ANC than the eligibility. This patient was included in the following analysis, though this patient dropped out of the study during NAC due to myelo-suppression. The PS of all 56 patients at enrollment was 0 in 28 patients, 1 in 18 patients, 2 in 7 patients, and 3 in 3 patients. The median age at enrollment was 55 (range, 33–73) years. The median follow-up period of the living patients was 39 (range, 34–46) months at the data cutoff in February 2007.

Accuracy of the clinical diagnosis

DLS was performed in all enrolled patients. Laparoscopic findings and histological findings revealed all 56 patients had MC with a histology corresponding to epithelial ovarian carcinoma. Concerning the stage of the disease, the diagnosis was stage III/IV in 53 patients by laparoscopic findings in combination with prelaparoscopic findings of the presence of distant metastases, malignant pleural effusion, and lymph node metastases. The PPV of prelaparoscopic diagnosis concerning the origin and histology was 100% (56/56), and both the PPVs of prelaparoscopic diagnosis concerning the stage and overall diagnosis were 95% (53/56). The histology of the diseases misdiagnosed in stage were endometrioid adenocarcinoma in 2 and serous adenocarcinoma in 1. Table 1 shows the prelaparoscopic and laparoscopic diagnoses of the disease.

Compliance to the treatment

The compliance to the treatment protocol is depicted in Fig. 1. Six patients successfully completed the treatment algorithm once they were off protocol due to toxicities. In one patient, after the discontinuation criteria were fulfilled during NAC, a similar treatment consisting of 3 cycles of chemotherapy as NAC, IDS and 6 cycles of postoperative chemotherapy was performed. In the other 5 patients, the same treatment was administered at a reduced dose and/or a delayed schedule.

Table 1
Prelaparoscopic and laparoscopic diagnosis of the disease

	Prelaparoscopic diagnosis		Laparoscopic diagnosis	
Origin[a]	Ovary	48	Ovary	47
	Tube	4	Tube	7
	Peritoneum	10	Peritoneum	12
Histology[b]	Adenocarcinoma (not specified)	56	Adenocarcinoma (not specified)	18
			Serous	29
			Mucinous	2
			Endometrioid	5
			Undifferentiated	2
T classification	T1c	0	T1c	1
	T2c	4	T2c	5
	T3	52	T3a	0
			T3b	12
			T3c	38
Stage	III	38	IC	1
	IV	18	IIC	2
			IIIA	0
			IIIB	4
			IIIC	31
			IV	18

[a] Selection of 2 or 3 sites from among the ovary, fallopian tube, and peritoneum was allowed in both prelaparoscopic and laparoscopic diagnosis.
[b] Histology by prelaparoscopic diagnosis has been estimated from cytological findings.

Safety of the treatment

The mean number of cycles of chemotherapy was 7.0 (range, 1–9) cycles. Dose reductions of chemotherapy were performed in 42% (22/53) of patients and 11% (39/371) of cycles. Discontinuation of treatment due to toxicities or patients' refusal in relation to toxicities occurred in 9 patients except 6 patients who continuously received the treatment by deviation. Table 2 shows the major toxicities of the chemotherapy. Grade 4 hematological toxicities, particularly neutropenia (>70%) and anemia (≥15%), were frequently observed during both neoadjuvant and postoperative chemotherapy. Concerning neutropenia, 74% (39/53) of patients and 49% (182/371) of cycles required G-CSF support. Although more than 10% of patients experienced grade 3 neutropenic fever, grade 4 was not observed. Other grade 3 non-hematological toxicities were rarely observed except for gastrointestinal toxicities. As a non-typical adverse event, grade 4 cerebral infarction was observed in 1 patient.

In 47 patients who underwent IDS, the median duration of the surgery and median blood loss were 330 (130–735) min and 1284 (280–4565) ml, respectively. Gastrointestinal resection excluding appendectomy was performed in 9% (4/47) of patients, and splenectomy was performed in 6% (3/47) of patients. Repair of the ureter or the colon because of operative injury was performed in 6% (3/47) of patients. Grade 3 or 4 toxicities observed during and/or after surgery were grade 3 hypotension in 19% (9/47), grade 3 bleeding without thrombocytopenia in 77% (36/47), and grade 3 ileus in 4% (2/47). Blood transfusion other than autotransfusion was required in 72% (34/47); only autotransfusion was performed in 4% (2/47).

There was no treatment-related mortality. There were 2 unexpected events: a primary aldosteronism and a metachronous lung cancer after the treatment protocol. Both events were judged as unlikely to be related with the treatment protocol by the Data and Safety Monitoring Committee of JCOG.

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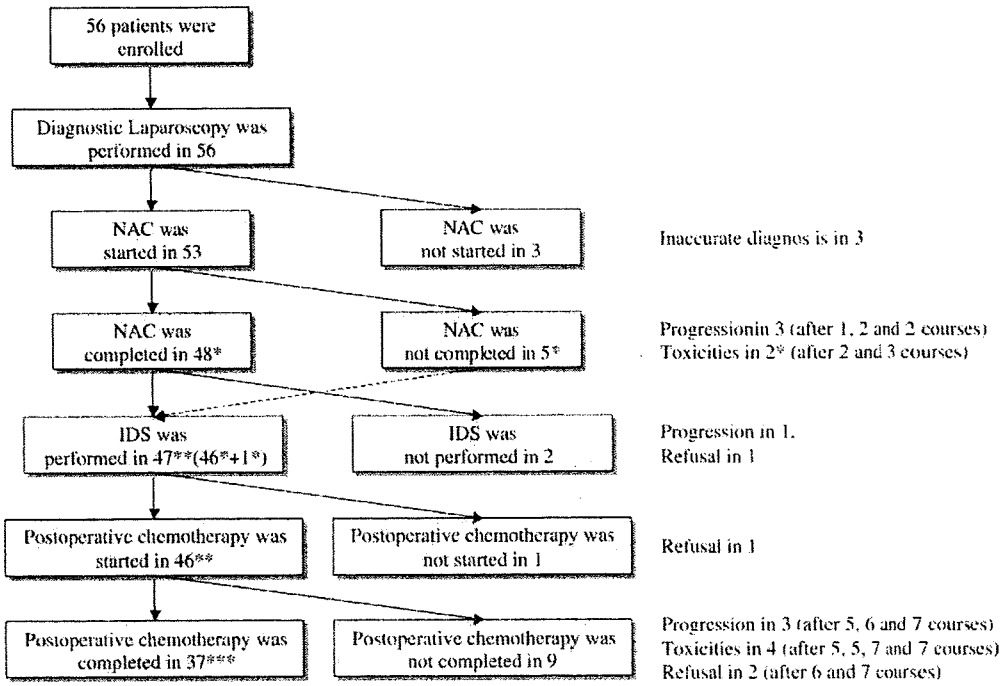

Fig. 1. Compliance of protocol treatment. Including 1 patients (*), 2 patients (**) and 6 patients (***) who deviated from the criteria for discontinuation. NAC, neoadjuvant chemotherapy; IDS, interval debulking surgery.

