Table 1. Characteristics of the endometrial carcinoma patients with suspected gross cervical involvement

Variables	RH ($n=74$)	mRH ($n=112$)	SH ($n=114$)	*P*-value
Age (years)				0.21
<55	39	47	46	
⩾55	35	65	68	
ECOG Performance status				0.056
0	68	104	97	
1,2,3	4	8	17	
DM				0.94
Yes	10	17	16	
No	64	95	98	
BMI				0.071
<25	55	72	66	
⩾25	19	40	48	
Preoperative evaluation for cervical involvement				<0.001
Glandular	19	64	54	
Stromal	55	48	60	
Lymphadenectomy				<0.001
None	0	3	43	
PN	25	49	32	
PN + PAN	49	60	39	
Postoperative therapy				0.17
None	14	40	39	
Chemotherapy(C)	46	50	58	
Radiation (R)	11	10	13	
R followed by C	3	2	4	

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; mRH = modified radical hysterectomy; PAN = paraaortic lymphadenectomy; PN = pelvic lymphadenectomy; RH = radical hysterectomy; SH = simple hysterectomy.

Table 2. Pathologic findings of the patients

Variables	RH ($n=74$)	mRH ($n=112$)	SH ($n=114$)	*P*-value
Histology				0.76
E, G1/2	58	90	84	
E,G3	6	7	12	
Others	10	15	18	
Pathological cervical involvement				0.26
None	12	27	28	
Glandular	13	29	25	
Stromal	49	56	61	
Parametrial invasion				0.18
Negative	66	107	108	
Positive	8	5	6	
Myometrial invasion of corpus				0.04
<1/2	28	63	59	
⩾1/2	46	49	55	
Lymph node involvement				<0.01
Negative	49	91	51	
Positive	25	18	20	
Not available	0	3	43	
Peritoneal cytology				0.08
Negative	56	95	83	
Positive	18	17	31	
Peritoneal implantation beyond pelvis				0.21
Negative	74	108	109	
Positive	0	4	5	

Abbreviations: E = endometrioid adenocarcinoma: G1/2 = grade 1 and 2; G3 = grade 3; mRH = modified radical hysterectomy; PAN = paraaortic lymphadenectomy; PN = pelvic lymphadenectomy; RH = radical hysterectomy; SH = simple hysterectomy.

(Figure 1A and B). Five-year local recurrence-free survival rates were 88.0% in RH, 89.6% in mRH, and 87.9% in SH group, respectively. Also, there was no significant difference in the patients that had pathological cervical stromal involvement among three groups.

There were no significant differences of PFS and OS among three operative procedures (Figure 2A and B). Five-year OS rates were 83.6% in RH, 85.6% in mRH, and 84% in SH group. Five-year progression-free survival rates were 71.6% in RH, 77.7% in mRH, and 66.4% in SH group, respectively. Moreover, OS and PFS curves of the patients with pathological stromal involvement without extra-uterine spread, which are currently categorised as FIGO stage II disease, were shown in Figure 3A and B. There were also no significant survival differences according to operative procedures. Distribution of operative procedure, estimated 5-year OS rate, and duration of follow-up in each institution was shown in Supplementary Table 1.

Multi-regression analysis revealed that age, grade, peritoneal cytology status, and lymph node involvement were identified as prognostic factors for OS (Table 3); however, type of hysterectomy was not selected as independent prognostic factor for local recurrence-free survival, PFS, and OS (Table 3 and Supplementary Table 2).

Adverse effects according to surgical procedures were shown in Table 4. Median operative time was significantly longer in RH and mRH group compared with SH group. Amount of blood loss and rate of blood transfusion were higher in RH group. In late adverse effects, urinary retention of grade ⩾2 was more frequently observed in RH group.

DISCUSSION

For patients with suspected or gross cervical involvement, cervical biopsy or MR images were recommended for preoperative diagnosis (Manfredi *et al*, 2004; Akin *et al*, 2007). It is sometimes difficult to distinguish primary cervical cancer from endometrial cancer with cervical involvement. Therefore, the recommendation was that RH should be considered for the cases with stage II endometrial cancers (NCCN Guidelines, 2013). The hypothesis is that RH could remove parametrial metastasis in the patients with cervical involvement, because the incidence of parametrial invasion occurred in 14% of the cases with cervical involvement (Lee *et al*, 2010). The present study indicated that pathological parametrial invasion was not an independent prognostic factor for not only OS, but also local recurrence-free survival. Actually, some reports implied that RH improved prognosis of endometrial cancers with cervical involvement (Mariani *et al*, 2001; Sartori *et al*, 2001); however, these results were not based on multivariate analysis. Additionally, other clinicopathologic factors, such as histological grade, degree of cervical involvement, lymph node metastasis, and myometrial invasion, affected the prognosis more strongly. Recently, a report including 1577 cases of stage II endometrial

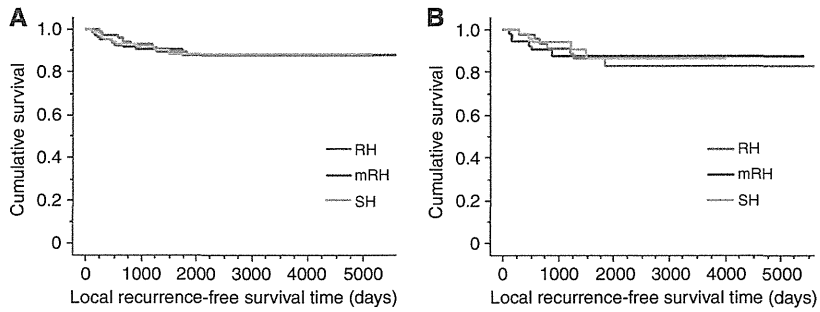

Figure 1. (A) Local recurrence-free curves of all patients according to the type of hysterectomy. There was no significant difference among three groups. Five-year survival rates were 88.0% in RH, 89.6% in mRH, and 87.9% in SH group, respectively. There was no significant difference among three groups. (B) Local recurrence-free curves of the patients that had pathological cervical stromal involvement according to the type of hysterectomy. There was no significant difference in OS among three groups. Five-year survival rates were 86.4% in RH, 87.9% in mRH, and 86.5% in SH group, respectively. There was no significant difference among three groups.

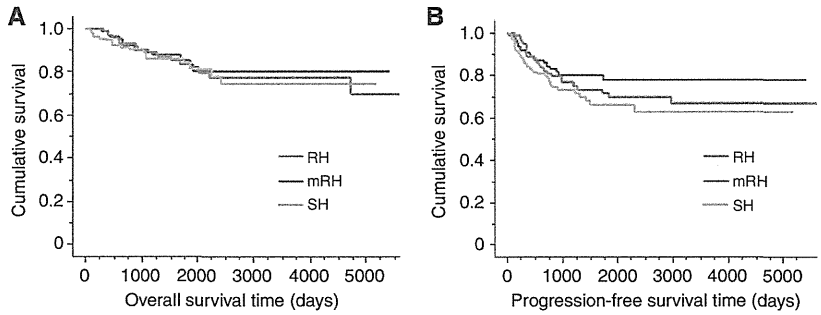

Figure 2. (A) Overall survival curves of all cases according to the type of hysterectomy. Five-year overall survival rates were 83.6% in RH, 85.6% in mRH, and 84% in SH group, respectively. There was no significant difference in OS among three groups. (B) PFS curves of all patients according to the type of hysterectomy. Five-year PFS rates were 71.6% in RH, 77.7% in mRH, and 66.4% in SH group, respectively. There was no significant difference in PFS among three groups.