Efficacy of the treatment

Responses to chemotherapy after 4 cycles of NAC were evaluated in 48 patients who completed NAC. Partial response or CR was obtained in 41 patients (77% of 53 patients), SD was observed in 6 patients (11%), and PD was observed in 1 patient (2%) according to RECIST criteria.

IDS was performed in 47 patients (89% of 53 patients), including a patient who underwent IDS after 3 cycles of NAC. Complete resection of all tumors was obtained in 29 patients (55% of 53 patients), residual disease became <1 cm in 9 patients (17%) and ≥1 cm was left in 9 patients (17%).

The entire treatment protocol was completed by 37 patients and cCR was obtained in 22 patients (42% of 53 patients), including 6 and 3 patients who deviated from the discontinuation criteria. The primary end point of %cCR was 42% [95% CI: 28%–56%].

The median and 3-year PFS of 53 patients was 14 months and 19% (Fig. 2). The median and 3-year OS of 53 patients was 45 months and 60% (Fig. 3).

Discussion

The purpose of this study was to assess the safety and efficacy of NAC and to determine whether advanced MC can be accurately diagnosed on the basis of imaging studies, cytological findings, and tumor markers.

As far as the safety is concerned, treatment initiation with NAC is well known as a safe treatment [4–7,13,14]. There was no treatment-related mortality, the drug-induced toxicities were easily manageable, and surgical toxicities or severe complications were rare. In this study, the safety of NAC was reconfirmed by a prospective study.

Table 2
Drug-induced toxicities

Toxicities	Neoadjuvant chemotherapy (n=53)				Postoperative chemotherapy (n=46)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hematological								
Leukopenia	4%	34%	53%	9%	2%	17%	72%	9%
Neutropenia	0%	6%	19%	75%	2%	0%	24%	73%
Thrombocytopenia	13%	26%	23%	2%	17%	22%	43%	2%
Anemia	9%	49%	26%	15%	11%	52%	20%	17%
Non-hematological								
Neutropenic fever	-	-	15%	0%	-	-	11%	0%
Allergy/Hypersensitivity	9%	2%	0%	0%	4%	0%	0%	0%
Fatigue	42%	9%	4%	0%	41%	9%	0%	0%
Alopecia	11%	89%	-	-	11%	84%	-	-
Arthralgia	32%	11%	0%	0%	37%	2%	2%	0%
Neuropathy (sensory)	55%	9%	0%	0%	52%	15%	0%	0%
Myalgia	38%	13%	2%	0%	26%	2%	2%	0%
Nausea	43%	23%	11%	-	46%	13%	2%	-
Vomiting	13%	6%	9%	0%	9%	9%	2%	0%
Diarrhea	15%	4%	6%	0%	11%	2%	2%	0%

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Regarding the efficacy of NAC, cCR according to our definition was achieved in 22 patients (42%). It is difficult to compare our results with those of the previous studies targeting surgical stage III/IV ovarian cancer because our target was clinically diagnosed stage III/IV disease. In addition, our definition of cCR is stricter than general definition. We set the CA125 titer at <20 U/ml rather than <35 U/ml. Taking into account these differences, we set, at the beginning of the study, the expected %cCR as 40% and an acceptable lowest %cCR of 20% for the statistical analysis of the primary end point, based on the results of previous studies [15–19]. According to the calculation of the exact binominal distribution, the 95% confidence interval of the %cCR of the target population was 28%–56%. Even if we omit 3 patients with deviation from the discontinuation criteria, the 95% confidence interval of %cCR of the target population would be 23% to 50%. In either case, the null hypothesis "the true proportion of cCR is <20%" was rejected. Furthermore, the median PFS and OS of 53 patients with stage III/IV disease (14 and 45 months, respectively) in the present study also represent promising results comparable with the results of treatments consisting of PDS and postoperative chemotherapy in the previous reports [15,16,20]. Although two Gynecologic Oncology Group studies showed much better PFS and OS with PDS and postoperative intravenous chemotherapy (21 and 57 months) [21] and with PDS and postoperative intra-peritoneal chemotherapy (23 and 66 months) [22], the subjects of both studies were only patients who had undergone optimal surgery. Thus, our results may be comparable to those of the other reports. From the analysis, we confirmed that NAC for advanced MC is sufficiently effective to be compared with current standard treatment.

With regard to the accuracy of clinical diagnosis, the overall diagnosis of the tumor origin, histology, and stage was confirmed by DLS in 53/56 patients (95%). According to the Bayesian method, the Bayesian posterior probability that PPV is <90% was 9.96%, indicating that the appropriate target diseases for NAC can be diagnosed with >90% accuracy without the need for DLS. Although misdiagnosis may occur in <10% cases, the most probable misdiagnosis is the stage of disease. Misdiagnosis of the stage is acceptable rather than the misdiagnosis of the origin or histology because the treatment strategy for stage IC/IIC MC is primarily the same as that for stage III/IV MC. Thus, we concluded that we could omit the staging procedure in a phase III study. Owing to this omission, both treatment arms of the phase III trial would become more practical.

Based on our promising results, we have already started the phase III study, JCOG0602 [23], for comparing NAC followed by IDS with PDS followed by postoperative chemotherapy, on the same subjects of this study. A similar phase III study has already been conducted by EORTC and CTU-MRC. Our study and EORTC study have been designed to prove the non-inferiority of NAC as compared to the standard treatment. Because of the expected lower surgical morbidity and mortality associated with NAC, NAC should become the new standard

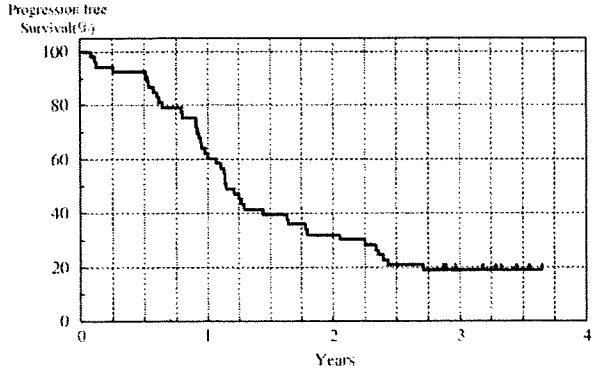

Fig. 2. Progression free survival of patients who received protocol treatment ($n=53$).

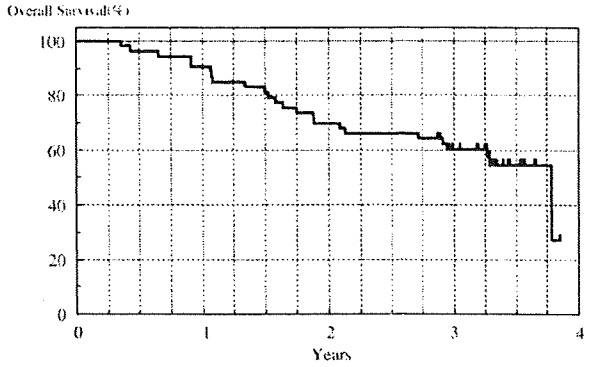

Fig. 3. Overall survival of patients who received protocol treatment ($n=53$).

treatment for patients with advanced MC if the non-inferior OS and lower treatment related morbidity and mortality are proven. The distinctiveness of our new study is that it omits the staging procedures, such as DLS, required in this feasibility study, implying the deletion of an extra procedure in both treatment regimens; thus, our new study highlights the advantage of NAC. Our ongoing phase III study should make it possible to compare both treatments in a more practical setting. From the results of ongoing phase III studies including our study, it is hoped that a new standard treatment regimen is established.

Conflict of interest statement
All authors declare that there are no conflicts of interest.

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Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial

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Summary

Background Paclitaxel and carboplatin given every 3 weeks is standard treatment for advanced ovarian carcinoma. Attempts to improve patient survival by including other drugs have yielded disappointing results. We compared a conventional regimen of paclitaxel and carboplatin with a dose-dense weekly regimen in women with advanced ovarian cancer.

Methods Patients with stage II to IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer were eligible for enrolment in this phase 3, open-label, randomised controlled trial at 85 centres in Japan. Patients were randomly assigned by computer-generated randomisation sequence to receive six cycles of either paclitaxel (180 mg/m²; 3-h intravenous infusion) plus carboplatin (area under the curve [AUC] 6 mg/mL per min), given on day 1 of a 21-day cycle (conventional regimen; n=320), or dose-dense paclitaxel (80 mg/m²; 1-h intravenous infusion) given on days 1, 8, and 15 plus carboplatin given on day 1 of a 21-day cycle (dose-dense regimen; n=317). The primary endpoint was progression-free survival. Analysis was by intention to treat (ITT). This trial is registered with ClinicalTrials.gov, number NCT00226915.

Findings 631 of the 637 enrolled patients were eligible for treatment and were included in the ITT population (dose-dense regimen, n=312; conventional regimen, n=319). Median progression-free survival was longer in the dose-dense treatment group (28·0 months, 95% CI 22·3–35·4) than in the conventional treatment group (17·2 months, 15·7–21·1; hazard ratio [HR] 0·71; 95% CI 0·58–0·88; p=0·0015). Overall survival at 3 years was higher in the dose-dense regimen group (72·1%) than in the conventional treatment group (65·1%; HR 0·75, 0·57–0·98; p=0·03). 165 patients assigned to the dose-dense regimen and 117 assigned to the conventional regimen discontinued treatment early. Reasons for participant dropout were balanced between the groups, apart from withdrawal because of toxicity, which was higher in the dose-dense regimen group than in the conventional regimen group (n=113 *vs* n=69). The most common adverse event was neutropenia (dose-dense regimen, 286 [92%] of 312; conventional regimen, 276 [88%] of 314). The frequency of grade 3 and 4 anaemia was higher in the dose-dense treatment group (214 [69%]) than in the conventional treatment group (137 [44%]; p<0·0001). The frequencies of other toxic effects were similar between groups.

Interpretation Dose-dense weekly paclitaxel plus carboplatin improved survival compared with the conventional regimen and represents a new treatment option in women with advanced epithelial ovarian cancer.

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Introduction

Paclitaxel and carboplatin given every 3 weeks is currently considered standard first-line chemotherapy for advanced epithelial ovarian cancer. The consensus statements on the management of ovarian cancer at the 3rd International Gynecologic Cancer Consensus Conference in 2004 recommended intravenous paclitaxel (175 mg/m² over 3 h) plus intravenous carboplatin (area under the curve [AUC] 5·0–7·5 mg/mL per min) given every 3 weeks for six cycles for first-line chemotherapy.[1] Paclitaxel and carboplatin have been combined with other drugs, given either concurrently or sequentially, in the hope of prolonging survival in women with advanced ovarian cancer, but the results of several randomised trials have been disappointing.[2–4] In particular, the recently reported randomised trial of the Gynecologic Oncology Group, an international collaborative study enrolling more than 4500 patients, showed that the addition of new cytotoxic drugs to paclitaxel plus carboplatin did not improve progression-free or overall survival.[2]

Dose-dense weekly administration of paclitaxel is another strategy to enhance antitumour activity and prolong survival. Preclinical studies have suggested that duration of exposure is an important determinant of the cytotoxic activity of paclitaxel.[5] Adequate cytotoxicity can be achieved at fairly low concentrations of the drug provided that exposure is extended.[5,6] Several phase 2 clinical trials of dose-dense weekly paclitaxel and carboplatin have shown promising efficacy and favourable tolerability in women with ovarian cancer.[7–9]

We undertook a phase 3, randomised controlled trial to compare conventional paclitaxel and carboplatin given every 3 weeks with dose-dense paclitaxel given every week plus carboplatin (every 3 weeks) as first-line treatment in women with advanced ovarian cancer.