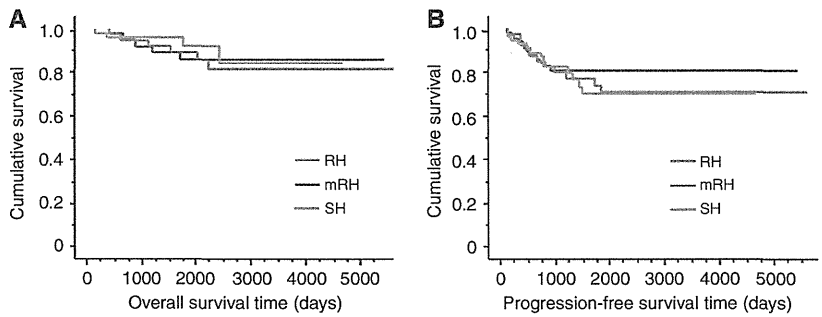

Figure 3. (A) Overall survival curves of the patients who had pathological cervical stromal involvement only (current FIGO stage II diseases) according to the type of hysterectomy. Five-year OS rates were 89.5% in RH, 86.0% in mRH, and 92.4% in SH group, respectively. There was no significant difference in OS among three groups. (B) PFS curves of the patients who had pathological cervical stromal involvement only (current FIGO stage II diseases) according to the type of hysterectomy. Five-year PFS rates were 74.1% in RH, 80.9% in mRH, and 70.1% in SH group, respectively. There was no significant difference in PFS among three groups.

cancers revealed that RH had no effect on survival (Wright *et al*, 2009); however, the conclusions were not based on multivariate analyses. The present study had the largest number of stage II cases of endometrial cancers that enabled multivariate analyses and revealed that procedures of hysterectomy were not prognostic factors for local recurrence-free survival, PFS, and OS.

Additionally, RH needed significantly longer operative time, and produced more amount of blood loss, increasing the rate of blood transfusion. Although there were no significant differences of acute side effects such as thrombosis and ileus, postoperative urinary dysfunction of grade $\geqslant 2$ occurred more frequently in patients with RH. Special caution is needed to avoid urinary dysfunction, because it continued long, and severely decreased the level of quality of life.

Adjuvant radiotherapy for early-stage endometrial cancer has been mainly limited to radiation therapy (NCCN Guidelines, 2013). Pelvic radiotherapy is the backbone of adjuvant therapy for stage II endometrial cancers: vaginal brachytherapy and/or pelvic radiation for grade 1, pelvic radiotherapy + vaginal brachytherapy for grade 2, and pelvic radiotherapy + vaginal brachytherapy ± chemotherapy for grade 3 tumours, respectively. The use of adjuvant chemotherapy in combination with radiotherapy was

Table 3. Multiple regression analysis for overall survival in the endometrial carcinoma patients with suspected gross cervical involvement

Variables	Hazard ratio	95% confidence interval	*P*-value
Age (years)			0.02
<54	1		
>55	2.41	1.15; 5.07	
Performance status			0.52
0	1		
1,2,3	1.35	0.54; 3.36	
Histology			0.02
E, G1/2	1		
E, G3 + others	2.25	1.14; 4.42	
Pathological invasion of cervix			0.92
None	1		
Glandular	1.15	0.52; 2.56	
Stromal	1.18	0.54; 2.58	
Parametrial invasion			0.87
Negative	1		
Positive	1.11	0.32; 3.98	
Myometrial invasion of corpus			0.32
⩽1/2	1		
>1/2	1.50	0.68; 3.32	
Lymph node metastasis			<0.01
No	1		
Yes	3.32	1.03; 10.63	
Not available	3.24	0.99; 10.64	
Ascites/malignant washing			<0.01
Negative	1		
Positive	3.34	1.63; 6.80	
Dissemination beyond pelvis			0.09
Negative	1		
Positive	2.88	0.85; 9.71	
Lymph-vascular invasion			0.39
Negative	1		
Positive	0.73	0.35; 1.50	
Type of hysterectomy			0.39
SH	1		
mRH	1.76	0.76; 4.07	
RH	1.56	0.67; 3.62	
Postoperative treatment			0.63
None	1		
Chemotherapy (C)	0.92	0.35; 2.39	
Radiotherapy (R)	0.97	0.29; 3.26	
R followed by C	0.35	0.06; 1.90	

Abbreviations: E = endometrioid adenocarcinoma: G1/2 = grade 1 and 2; G3 = grade 3; RH = radical hysterectomy; mRH = modified radical hysterectomy; SH = simple hysterectomy.

Table 4. Adverse effects according to surgical procedures

Variables	RH (*n* = 74)	mRH (*n* = 112)	SH (*n* = 114)	*P*-value
Perioperative adverse effects				
Operative time (minutes)				0.058[a] <0.01[b]
Median	292	282	184	
Range	174–677	187–475	81–288	
Blood loss (g)				<0.01[a]
Median	1162	855	355	<0.01[b]
Range	320–6000	120–4060	30–3140	
Blood transfusion				<0.01
Yes	43	47	18	
No	31	65	96	
Deep vein thrombosis, or pulmonary embolism (grade ⩾2)				0.25
Yes	2	2	0	
No	72	110	114	
Ileus (grade ⩾2)				0.87
Yes	2	3	2	
No	72	109	112	
Late adverse effects [c]				
Lymphedema (grade ⩾2)				0.18
Yes	9	7	6	
No	65	105	108	
Urinary retention (grade ⩾2)				<0.01
Yes	11	1	0	
No	63	111	114	

Abbreviations: mRH = modified radical hysterectomy; RH = radical hysterectomy; SH = simple hysterectomy.
[a]RH *vs* mRH.
[b]mRH *vs* SH.
[c]Judged by Common Terminology Criteria for Adverse Events v4.0.

recommended for grade 3 tumours from the results of two randomized trials (Hogberg *et al*, 2010); however, the addition of chemotherapy was related with only improved PFS, and there was no effect on OS. In contrast, the effect of systematic chemotherapy as adjuvant therapy has been evaluated for the patients with intermediate–high risk endometrial cancers. The Japanese Gynecologic Oncology Group compared pelvic radiotherapy and chemotherapy with cyclophosphamide, doxorubicin, and cisplatin in patients with stage IC–IIIC endometrial cancer, and suggested a survival advantage of chemotherapy in the women from the high-to-intermediate risk group (stage IC, >70 years of age, grade 3, stage II, or positive cytology with >50% myometrial invasion) (Susumu *et al*, 2008). Moreover, The Gynecologic Oncology Group study 122 revealed that chemotherapy with doxorubicin plus cisplatin was associated with superior PFS in patients with stage III–IV endometrial cancer along with a minimal residual tumour, compared with radiation therapy (Randall *et al*, 2006). These results have had a significant impact on clinical practice in the Japanese gynaecologic oncology community, and adjuvant chemotherapy was often used for the endometrial cancer patients with high-to-intermediate risk group including stage II disease. The present study included a higher abundance of patients treated with adjuvant chemotherapy, which might be reflecting completely different preference of Japanese physicians. However, the survival data of these series were not inferior to the previous reports that investigated stage II patients (Mariani *et al*, 2001; Sartori *et al*, 2001). Chemotherapy could be potentially a candidate for adjuvant therapy for endometrial cancers with intermediate–high risk. In the present study, there were no significant differences of

adjuvant therapy on survival. Of note, radiotherapy followed by chemotherapy produced lowest hazard ratio in local recurrence-free survival (HR = 0.28) and OS (HR = 0.35), although it did not reach statistical significance. Further analyses are needed to elucidate to select adjuvant therapy for the disease.

The limitation of the present study included a retrospective investigation and multi-institutional analysis. Also, the results obtained by the present study could potentially have a bias such as selection bias, and further prospective investigation is needed to confirm the impact of operative procedures. Nevertheless, the survival improvement was not observed by RH for endometrial cancer patients with suspected cervical involvement by multivariate analyses. The necessity of RH in these patients should be evaluated in further clinical studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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FULL PAPER

BJC

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Keywords: S-1; long-term; adjuvant chemotherapy; non-small cell lung cancer

Feasibility trial for adjuvant chemotherapy with docetaxel plus cisplatin followed by single agent long-term administration of S-1 chemotherapy in patients with completely resected non-small cell lung cancer: Thoracic Oncology Research Group Study 0809

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Background: We conducted a multicentre feasibility study for single agent long-term S-1 chemotherapy following docetaxel plus cisplatin in patients with curatively resected stage II–IIIA non-small cell lung cancer.