Methods

Patients

Patients from 85 centres in Japan were eligible for enrolment in this phase 3, open-label, randomised trial if they had a histologically or cytologically proven diagnosis of stage II to IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. If only the results of cytological examinations were available, patients needed to have the following criteria: (1) a cytological diagnosis of adenocarcinoma; (2) an abdominal mass more than 2 cm in diameter on abdominal images; and (3) a CA125/carcinoembryonic antigen (CEA) ratio[10] of more than 25, or no evidence of gastrointestinal cancer if CA125/CEA ratio was less than or equal to 25. Previous chemotherapy was not allowed. Patients needed to be aged 20 years or older, to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3,[11] and to have adequate organ functions, defined as absolute neutrophil count 1·5 cells×10^9 per L or more, platelet count 100×10^9 per L or more, serum bilirubin 25·7 μmol/L or less, serum aspartate aminotransferase 100 IU/L or less, and serum creatinine 132·6 μmol/L or less. Patients were excluded if they had an ovarian tumour with a low malignant potential, or synchronous or metachronous (within 5 years) malignant disease other than carcinoma in situ.

All patients gave written informed consent before enrolment in this study. The study protocol was approved by the institutional review boards at all participating centres. The protocol was coordinated by the Japanese Gynecologic Oncology Group (protocol number 3016).

Randomisation and masking

Patients were randomly assigned to receive paclitaxel and carboplatin in either a conventional regimen (control) or a dose-dense regimen (intervention). Randomisation was by telephone or fax from a central registration centre located at University of Toyama (Toyama, Japan), and the random allocation table was computer-generated by use of the SAS PROC PLAN. Randomisation was stratified by residual disease (≤1 cm *vs* >1 cm), International Federation of Gynecology and Obstetrics (FIGO) stage (II *vs* III *vs* IV),[12] and histological type (clear-cell or mucinous tumours *vs* serous or other tumours), with adequate balancing within each institution. Patients and clinicians were not masked to treatment assignment.

Procedures

Both study groups received carboplatin at a dose calculated to produce an AUC of 6 mg/mL per min on day 1 of a 21-day cycle. Carboplatin was given as an intravenous infusion over 1 h. The control group also received paclitaxel given as a 3-h intravenous infusion at a dose of 180 mg/m² on day 1. In the dose-dense group, paclitaxel was given as a 1-h intravenous infusion at a dose of 80 mg/m² on days 1, 8, and 15. The dose of carboplatin was calculated with the formula of Calvert and colleagues,[13] by use of creatinine clearance instead of glomerular filtration rate. Creatinine clearance was calculated with the formula of Jelliffe.[14] Standard premedication was given to prevent hypersensitivity reactions to paclitaxel. The treatments were repeated every 3 weeks for six cycles. Patients with measurable lesions who had a partial response or complete response received three additional cycles of chemotherapy.

Patients needed to have an absolute neutrophil count of 1·0×10^9 cells per L (amended from 1·5×10^9 cells per L on April 11, 2005, because of frequent occurrence of delaying) or more and a platelet count of 75×10^9 per L or more to receive subsequent cycles of therapy in both groups. Patients in the dose-dense regimen group also had to have an absolute neutrophil count of 0·5×10^9 cells per L or more and a platelet count of 50×10^9 per L (amended from 75×10^9 per L on April 11, 2005) or more before they received paclitaxel on days 8 and 15. Treatment was delayed for a maximum of 3 weeks (amended from 2 weeks on April 11, 2005).

The dose of carboplatin was reduced for haematological toxicity, and paclitaxel was reduced for non-haematological toxicity with dose reduction levels as follows: carboplatin AUC 5 mg/mL per min (level 1) or AUC 4 mg/mL per min (level 2) in both groups; paclitaxel 135 mg/m² (level 1) or 110 mg/m² (level 2) in the conventional treatment group, and paclitaxel 70 mg/m² (level 1) or 60 mg/m² (level 2) in the dose-dense treatment group. The carboplatin dose was reduced when febrile neutropenia occurred, an absolute neutrophil count less than 0·5×10^9 cells per L persisted for 7 days or more, the platelet count was less than 10×10^9 per L, the platelet count was between 10×10^9 per L and 50×10^9 per L with bleeding tendencies, or the treatment was delayed for haematological toxicity for more than 1 week. In general, patients did not receive prophylactic granulocyte-colony stimulating factor (G-CSF) unless they had treatment delays or neutropenic complications after treatment. The dose of paclitaxel was reduced in patients who had grade 2 or higher peripheral neuropathy.

Interval debulking surgery after two to four cycles of chemotherapy, secondary debulking or second-look surgery after six cycles of chemotherapy, or both, were allowed. These procedures were done within 6 weeks after chemotherapy, and subsequent chemotherapy was restarted within 6 weeks after surgery.

The primary endpoint of this trial was progression-free survival, defined as the time from the date of randomisation to the date of the first occurrence of any of the following events: death from any cause; appearance of any new lesions that could be measured or assessed clinically;

or CA125 criteria of disease progression.[15] The CA125 criteria of disease progression were defined as (1) patients with raised CA125 concentration before treatment with a return to normal after treatment needed to show re-elevation of CA125 greater than or equal to two times the upper normal limit; (2) patients with raised CA125 before treatment that did not return to normal needed to show evidence of CA125 greater than or equal to two times the nadir value; or (3) patients with CA125 in the normal range before treatment needed to show evidence of CA125 greater than or equal to two times the upper normal limit, with raised CA125 recorded on two occasions at least 1 week apart. In patients with measurable disease, clinical or radiographical tumour measurements had priority over CA125 concentration, and progression during treatment could not be declared on the basis of CA125 alone.

Secondary endpoints were overall survival, response rate, and adverse events. The planned analyses of progression-free survival and overall survival included data on eligible patients according to the intention-to-treat (ITT) principle. Clinical response was assessed in eligible patients with lesions that could be measured in two dimensions. The assessment of response had to be confirmed on two occasions at least 4 weeks apart. A complete response was defined as the complete disappearance of all measurable and assessable lesions, determined by two observations not less than 4 weeks apart. A partial reponse was defined as a 50% or greater decrease in the sum of the products of the perpendicular diameters of measurable lesions, determined by two observations not less than 4 weeks apart. Stable disease was defined as a steady state of response less than a partial response or as an increase of less than 25% in the sum of the products of the perpendicular diameters of measurable lesions, lasting at least 4 weeks. Progressive disease was defined as an unequivocal increase of at least 25% in the sum of the products of the perpendicular diameters of measurable lesions. The appearance of new lesions also constituted progressive disease. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.[16]

Radiological studies to record the status of all measurable lesions noted at baseline were repeated after two, four, and six cycles of chemotherapy. Once patients discontinued the protocol therapy, disease status was assessed every 3 months for the first 2 years and every 6 months thereafter. Follow-up monitoring included clinical examinations and CA125 concentration estimation; routine CT scans were not required, but were requested if CA125 concentration rose, symptoms of relapse developed, or both.