Methods: Patients received three cycles of docetaxel (60 mg m^{-2}) plus cisplatin (80 mg m^{-2}) and then received S-1 (40 mg m^{-2} twice daily) for 14 consecutive days with a 1-week rest for >6 months (maximum, 1 year). The primary end point was feasibility, which was defined as the proportion of patients who completed eight or more cycles of S-1 chemotherapy. If the lower 95% confidence interval (CI) of this proportion was 50% or more, then the treatment was considered as feasible. The sample size was set at 125 patients.

Results: One hundred and thirty-one patients were enrolled, of whom 129 patients were eligible and assessable. In all, 109 patients (84.5%) completed 3 cycles of docetaxel plus cisplatin and 66 patients (51.2%, 95% CI: 42.5–59.8) completed 8 or more cycles of S-1 treatment. Grade 3/4 toxicities during the S-1 chemotherapy included anaemia (7.3%), neutropaenia (3.7%), and anorexia (3.7%).

Conclusion: The toxicity level was acceptable, although the results did not meet our criterion for feasibility. Modification of the treatment schedule for S-1 chemotherapy might improve the treatment compliance.

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Primary surgery is the standard of care for resectable clinical stage I or II non-small cell lung cancer (NSCLC). The 5-year survival rate for patients with clinical stage IB and stage II surgically resected NSCLC was ~66% and 50%, respectively. The majority of patients with recurrences have distant metastases, indicating that systemic micrometastases are common in patients with completely resected NSCLC. To control distant micrometastasis and to improve patients' survival, adjuvant chemotherapy has been examined in patients with completely resected NSCLC of pathological stage I–III. Several randomised studies and meta-analyses have demonstrated that cisplatin-based adjuvant chemotherapy improved the overall survival (OS) in patients with pathological stage IB to III NSCLC (Arriagada *et al*, 2004; Hotta *et al*, 2004; Winton *et al*, 2005; Douillard *et al*, 2006; Pignon *et al*, 2006). However, the absolute increase in survival was only 4% at 5 years. Thus, new treatment strategies or drugs are needed to improve the clinical outcome in patients with resectable NSCLC.

A randomised phase III study demonstrated that adjuvant chemotherapy with uracil-tegafur (UFT) improved survival among patients with completely resected pathological stage I adenocarcinoma of the lung. The 5-year OS was 88% in the UFT group and 85% in the control group (hazard ratio 0.71, 95% confidence interval (CI) 0.52–0.98) (Kato *et al*, 2004). S-1 is an oral anticancer agent comprises tegafur, gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxicity of fluorouracil) in a molar ratio of 1 : 0.4 : 1 (Shirasaka *et al*, 1996). S-1 is approved for the treatment of NSCLC as well as gastric, colorectal, head and neck, breast, pancreatic, and biliary tract cancer in Japan. In a phase II trial, S-1 monotherapy produced a response rate of 22% as a first-line treatment in patients with advanced NSCLC (Kawahara *et al*, 2001). S-1 is believed to have a stronger antitumour activity against NSCLC than UFT, since UFT monotherapy produced a response rate of only 6% in another phase II study (Keicho *et al*, 1986). A randomised phase III trial demonstrated that S-1 plus carboplatin (CBDCA) was non-inferior in terms of OS, compared with paclitaxel plus CBDCA, in patients with advanced NSCLC (Okamoto *et al*, 2010). Another randomised phase III trial also demonstrated that S-1 plus CDDP was non-inferior in terms of OS, compared with docetaxel plus CDDP, in patients with advanced NSCLC (Katakami *et al*, 2012). Previous phase II trials demonstrated that S-1 monotherapy produced a response rate of 7–14% as a second-line treatment for advanced NSCLC (Totani *et al*, 2009; Govindan *et al*, 2011; Shiroyama *et al*, 2011).

Recent phase III trials have demonstrated that switch maintenance chemotherapy consisting of pemetrexed or erlotinib prolonged the OS of patients with advanced NSCLC who showed no signs of progression after four cycles of platinum-based chemotherapy (Ciuleanu *et al*, 2009; Cappuzzo *et al*, 2010). Continuation maintenance with pemetrexed also prolonged the OS in patients with non-squamous NSCLC in another randomised trial (Paz-Ares *et al*, 2012a,b). Maintenance chemotherapy has thus received considerable attention.

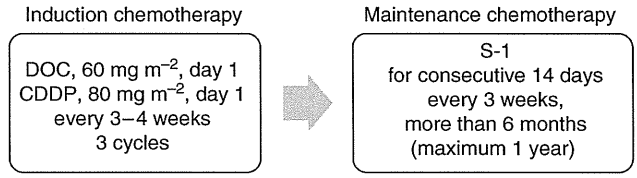
The Thoracic Oncology Research Group (TORG) conducted a randomised phase II study comparing docetaxel (DOC) plus CDDP with paclitaxel (PTX) plus CBDCA as an adjuvant chemotherapy in patients with completely resected stage IB to IIIA NSCLC (TORG 0503). This study showed that DOC plus CDDP had a promising activity with a favourable 2-year recurrence-free survival (RFS) rate (74.1% *vs* 72.5%, respectively) (Ohira *et al*, 2011). Taking these rationales into consideration, we conducted a feasibility study for adjuvant chemotherapy consisting of DOC plus CDDP followed by single agent long-term S-1 chemotherapy in patients with completely resected NSCLC (TORG 0809).

PATIENTS AND METHODS

Patient population. Patients were required to have completely resected stage II or IIIA (according to the Union Internationale Contre le Cancer (UICC) fifth TNM edition) NSCLC, an age of 20–74 years, and an ECOG performance status (PS) of 0 or 1. Other criteria included a PaO_2 at room air $\geqslant$70 torr or an SpO_2 at room air $\geqslant$95%, and adequate organ function (i.e., total bilirubin $\leqslant$1.2 mg dl^{-1}, AST and ALT $\leqslant$100 IU l^{-1}, serum creatinine $\leqslant$1.2 mg dl^{-1}, creatinine clearance $\geqslant$60 ml min^{-1}, leukocyte count $\geqslant$4000 per mm^3 and $\leqslant$12 000 per mm^3, neutrophil count $\geqslant$2000 per mm^3, haemoglobin $\geqslant$10.0 g dl^{-1}, and platelets $\geqslant$100 000 per mm^3). Patients were required to start the protocol treatment within 10 weeks after surgical resection.

Key exclusion criteria were a lack of recovery from surgical complications; active infection; interstitial pneumonia as determined using computed tomography (CT) of the chest; acute cardiac infarction within 6 months; uncontrolled heart disease, liver dysfunction, or diabetes mellitus; grade 2 or worse peripheral neuropathy; active concomitant malignancy; pregnancy or breast-feeding; a history of hypersensitivity to drugs including polysorbate-80; and the concurrent use of flucytosine. Patients who had undergone a pneumonectomy were also excluded. All the patients were required to provide written informed consent.

Treatment plan. The treatment schema is shown in Figure 1. Treatment was started within 1 week after enrolment in the study. Patients received adjuvant chemotherapy with DOC (60 mg m^{-2}, day 1) and CDDP (80 mg m^{-2}, day 1) every 3–4 weeks for up to three cycles. After the completion of adjuvant chemotherapy with DOC plus CDDP, if the leukocyte count was $\geqslant$3000 per mm^3, the neutrophil count was $\geqslant$1500 per mm^3, the platelet count was $\geqslant$100 000 per mm^3, the AST and/or ALT level was $\leqslant$100 IU l^{-1}, the total bilirubin level was $\leqslant$1.5 mg dl^{-1}, the serum creatinine level was $<$1.5 mg dl^{-1}, and all other non-haematological toxicities were grade 1 or better with the exception of alopecia, body weight loss, and hyponatraemia, then the patients were treated with oral S-1 at a dose of 40 mg m^{-2} twice daily for 14 consecutive days, followed by a 1-week rest. The actual dose of S-1 was selected as follows: patients with a body surface area (BSA) of $<$1.25 m^2 received 80 mg daily; those with a BSA of 1.25 m^2 or more but $<$1.5 m^2 received 100 mg daily; and those with a BSA of 1.5 m^2 or more received 120 mg daily. If the serum creatinine level was 1.2 mg dl^{-1} or more but $<$1.5 mg dl^{-1} before the initiation of S-1 chemotherapy, then the S-1 dose was reduced to a lower level. This 3-week cycle was repeated for 6 months (maximum, 1 year) if neither unacceptable toxicity nor tumour recurrence was observed. In the event of a leukocyte count of $<$2000 per mm^3, a platelet count of $<$75 000 per mm^3, an AST and/or ALT level of $\geqslant$100 IU l^{-1}, a total bilirubin level of $\geqslant$2.5 mg dl^{-1}, a serum



	S-1
BSA < 1.25 m^2	40 mg, b.i.d.
1.25 m^2 ⩽ BSA < 1.5 m^2	50 mg, b.i.d.
1.5 m^2 ⩽ BSA	60 mg, b.i.d.

BSA, body surface area.

Figure 1. **Treatment schema for this study.**

creatinine level of $\geqslant 1.5\,mg\,dl^{-1}$, appetite loss, diarrhoea, mucositis, nausea/vomiting of grade 2 or worse despite appropriate antiemetic therapy, and/or other grade 2 non-haematological toxicities other than body weight loss, alopecia, or hyponatraemia, the daily dose of S-1 was reduced from 120 to 100 mg, 100 to 80 mg, or 80 to 50 mg in the next cycle. If the patients experienced the above-mentioned toxicities after the dose reduction, then their daily dose of S-1 was reduced from 100 to 80 mg, or 80 to 50 mg. If a patient with a BSA of $<1.25\,m^2$ experienced the above toxicities at 50 mg, then the S-1 chemotherapy was terminated. If the adjuvant chemotherapy of DOC + CDDP was terminated after one or two cycles, then a shift to S-1 chemotherapy was allowed. However, these patients were not considered to have completed the protocol treatment.

Safety assessment and follow-up. For the toxicity assessment, blood samples were obtained before the start of each cycle. A chest X-ray examination was performed monthly throughout the study period. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. A CT examination of the chest was performed at 1, 2, 3, and 5 years after the initiation of the protocol treatment.

Study design and statistical analysis. This trial was designed as a multicentre, prospective, single-arm, feasibility study and the study protocol was approved by the institutional review board of each participating institution. All the study data were managed by the TORG0809 data centre at Kitasato University Research Center for Clinical Pharmacology.

The primary end point of this study was feasibility, which was defined as the proportion of patients who had completed eight or more cycles of S-1 chemotherapy. If the lower 95% CI of this proportion was 50% or more, then the treatment was considered as feasible. If a patient received 75% or more of S-1 in a cycle, that is, 21 times per cycle, this patient was considered to have completed the treatment cycle. If 72 out of 120 patients (60%) completed the protocol treatment, then the 95% CI of the proportion of the treatment completion was 51.2–68.8%. Considering the possibility of ineligible patients, the sample size was set at 125 patients.

The secondary end points included adverse events, OS, RFS, and recurrence pattern. Because of the short follow-up period, we will report the OS and RFS data elsewhere. We plan to analyse the OS and RFS at 5 years after the last enrolment, as described in the study protocol. The statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

This study was registered with the UMIN Clinical Trials Registry (number UMIN000001779).

RESULTS

Patient population. A total of 131 patients were enrolled in this study between January 2009 and November 2010 from 20 institutions in Japan. One patient did not receive any protocol treatment at the patient's request. Another patient was enrolled as p-stage IIIA according to the UICC 7th edition; however, the p-stage corresponded to IIIB according to the UICC 5th edition, making this patient ineligible. This patient received three cycles of docetaxel plus cisplatin and two cycles of S-1 chemotherapy, and she was included in the safety analysis. A total of 129 patients were eligible (Figure 2). The patient characteristics are listed in Table 1. Sixty-four percent of the patients were male; the median age was 63 years. Seventy-eight percent of the patients had an adenocarcinoma histology.

Treatment delivery and protocol compliance. Overall, 114 patients received two cycles or more of DOC + CDDP. Of these, 67 patients (58.8%) required a dose reduction of DOC or CDDP. The most common reason for the dose reduction of DOC and CDDP was grade 4 neutropaenia ($n = 63$), followed by a fever of 38.0 °C or higher ($n = 16$). The dose of CDDP was reduced because of anorexia, nausea, and/or vomiting of grade 2 or worse for more than a week ($n = 16$) and an elevated serum creatinine level of $1.5\,mg\,dl^{-1}$ or more ($n = 6$).

In total, 109 patients (84.5%) completed three cycles of adjuvant chemotherapy consisting of DOC + CDDP (Table 2). The main reasons for the discontinuation of the adjuvant chemotherapy were toxicity ($n = 15$) and patient refusal because of toxicity ($n = 7$) (Table 3). One patient terminated the DOC + CDDP treatment after one cycle and completed eight cycles of S-1 chemotherapy. Another patient terminated the DOC + CDDP treatment after two cycles and received three cycles of S-1 chemotherapy.

One hundred and eight patients received S-1 chemotherapy. Of these, 34 patients (31.5%) required the interruption of S-1 during a treatment cycle. Thirty-one patients (28.7%) required a dose reduction of S-1. The majority of the reasons for the interruption

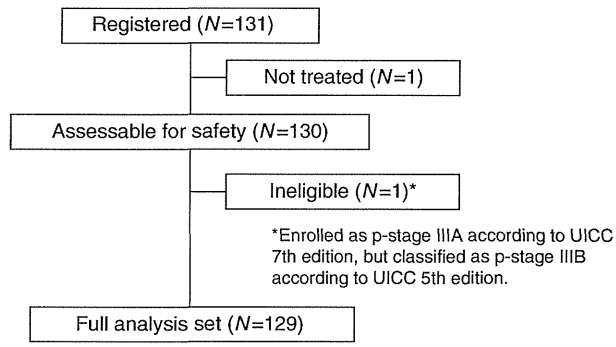


Figure 2. **CONSORT diagram.**

Table 1. Patient characteristics of 129 eligible patients

Characteristic	Number of patients
Sex	
Male	83
Female	46
Age (years)	
Median	63
Range	23–74
PS status	
0	107
1	22
Pathological stage[a]	
IIA	17
IIB	32
IIIA	80
Histological type	
Adenocarcinoma	100
Squamous cell carcinoma	25
Others	4

Abbreviations: PS = performance status; TNM = tumour-node-metastasis.
[a]Pathological stage was based on the Union Internationale Contre le Cancer fifth TNM edition.

or dose reduction of S-1 were appetite loss, diarrhoea, mucositis, or nausea/vomiting of grade 2 or worse ($n=27$), followed by other non-haematologic toxicities of grade 2 or worse ($n=20$).

One hundred and six patients (82.2%) completed three cycles of DOC + CDDP and subsequently switched to S-1 chemotherapy. Of these, 31 patients terminated the S-1 chemotherapy after receiving 3 or fewer cycles. A total of 66 patients (51.2%; 95% CI, 42.5–59.8%) completed 8 cycles or more of S-1 treatment (Table 2). The lower limit of the 95% CI for the completion rate was 42.5%, which was less than our previously defined criterion for treatment feasibility. The reasons for the discontinuation of the S-1 chemotherapy included toxicity ($n=17$), patient refusal because of toxicity ($n=15$), and recurrence ($n=6$) (Table 3).