Statistical analysis

Our hypothesis was that the dose-dense regimen would prolong progression-free survival compared with the conventional regimen. At the beginning of the study in April, 2003, a sample size of 380 patients with no interim analysis was initially planned to detect a 37·5% improvement in median progression-free survival in the conventional regimen group (from 16 months to 22 months) with 80% power, two-sided log-rank test, and alpha level of 0·05. In January, 2005, the sample size was increased to 600 patients during the trial to account for the higher accrual of patients and to detect a shorter prolongation of progression-free survival. This amendment of the protocol was made without interim analysis and was approved by the data and safety monitoring committee. The increased sample size would enable the detection of a 31·3% improvement (from 16 months to 21 months) in median progression-free survival with 80% power, two-sided log-rank test, at an alpha level of 0·05, an accrual of 3 years, and a follow-up of 1·5 years. Following the data safety monitoring committee's instructions, interim analysis was planned after 380 patients had been randomly assigned to treatment, and multiplicity by multiple look was adjusted with the

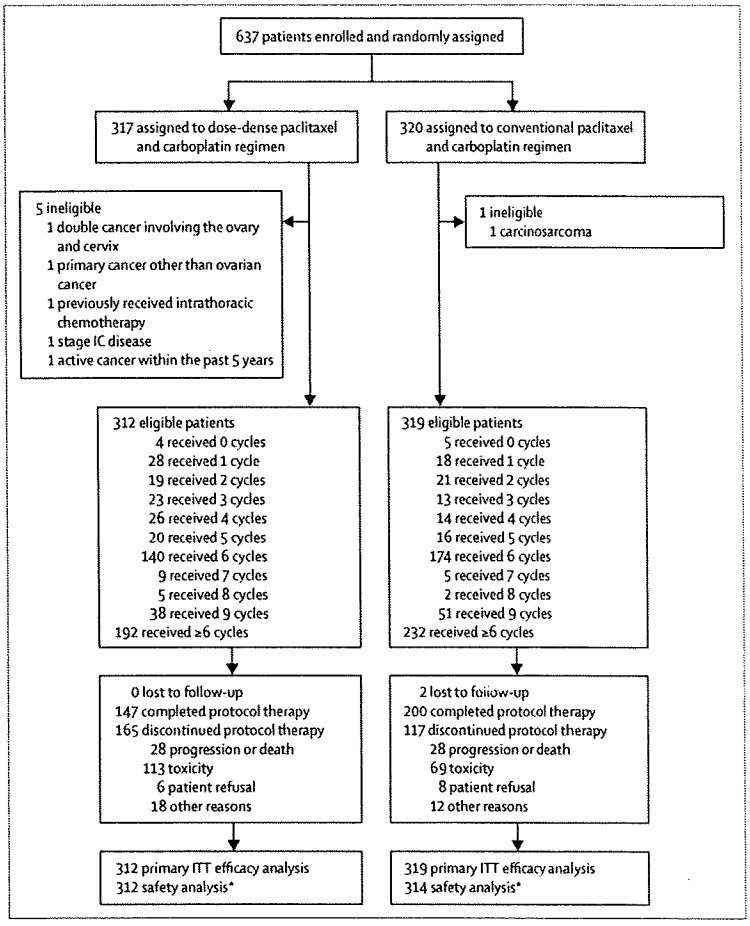

Figure 1: **Trial profile**
ITT=intention-to-treat. *Analysis of safety includes all randomised women who had received at least one cycle of treatment (one ineligible patient in each group did not receive treatment).

	Dose-dense regimen group (n=312)	Conventional regimen group (n=319)
Age (years)	57 (25–87)	57 (25–84)
FIGO stage		
II	62 (20%)	54 (17%)
III	202 (65%)	215 (67%)
IV	48 (15%)	50 (16%)
ECOG performance status		
0 or 1	283 (91%)	287 (90%)
2	23 (7%)	20 (6%)
3	6 (2%)	12 (4%)
Disease		
Ovarian	260 (83%)	276 (87%)
Fallopian tube	14 (4%)	18 (6%)
Primary peritoneal	38 (12%)	25 (8%)
Surgery		
Cytology only	35 (11%)	35 (11%)
Primary debulking	277 (89%)	284 (89%)
Interval debulking	34 (11%)	29 (9%)
Secondary/second-look	38 (12%)	56 (18%)
Residual disease		
≤1 cm	144 (46%)	145 (45%)
>1 cm	168 (54%)	174 (55%)
Histological type		
Serous adenocarcinoma	173 (55%)	182 (57%)
Endometrioid adenocarcinoma	38 (12%)	39 (12%)
Clear-cell carcinoma	31 (10%)	37 (12%)
Mucinous adenocarcinoma	23 (7%)	11 (3%)
Other types	47 (15%)	50 (16%)
Histological grade		
Well differentiated	42 (13%)	40 (13%)
Moderately differentiated	60 (19%)	71 (22%)
Poorly differentiated	79 (25%)	72 (23%)
Unknown/not applicable	131 (42%)	136 (43%)

Data are n (%) or median (range). FIGO=International Federation of Gynecology and Obstetrics. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics of study patients**

O'Brien-Fleming alpha-spending function. At the first interim analysis in December, 2005, the data safety monitoring committee reviewed the results and approved continuation of the planned follow-up.

The cumulative survival curve and median progression-free survival time were estimated by use of the Kaplan-Meier method. Adverse events were analysed in all randomised women who had received at least one cycle of treatment. Proportions of adverse events were compared between the groups by the use of two-sided χ^2 tests or two-sided Fisher's exact tests. Responses were compared by the use of Fisher's exact test. All analyses were performed with SAS software, version 8.2. This trial is registered with ClinicalTrials.gov, number NCT00226915.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April, 2003, and December, 2005, 637 patients were enrolled at 85 centres. Figure 1 shows the trial profile. Table 1 shows the baseline characteristics of the 631 eligible patients whose data were included in the ITT analysis.