Safety and toxicity. The most common grade 3 or 4 toxicity experienced during the DOC + CDDP treatment was neutropaenia (78.5%) (Table 4). Ten patients (7.7%) developed febrile neutropaenia; however, all these patients recovered after receiving appropriate antibiotic therapy. Two patients experienced grade 3 or 4 allergic reactions to DOC during the first cycle, resulting in treatment termination.

Grade 3 or 4 toxicities during the S-1 chemotherapy included anaemia (7.3%), neutropaenia (3.7%), anorexia (3.7%), dyspnoea (1.8%), and infection with neutropaenia of grade 0–2 (1.8%). Febrile neutropaenia was not observed. One treatment-related death occurred during the study. This patient was a 63-year-old man. After two cycles of S-1 chemotherapy, he developed grade 3 fatigue. On day 36 of the second cycle of S-1, grade 3 dyspnoea was observed, and his SpO_2 was 92% in room air. A CT scan of the chest revealed bilateral diffuse ground-glass opacities. Prednisolone (80 mg day^{-1}; 1 mg kg^{-1} per day) was administered, and an improvement in the opacities was observed. The prednisolone was tapered to 30 mg day^{-1} for 6 weeks; however, multiple cavity lesions were visible on a chest CT image obtained 2 months after the initiation of the steroid therapy. Multiple abscesses at the neck, axilla, chest, and femur were noted, and the patient developed hypotension. *Nocardia* was isolated in blood and abscess samples, with a diagnosis of disseminated nocardiosis. Sulfamethoxazole/trimethoprim and antibiotics were administered and artificial ventilation therapy was performed. The patient was taken off the respirator once, but the pneumonitis recurred and disseminated intravascular coagulation also developed, leading to death.

Table 2. Treatment delivery in 129 eligible patients

Treatment	Cycle	Number of patients	%	95% Confidence interval
Docetaxel + cisplatin	1	129	100	
	2	114	88.4	
	3	109	84.5	
Maintenance chemotherapy using S-1	1	106	82.2	
	2	97	75.2	
	3	86	66.7	
	4	75	58.1	
	5	73	56.6	
	6	72	55.8	
	7	71	55	
	8	67	51.9	
Completion		66	51.2	42.5–59.8

Table 3. Reason for discontinuation of the treatment

Reasons	Docetaxel + cisplatin	Maintenance chemotherapy using S-1
Recurrence	1	6
Toxicity	15	17
Patient refusal because of toxicity	7	15
Others	0	2

DISCUSSION

This feasibility study was designed to evaluate the tolerability, safety, and efficacy of single agent long-term administration of S-1 chemotherapy following three cycles of DOC plus CDDP in patients with completely resected stage II or IIIA NSCLC. Fifty-one percent of the patients (95% CI, 42.5–59.8%) completed three cycles of DOC plus CDDP and eight cycles or more of S-1 chemotherapy. The lower limit of the CI for this proportion was lower than the predefined criterion of 50%. Grade 3–4 haematologic toxicities were observed in 7.3% of patients, while grade 3–4 non-haematologic toxicities were observed in only 4%. However, grade 1–2 anorexia and/or fatigue were common, with rates of ~50–60%. S-1 was administered for 2 weeks with a 1-week rest. The long duration of S-1 administration might have been responsible for the low-grade but extended non-haematologic toxicities and might have been too intensive for patients especially after platinum-doublet chemotherapy. In a previous phase III study of adjuvant chemotherapy for gastric cancer with single agent of S-1, 78% of patients received S-1 for at least 6 months (Sakuramoto *et al*, 2007). Adjuvant chemotherapy of DOC + CDDP probably affected the compliance of S-1 chemotherapy negatively in our study. A modification of the treatment schedule for S-1 chemotherapy, such as a 2-week rest period rather than a 1-week rest period, might improve treatment compliance.

Efficacious treatment for advanced stage disease has been introduced and investigated in an adjuvant setting, such as bevacizumab plus platinum-doublet chemotherapy in patients with non-squamous cell carcinoma or erlotinib in patients with a mutated epidermal growth factor receptor gene. Recent phase III trials have demonstrated that switch maintenance chemotherapy consisting of pemetrexed or erlotinib, which were efficacious for second-line chemotherapy, prolonged the OS in patients with advanced NSCLC (Ciuleanu *et al*, 2009; Cappuzzo *et al*, 2010). Switch maintenance chemotherapy can be recognised as an early second-line chemotherapy. The purpose of adjuvant chemotherapy is to control micrometastasis and to prevent recurrence. Switch maintenance chemotherapy is considered to enhance the efficacy of adjuvant chemotherapy. Previous phase II trials have demonstrated that S-1 monotherapy produced a response rate of 7–14%, a median progression-free survival (PFS) of 3–4 months, and a median OS of 7–16 months as a second-line treatment for advanced NSCLC (Totani *et al*, 2009; Govindan *et al*, 2011; Shiroyama *et al*, 2011). Pemetrexed is effective against non-squamous NSCLC; on the other hand, S-1 is effective against both non-squamous and squamous NSCLC. A randomised trial comparing S-1 and docetaxel as a second- or third-line chemotherapy is now underway in Asia. Switch maintenance chemotherapy using S-1 is also being evaluated as a first-line chemotherapy for patients with advanced NSCLC in a phase II study (UMIN000003676). If promising RFS or OS data in this trial are obtained, then a prospective randomised trial will be warranted to compare adjuvant chemotherapy with or without single agent long-term administration of S-1 chemotherapy.

Table 4. Toxicity

	Docetaxel + cisplatin ($n = 130$)					Maintenance chemotherapy using S-1 ($n = 109$)					
Toxicity	**Toxicity grade**					**Toxicity grade**					
	1	2	3	4	%3–4	1	2	3	4	5	%3–5
Haematologic											
Neutropaenia	4	14	39	63	78.5	20	18	4	0	0	3.7
Anaemia	52	31	1	0	0.8	26	38	6	2	0	7.3
Thrombocytopaenia	30	6	0	0	0	35	0	0	0	0	0
Gastrointestinal											
Anorexia	55	47	22	0	16.9	43	21	4	0	0	3.7
Vomiting	23	20	5	0	3.8	11	5	1	0	0	0.9
Diarrhoea	35	11	15	0	11.5	19	3	1	0	0	0.9
Mucositis	12	4	0	0	0	23	7	0	0	0	0
Hepatic											
AST	14	5	2	0	1.5	25	5	0	0	0	0
ALT	25	9	1	0	0.8	24	4	0	0	0	0
Renal											
Creatinine	39	9	0	0	0	30	8	0	0	0	0
Neurologic											
Neuropathy (sensory)	9	4	0	0	0	19	2	2	0	0	1.8
Others											
Hyponatraemia	57	—	18	5	17.7	16	—	0	0	0	0
Fatigue	57	21	5	0	3.8	41	9	2	0	0	1.8
Allergic reaction	7	0	1	1	1.5	1	0	0	0	0	0
Dehydration	0	0	2	0	1.5	0	0	0	0	0	0
Alopecia	68	29	0	0	0	35	10	0	0	0	0
Febrile neutropaenia	—	—	10	0	7.7	—	—	0	0	0	0
Infection with G3–4 neutropaenia	0	3	5	0	3.8	0	0	0	0	0	0
Infection with G0–2 neutropaenia	0	3	2	1	2.3	1	3	1	0	1	1.8
Pneumonitis	1	0	0	0	0	0	1	1	0	0	0.9
Dyspnoea	0	1	0	0	0	8	2	2	0	0	1.8

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; G = grade.

A recent phase III trial has also demonstrated that continuation maintenance chemotherapy consisting of pemetrexed prolonged the OS and PFS in patients with advanced non-squamous NSCLC. However, concurrent chemoradiotherapy consisting of pemetrexed plus CDDP followed by four cycles of pemetrexed did not improve OS over concurrent chemoradiotherapy consisting of etoposide plus CDDP in patients with stage III non-squamous NSCLC (PROCLAIM study). Up to four cycles of pemetrexed in the PROCLAIM study, comparable to S-1 chemotherapy in our study, might be unable to enhance curative treatment effect. We might have to distinguish strategy for stage IV disease from that for curative situations in completely resected stage II/III disease.

Combination chemotherapy consisting of DOC plus CDDP is a standard regimen for the treatment of patients with advanced NSCLC. A randomised trial demonstrated that DOC + CDDP resulted in a more favourable response rate and OS than vinorelbine (VNR) plus CDDP in chemo-naïve patients with advanced NSCLC. The median OS period was 11.3 months for patients treated with DOC plus CDDP and 10.1 months for patients treated with VNR plus CDDP. The hazard ratio was 1.183 (97.2% CI, 0.989–1.416) (Fossella *et al*, 2003). A higher incidence of grade 3–4 anaemia, nausea, and vomiting was observed in VNR + CDDP arm, compared with DOC + CDDP arm. Febrile neutropaenia occurred in <5% of patients in both regimens. Furthermore, the single agent DOC had a more favourable OS period than the single agent VNR in both first-line and second-line settings in patients with advanced NSCLC (Fossella *et al*, 2000). TORG0503 study demonstrated that >90% of patients completed three planned cycles of adjuvant chemotherapy in both DOC + CDDP and PTX + CBDCA arms. On the other hand, the most common regimen for adjuvant chemotherapy for pathological stage II or III NSCLC is VNR + CDDP, because most randomised trials, which resulted in positive results, adopted VNR + CDDP. Considering the promising results of clinical trials for advanced NSCLC, it might be reasonable to select DOC + CDDP as an adjuvant chemotherapy in patients with completely resected stage II or III NSCLC. Indeed, DOC + CDDP has been selected as one of the standard adjuvant chemotherapy regimens in ECOG1505 study, which is a randomised phase III trial of adjuvant chemotherapy with or without bevacizumab in patients with completed resected early-stage NSCLC (Wakelee *et al*, 2011). However, 7.7% of patients experienced grade 3 febrile neutropaenia

during the chemotherapy of DOC + CDDP in our study. Relatively high incidence of febrile neutropaenia could not support the use of adjuvant chemotherapy with DOC + CDDP as a new alternative. Four cycles of VNR + CDDP followed by long-term administration of S-1 might be a better strategy in a future study.

The treatment cycle for DOC plus CDDP was set at three because the actual median numbers of cycles delivered in previous phase III studies of adjuvant chemotherapy were three or four (Winton *et al*, 2005; Douillard *et al*, 2006), and a randomised study demonstrated that four cycles or more of platinum-based chemotherapy did not improve the OS in patients with advanced NSCLC (Smith *et al*, 2001). In the TORG0503 study, the number of treatment cycles for DOC plus CDDP or for PTX plus CBDCA as an adjuvant chemotherapy was also set at three, and a favourable 2-year RFS rate was observed (Ohira *et al*, 2011).

A previous randomised phase II study demonstrated that adjuvant chemotherapy with pemetrexed plus CDDP was safe and feasible with less toxicity and superior dose delivery compared with VNR + CDDP (Kreuter *et al*, 2013). Pemetrexed plus CDDP is considered as suitable for adjuvant chemotherapy because of relatively less toxic and promising antitumour activity in patients with non-squamous NSCLC. A randomised phase III study is underway comparing pemetrexed plus CDDP and VNR + CDDP in patients with completely resected stage II–IIIA non-squamous NSCLC in Japan. However, it is difficult to conduct a randomised phase III study of adjuvant chemotherapy in patients with NSCLC, because large sample size and long-term follow-up are needed. Therefore, a randomised phase II study containing control arm should be taken into consideration to select appropriate experimental treatment.

Aprepitant, a standard antiemetic drug for cisplatin therapy, was approved in December 2009 in Japan. As a result, ~20 patients did not receive aprepitant. If aprepitant had been available for all the enrolled patients, then the treatment compliance might have improved. Furthermore, 2 out of the 129 patients experienced grade 3 or 4 allergic reactions to DOC during the first cycle, resulting in treatment termination. Premedication for DOC + CDDP included dexamethasone only on day 1 in this study. The administration of dexamethasone on the day before the initiation of DOC + CDDP and an antihistamine on day 1 might be recommended in future clinical trials to prevent anaphylaxis in response to DOC.

In conclusion, the toxicity level of S-1 chemotherapy was acceptable, although the treatment completion rate did not meet our criterion for feasibility. A modification of the treatment schedule for S-1 chemotherapy, such as a 2-week rest period rather than a 1-week rest period, might improve treatment compliance. After referring to the results for OS and RFS, we would like to plan a randomised trial to investigate whether platinum-based chemotherapy followed by single agent long-term administration of S-1 chemotherapy improves survival in patients with completely resected stage II or III NSCLC.

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Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial

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See Online for appendix

Summary

Background **The primary analysis of the JGOG 3016 trial showed that a dose-dense paclitaxel and carboplatin regimen significantly improves progression-free and overall survival compared with the conventional regimen as first-line chemotherapy for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer. We report the long-term follow-up results for survival.**

Methods **This randomised controlled trial was done at 85 centres in Japan. Patients with stage II–IV ovarian cancer were randomly assigned to receive conventional treatment (carboplatin area under the curve [AUC] 6 mg/mL per min and paclitaxel 180 mg/m² on day 1) or dose-dense treatment (carboplatin AUC 6 mg/mL per min on day 1 and paclitaxel 80 mg/m² on days 1, 8, and 15). The treatments were repeated every 3 weeks for six cycles; responding patients had three additional cycles. The randomisation was done centrally by telephone or fax, stratified by residual disease, stage, and histological type. The primary endpoint was progression-free survival; overall survival was a secondary endpoint. Long-term information on adverse events was not collected. Efficacy analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00226915.**

Findings **637 patients were enrolled, of whom 631 were analysed (312 assigned to the dose-dense regimen, 319 to the conventional regimen). Median follow-up was 76·8 months (IQR 68·9–85·6). Median progression-free survival was significantly longer in the dose-dense treatment group than in the conventional treatment group (28·2 months [95% CI 22·3–33·8] *vs* 17·5 months [15·7–21·7]; hazard ratio [HR] 0·76, 95% CI 0·62–0·91; p=0·0037). Median overall survival was 100·5 months (95% CI 65·2–∞) in the dose-dense treatment group and 62·2 months (52·1–82·6) in the conventional treatment group (HR 0·79, 95% CI 0·63–0·99; p=0·039).**

Interpretation **Dose-dense treatment offers better survival than conventional treatment and is a potential new standard of care for first-line chemotherapy for patients with advanced epithelial ovarian cancer.**

Funding **Japanese Gynecologic Oncology Group, Bristol-Myers Squibb.**

Introduction

A combination of paclitaxel and carboplatin is the standard first-line chemotherapy regimen for treatment of ovarian cancer. In the most recent consensus statements for management of ovarian cancer[1] from the 4th International Ovarian Cancer Consensus Conference, the Gynecologic Cancer InterGroup recommended the use of paclitaxel 175 mg/m², administered intravenously over 3 h, followed by carboplatin as an intravenous infusion over 30–60 min at an area under the curve of 5–6 mg/mL per min repeated every 3 weeks for six cycles. Further treatment options recommended by the group include intraperitoneal treatment for patients with small-volume residual disease and dose-dense weekly paclitaxel in combination with carboplatin every 3 weeks. These recommendations were based on the results of JGOG 3016,[2] in which the Japanese Gynecologic Oncology Group showed that progression-free survival was significantly improved in patients taking dose-dense paclitaxel and carboplatin (28·0 months), compared with those taking conventional paclitaxel and carboplatin every 3 weeks (17·2 months), as a first-line chemotherapy regimen for stage II–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer (hazard ratio [HR] 0·71, 95% CI 0·58–0·88; log-rank p=0·0015).