The median number of treatment cycles was six in both groups (figure 1). The proportion of patients who received six or more cycles of treatment was higher in the conventional regimen group (232 [73%] of 319) than in the dose-dense regimen group (192 [62%] of 312). The main reason for discontinuing treatment was toxicity. Haematological toxicity was the most common form of toxicity leading to the discontinuation of treatment (68 [60%] of 113 patients assigned to the dose-dense regimen *vs* 30 [43%] of 69 assigned to the conventional regimen; p=0·03). The proportions of patients who discontinued treatment because of neurotoxicity were low in both groups (three [3%] *vs* five [7%]). Other reasons for discontinuation of treatment because of toxic effects were patient refusal (13 [12%] *vs* 12 [17%]), allergic reaction (four [4%] *vs* seven [10%]), and other toxic effects (25 [22%] *vs* 15 [22%]).

At least one treatment cycle was delayed in a higher proportion of patients in the dose-dense treatment group (236 [76%] of 312) than in the conventional treatment group (213 [67%] of 319; p=0·02). The dose of the study drugs was reduced in a higher proportion of patients assigned to the dose-dense regimen (150 [48%] of 312) than in those assigned to the conventional regimen (112 [35%] of 319; p=0·001). The mean delivered dose intensity of carboplatin was lower in the dose-dense regimen group (AUC per week 1·54 mg/mL per min [SD 0·37]) than in the conventional regimen group (AUC per week 1·71 mg/mL per min [SD 0·36]), and the mean delivered dose-intensity of paclitaxel was higher (63·0 mg/m² per week [SD 13·0] *vs* 51·7 mg/m² per week [SD 10·6]). The mean relative dose intensities of carboplatin and paclitaxel were both lower in the dose-dense regimen group (77% [SD 18] and 79% [SD 15], respectively) than in the conventional regimen group (85% [SD 18], and 86% [SD 18], respectively).

At the time of last follow-up (December, 2007), with a median duration of follow-up of 29 months, there had been 160 disease progression events in the dose-dense treatment group and 200 in the conventional treatment group. Median progression-free survival was 28·0 months (95% CI 22·3–35·4) in the dose-dense treatment group and 17·2 months (15·7–21·1) in the

conventional treatment group (figure 2; unadjusted hazard ratio [HR] 0·71, 95% CI 0·58–0·88; p=0·0015, log-rank test). When the analysis was done with data from all 637 patients who were randomly assigned to treatment, the result was similar (p=0·0019). After adjustment for FIGO stage, residual disease, and histological type according to the preplanned analysis, the HR was 0·65 (0·53–0·80; p=0·0001). We subsequently undertook unplanned sensitivity analyses. The differences between groups were still significant when only clinical progression was defined as progression (p=0·0018), when data on patients who received second-line therapy before progression were censored (dose-dense regimen, n=3; conventional regimen, n=5; p=0·0018), or when data on patients who underwent interval or secondary surgery, or both, were censored (dose-dense regimen, n=71; conventional regimen, n=85; p=0·0092).

Analysis of overall survival was done in December, 2007, at the same time as the analysis of progression-free survival. The overall survival at 2 years was 83·6% in the dose-dense treatment group and 77·7% in the conventional treatment group (p=0·049). We updated the overall survival analysis in December, 2008, with median follow-up period of 42 months. Although median overall survival had not been reached in either group, overall survival at 3 years was higher in the dose-dense treatment group (72·1%) than in the conventional treatment group (65·1%; unadjusted HR 0·75, 0·57–0·98; p=0·03 log-rank test; figure 2).

A Cox proportional-hazards model was used to examine the effect of baseline clinical characteristics and conventional prognostic factors on the treatment effect (figure 3). Progression-free survival was longer in the dose-dense treatment group than in the conventional treatment group across all subgroups of patients apart from in those with clear-cell or mucinous tumours. In this subgroup of patients, the HR in the dose-dense treatment group was similar to that in the conventional treatment group.

Clinical response was assessed in 282 patients who had measurable disease at study entry. The overall response rate was similar between groups (conventional regimen, 72 [53%] of 135 patients; dose-dense regimen, 82 [56%] of 147 patients; p=0·72; table 2). Because patients who underwent suboptimally debulked surgery (>1 cm of residual disease) were allowed to undergo interval debulking surgery in this study, response sometimes could not be confirmed on repeated imaging. If these unconfirmed responses are taken into account (44 patients), the overall response rate was 70% (94 of 135 patients) in the conventional treatment group compared with 71% (104 of 147 patients) in the dose-dense treatment group (p=0·90).

Treatment-related adverse events were analysed in patients who received at least one cycle of the study treatment (table 3). The frequency of grade 3 or 4 anaemia was higher in the dose-dense treatment group than in the conventional treatment group (p<0·0001). Recombinant erythropoietin was not used to treat anaemia because it was not approved in Japan. G-CSF was used in 187 (60%) patients assigned to the dose-dense regimen and in 214 (67%) assigned to the conventional regimen. The frequency of neuropathy did not differ between study groups.