Dose-dense paclitaxel and carboplatin prolonged progression-free survival by 11 months in the primary analysis at a median follow-up of 29 months, despite a higher proportion of patients discontinuing treatment in the dose-dense paclitaxel and carboplatin group (53% *vs* 37%).[2] Overall survival at 3 years was 72·1% in the dose-dense group and 65·1% in the conventional group (HR 0·75, 95% CI 0·57–0·98; p=0·03). Severe haematological and non-haematological toxic effects, including

neuropathy, were much the same between groups except for anaemia, which was significantly more common in the dose-dense paclitaxel and carboplatin group. Here, we report the long-term follow-up results for progression-free and overall survival from a post-hoc analysis.

Methods

Participants

JGOG 3016 was a randomised, controlled trial[2]—details of the study have been published previously. The study was done in 85 centres in Japan. Patients with histologically identified stage II–IV epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer were eligible. If the results of only cytological examinations were available, patients had to meet 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[3] of more than 1:25 or no evidence of gastrointestinal cancer if the CA125:CEA ratio was less than or equal to 1:25. Patients also had to be aged 20 years or older, have an Eastern Cooperative Oncology Group performance status of 0–3, and have adequate organ function. Patients were excluded if they had an ovarian tumour with a low malignant potential or a synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ.

All patients gave written informed consent before enrolment. The study was approved by the institutional review boards of all participating centres.

Randomisation and masking

We did randomisation centrally by telephone or fax, stratified by residual disease (≤1 cm *vs* >1 cm), International Federation of Gynecology and Obstetrics stage (stage II *vs* stage III *vs* stage IV), and histological type (clear-cell or mucinous *vs* serous or other) with an option to avoid imbalances greater than two within each institution. The randomisation sequence was generated by an independent registration office using a validated computer system. The trial was open-label.

Procedures

Patients were randomly assigned to receive paclitaxel and carboplatin as either a conventional regimen or a dose-dense regimen. Both groups received carboplatin at a dose calculated to produce an area under the curve (AUC) of 6 mg/mL per min on day 1 of a 21-day cycle, given as an intravenous infusion over 1 h. Patients given the conventional regimen also received paclitaxel, 180 mg/m² on day 1, given as a 3 h intravenous infusion. 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 using creatinine clearance instead of the glomerular filtration rate. Creatinine clearance was calculated with the formula of Jelliffe.[4] Irrespective of the calculated doses, the maximum absolute dose given to each patient was limited to 1000 mg. Treatments were repeated every 3 weeks for six cycles. Patients with measurable lesions who had a partial response or a complete response received three additional cycles of chemotherapy.

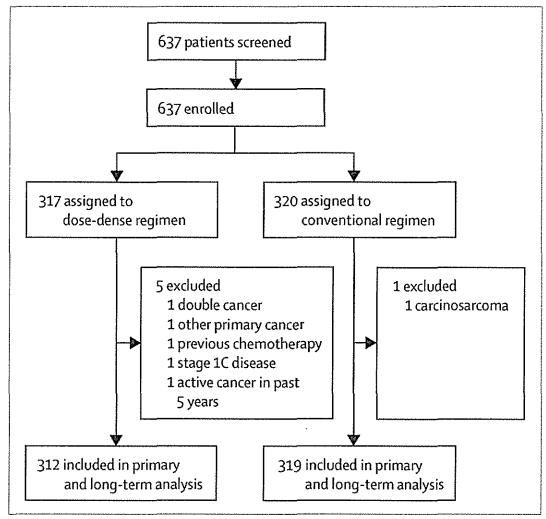

Figure 1: Trial profile

Patients in both groups had to have an absolute neutrophil count of 1000 cells per μL or greater and a platelet count of 75 000 platelets per μL or greater to receive subsequent cycles of treatment. Patients taking the dose-dense regimen also had to have an absolute neutrophil count of 500 cells per μL or greater and a platelet count of 50 000 platelets per μL or greater before they received paclitaxel on days 8 and 15. Treatment was delayed for a maximum of 3 weeks. The carboplatin dose was reduced when febrile neutropenia occurred, an absolute neutrophil count of less than 500 cells per μL persisted for 7 days or longer, platelet count was less than 10 000 platelets per μL, platelet count was 10 000–50 000 platelets per μL accompanied by signs of bleeding, or treatment was delayed because of haematological toxic effects for more than 1 week. The dose of paclitaxel was reduced in patients with grade 2 or higher peripheral neuropathy. Patients could have interval debulking surgery after two to four cycles of chemotherapy, secondary debulking or second-look surgery after six cycles of chemotherapy, or both.

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

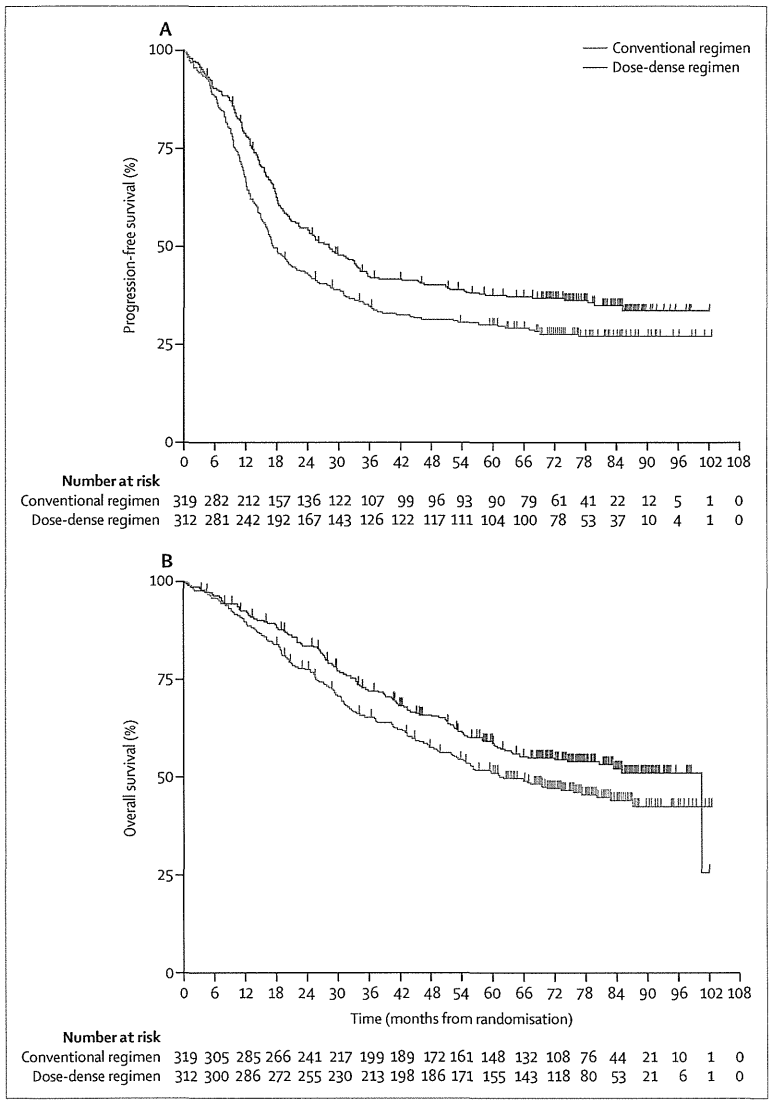

Figure 2: **Kaplan-Meier analyses of survival by treatment regimen**
Progression-free survival (A) and overall survival (B) in each treatment group.

The primary endpoint was progression-free survival, secondary endpoints were overall survival, response rate, and adverse events. In the present analysis we assessed long-term progression-free survival and overall survival. Long-term information on adverse events was not collected.