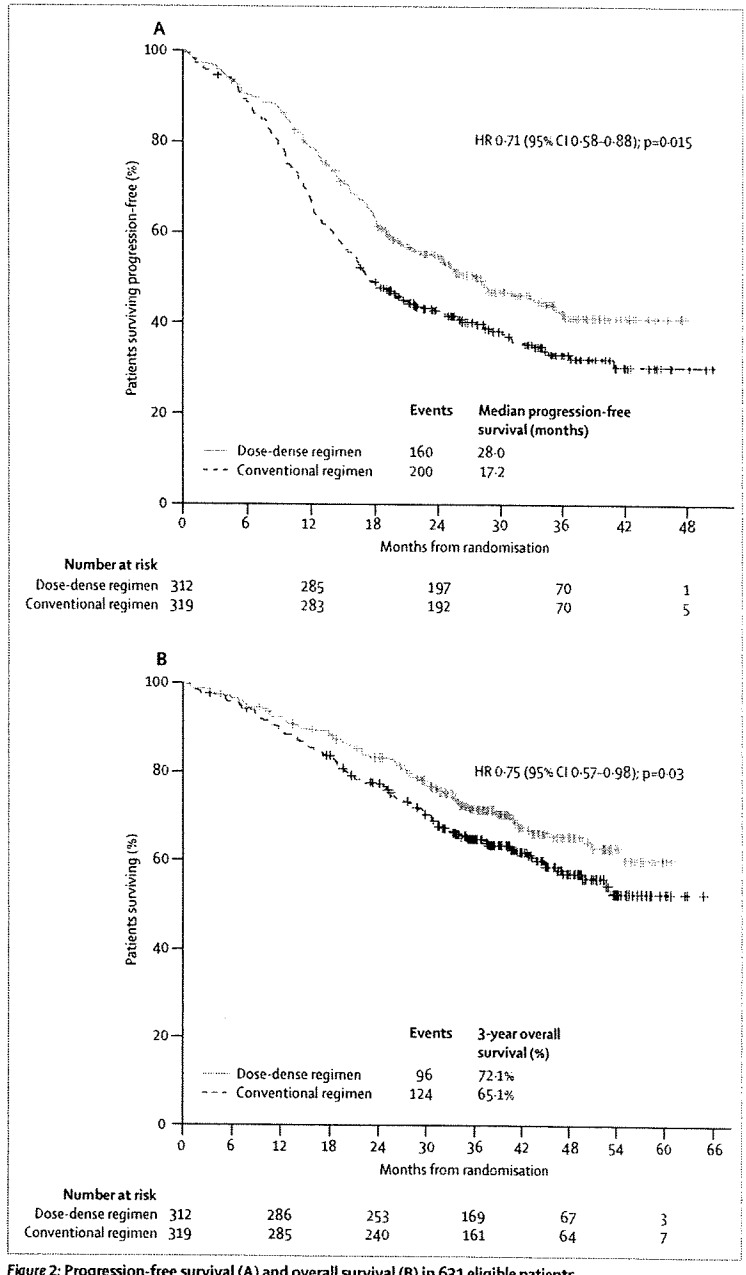

Figure 2: **Progression-free survival (A) and overall survival (B) in 631 eligible patients**
HR=hazard ratio.

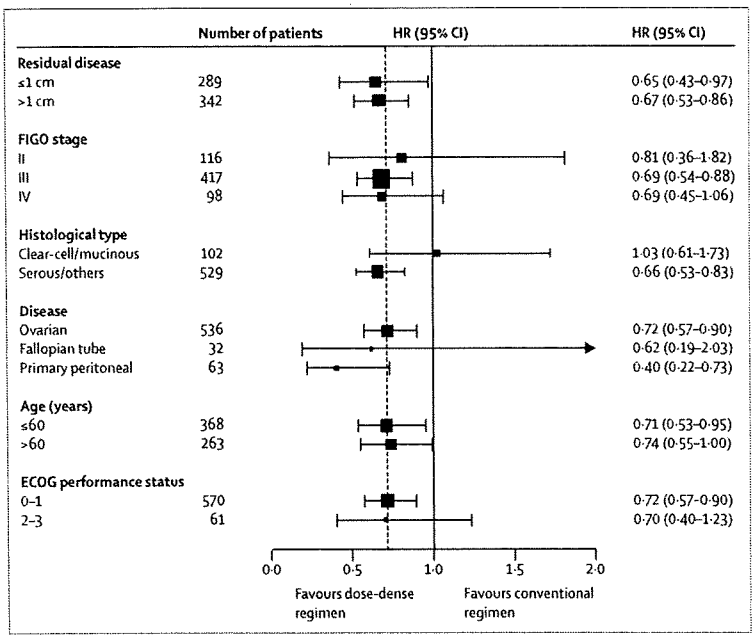

Figure 3: **Progression-free survival according to baseline characteristics**
FIGO=International Federation of Gynecology and Obstetrics. ECOG=Eastern Cooperative Oncology Group. The hazard ratios (HRs; 95% CIs) are for patients assigned to conventional paclitaxel and carboplatin, compared with those assigned to dose-dense paclitaxel and carboplatin, and were obtained from the unadjusted Cox model. The dashed vertical line indicates a hazard ratio of 0·71, which is the value for all patients, and the solid vertical line indicates a hazard ratio of 1·00, which is the null-hypothesis value.

	Dose-dense regimen group (n=147)	Conventional regimen group (n=135)	p value
Complete response	29 (20%)	21 (16%)	0·44
Partial response	53 (36%)	51 (38%)	0·81
Stable disease	43 (29%)	42 (31%)	0·80
Progressive disease	4 (3%)	9 (7%)	0·16
Not evaluable	18 (12%)	12 (9%)	0·44

See Methods section for definitions of responses.

Table 2: **Clinical response in patients with measurable lesions**

	Dose-dense regimen group (n=312)	Conventional regimen group (n=314)	p value
Neutropenia	286 (92%)	276 (88%)	0·15
Thrombocytopenia	136 (44%)	120 (38%)	0·19
Anaemia	214 (69%)	137 (44%)	<0·0001
Febrile neutropenia	29 (9%)	29 (9%)	1·00
Nausea	32 (10%)	36 (11%)	0·70
Vomiting	9 (3%)	11 (4%)	0·82
Diarrhoea	10 (3%)	8 (3%)	0·64
Fatigue	15 (5%)	8 (3%)	0·14
Arthralgia	3 (1%)	5 (2%)	0·72
Myalgia	2 (1%)	4 (1%)	0·69
Neuropathy (motor)	15 (5%)	12 (4%)	0·56
Neuropathy (sensory)	21 (7%)	20 (6%)	0·87

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.[14]

Table 3: **Frequency of grade 3 or 4 adverse events**

Discussion

Our study showed that compared with a conventional regimen, dose-dense treatment with paclitaxel and carboplatin improved progression-free survival in women with newly diagnosed, stage II to IV ovarian cancer. Women assigned to dose-dense paclitaxel and carboplatin had a 29% lower risk of disease progression and a 25% lower risk of death than did patients assigned to the conventional regimen. Benefits of this magnitude have been rare in women with advanced ovarian cancer, including those with suboptimally debulked stage III and IV disease, since the approval of paclitaxel for the indication of ovarian cancer.

The concept of dose density is based on the hypothesis that a shorter interval between doses of cytotoxic therapy would more effectively reduce tumour burden than would dose escalation.[17] In breast cancer, recently published phase 3 trials have shown that paclitaxel given every week improves response and survival.[18,19] Consistent with these findings, our study showed that progression-free survival and overall survival were significantly longer in the dose-dense regimen group than in the conventional regimen group. Increased doses of paclitaxel of 225 mg/m² or 250 mg/m² given every 3 weeks have been compared with the standard dose (ie, 175 mg/m²) in women with ovarian cancer, but showed no benefit in survival.[20,21] Our study showed a survival advantage with an increased total dose of 240 mg/m², given in three divided doses during a 21-day cycle, suggesting that dose density is more important than increased dose intensity.

There was greater haematological toxicity in the dose-dense treatment group than in the conventional treatment group, which resulted in more delays and dose modifications. The optimum dose and schedule of dose-dense paclitaxel and carboplatin have not yet been established. Rose and colleagues[8] reported that weekly paclitaxel at a dose of 60 mg/m² in combination with carboplatin at an AUC of 5 mg/mL per min was tolerated and active in patients with recurrent ovarian cancer. An alternative schedule of dose-dense treatment is to give both paclitaxel and carboplatin every week. Sehouli and co-workers[9] showed that weekly paclitaxel at a dose of 100 mg/m² and weekly carboplatin at an AUC of 2 mg/mL per min showed substantial activity and tolerability in patients with primary ovarian cancer. A treatment delay occurred in only 2·8% of cycles and the frequency of grade 3 neurotoxicity (2% [three of 129 patients]) was lower than that reported in our study. Additionally, weekly carboplatin of AUC 2 mg/mL per min and weekly paclitaxel of 60 mg/m² on days 1, 8, and

15 every 4 weeks showed a favourable toxicity profile in elderly ovarian cancer patients.[22]

The response rate did not differ between groups. Virtually all previous randomised trials in ovarian cancer that showed an improvement in progression-free survival and overall survival also had a higher response rate for the more effective treatment. A lower dose of paclitaxel had antiangiogenic activity in a xenograft model.[23] Antiangiogenic agents might promote tumour dormancy by maintaining tumour size and preventing outgrowth.[24] Vascular endothelial growth factor (VEGF) is frequently expressed in ovarian cancer, and might be an important therapeutic target. Longer survival in the dose-dense regimen group without an improved response rate might be attributed to the antiangiogenic effect of paclitaxel. Anti-VEGF agents such as bevacizumab combined with the dose-dense treatment will be assessed in future trials.

Neurotoxicity is the adverse reaction of greatest concern in patients who receive a combination of paclitaxel and carboplatin. In breast cancer trials, the incidence of neurotoxicity was higher in patients given paclitaxel every week than in patients given paclitaxel every 3 weeks.[19] In our study, however, the frequency of neurotoxicity was similar in both groups. This finding might be because patients in the dose-dense treatment group discontinued treatment more often than did those in the conventional treatment group.

Fewer than half the patients assigned to the dose-dense regimen completed treatment according to the study protocol. When designing the protocol, we debated whether patients who responded to six cycles of chemotherapy should receive three more cycles. However, this study was not designed to assess the relation between the duration of treatment and clinical outcomes, and there is little evidence to suggest that more than six cycles of chemotherapy would prolong survival. About 60% of patients in the dose-dense regimen group received six or more cycles of chemotherapy. Treatment cycles were more frequently delayed in the dose-dense treatment group than in the conventional treatment group, mainly because of neutropenia.

Clear-cell and mucinous adenocarcinoma of the ovary is associated with low sensitivity to chemotherapy and poor survival.[25,26] In our study, neither dose-dense nor conventional treatment seemed effective against clear-cell or mucinous ovarian carcinoma, which suggests that other treatment strategies are needed.

Thus, our study showed that a dose-dense regimen of paclitaxel once a week plus carboplatin every 3 weeks is associated with longer progression-free and overall survival than a conventional regimen of paclitaxel and carboplatin given every 3 weeks in women with advanced epithelial ovarian cancer.

Contributors

NK, MY, FT, SI, TS, EK, and KO conceived and designed the study with the Japanese Gynecologic Oncology Group. MY was the coordinating principal investigator for the study. NK and FT analysed and interpreted the results. NK drafted the report. KN was responsible for the overall planning and conduct of the study. NK, MY, SI, TJ, DA, HT, TS, SK, EK, and KO were involved in the provision of study material or patients, or data acquisition. NK, MY, TS, EK, and KO were members of the steering committee. All authors were involved in writing the report and approved the final version of the manuscript.

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Conflicts of interest

SI and DA have received honoraria from Bristol-Myers Squibb. DA and HT have received grant support from Bristol-Myers Squibb. All other authors declare that they have no conflicts of interest.

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Clinical Significance of UDP-Glucuronosyltransferase 1A1*6 for Toxicities of Combination Chemotherapy with Irinotecan and Cisplatin in Gynecologic Cancers

A Prospective Multi-Institutional Study

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Key Words
Cisplatin · Gynecologic cancer · Irinotecan · UDP-glucuronosyltransferase 1A1 · UGT1A1 · UGT1A1*6

Abstract
Background: To investigate the effects of UDP-glucuronosyltransferase 1A1 (UGT1A1) *28, *6 and *27 in patients with gynecologic cancer who received chemotherapy with irinotecan and cisplatin. ***Methods:*** Patients eligible for this study had cervical or ovarian cancer treated with chemotherapy; a course of the regimen consisted of 60 mg/m^2 of irinotecan on days 1, 8 and 15, and 60 mg/m^2 of cisplatin on day 1 every 4 weeks. UGT1A1 polymorphisms and toxicities were analyzed. ***Results:*** From March 2007 to December 2007, 30 Japanese patients were enrolled; 24 ovarian carcinoma patients and 6 cervical cancer patients. The following genotypes of UGT1A1 were found: wild type in 17 patients (57%), *28 in 4 patients (13%), *6 in 8 patients (27%), *28*6 in 1 case (3%) and no case of *27 (0%). Grade 3/4 neutropenia, thrombocytopenia and diarrhea were significantly more frequent in *6 patients compared with wild-type patients. Also, in *6 patients irinotecan administration on days 8 or 15 was significantly more often omitted due to toxicities. In patients with *28 or *28*6, side effects were similar to those in patients with *6. ***Conclusion:*** In addition to UGT1A1*28, UGT1A1*6 might also be a key candidate to determine the dose of combination chemotherapy with irinotecan and cisplatin.

Introduction

Irinotecan hydrochloride is widely used for a multiplicity of carcinomas, including colorectal and lung cancers. Irinotecan is often used for relapsed gynecologic cancer in combination with platinum [1, 2]. Recently, combination therapy with irinotecan and cisplatin has been ascribed a potential therapeutic effect for clear cell carcinoma of the ovary [3–5], and the efficacy of this

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