Statistical analysis

This post-hoc analysis of the trial was triggered after a median of more than 5 years' follow-up in the surviving patients, with a data cutoff date of Oct 31, 2011. The planned analyses of progression-free survival and overall survival included data on eligible patients according to the intention-to-treat principle. Progression-free survival was defined as the time from the date of randomisation to the date of the first occurrence of any of: death from any cause, appearance of any new lesions that could be measured or assessed clinically, or meeting the CA125 criteria for disease progression.[5] Overall survival was defined as the time from the date of randomisation to the date of death resulting from any cause. In January, 2005, the protocol was amended to have a sample size of 600 patients. This 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.

We evaluated survival by the Kaplan-Meier method, and compared treatment groups with the log-rank test. We used a Cox proportional hazards model to calculate HRs and 95% CIs. We also used a Cox proportional hazards model to assess the effect of treatment after adjustment for histological subtypes, residual disease, and performance status. Subgroup analyses included a log-rank test stratified for factors used for randomisation and interaction analyses based on stratification factors. All the analyses were done with SAS software (version 9.2).

This study 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. NK, FT, and HM had access to the raw data. 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 28, 2003 and Dec 28, 2005, 637 patients were enrolled. 631 patients (312 patients in the dose-dense regimen group and 319 patients in the conventional regimen group) were evaluable in the analysis of long-term outcomes (figure 1).

At the time of the final follow-up (Oct 31, 2011), median follow-up was 76·8 months (IQR 68·9–85·6) for patients with censored data. 426 patients had progressed or died and 307 deaths had been recorded.

Both progression-free survival and overall survival were significantly longer in the dose-dense regimen group than in the conventional regimen group (figure 2). Median progression-free survival was 28·2 months (95% CI 22·3–33·8) in the dose-dense regimen group and 17·5 months (15·7–21·7) in the conventional regimen group (HR 0·76, 95% CI 0·62–0·91; p=0·0037). Median overall survival was 100·5 months (95% CI 65·2–∞) in the dose-dense regimen group versus 62·2 months (52·1–82·6) in the conventional regimen group (HR 0·79, 95% CI 0·63–0·99; p=0·039). 5-year overall survival was 58·7%

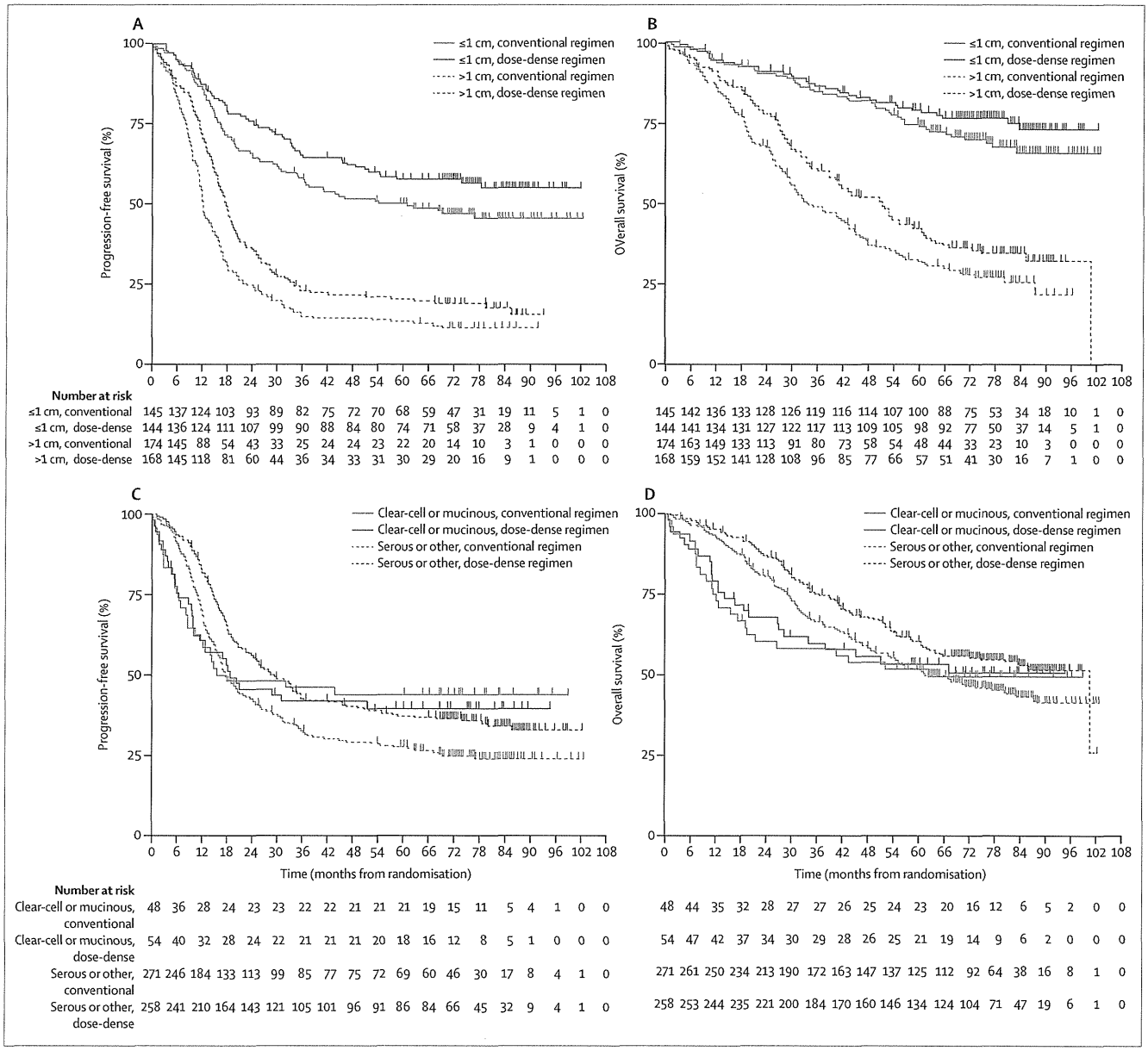

Figure 3: **Kaplan-Meier analyses of survival by treatment regimen in subgroups**
Progression-free survival (A) and overall survival (B) in each treatment group, stratified by residual disease (≤1 cm *vs* >1 cm), and progression-free survival (C) and overall survival (D) in each treatment group, stratified by histological type.

(95% CI 52·9–64·1) in the dose-dense group versus 51·1% (45·4–56·6) in the conventional regimen group.

Figure 3 and the appendix show survival by the stratification subgroups. Median progression-free survival in patients with residual disease at least 1 cm was higher for those dose-dense regimen group than for those in the conventional regimen group (17·6 months, 95% CI 15·6–19·4 *vs* 12·1 months, 11·2–14·3; HR 0·71, 95% CI 0·56–0·89; p=0·0029; figure 3A). Median progression-free survival in patients with residual disease less than 1 cm tended did not differ significantly between groups (not reached *vs* 60·9 months, 35·0–∞; HR 0·74, 95% CI 0·53–1·04; p=0·08; figure 3A). Median overall survival of patients with residual disease at least 1 cm was better in the dose-dense regimen group versus the conventional regimen group (51·2 months,

	Progression-free survival		Overall survival	
	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Conventional regimen *vs* dose-dense regimen	0·72 (0·60–0·88)	0·0009	0·79 (0·63–0·99)	0·0403
Stage				
II *vs* III	3·33 (2·24–4·94)	<0·0001	3·24 (1·92–5·47)	<0·0001
II *vs* IV	4·49 (2·86–7·06)	<0·0001	4·27 (2·40–7·59)	<0·0001
Residual disease (≤1 cm *vs* >1 cm)	2·17 (1·75–2·71)	<0·0001	2·58 (1·96–3·39)	<0·0001
Performance status (0–1 *vs* 2–3)	1·50 (1·11–2·03)	0·0085	1·70 (1·23–2·35)	0·0015

HR=hazard ratio.

Table: Results of multivariate analysis for progression-free survival and overall survival

40·1–58·3 *vs* 33·5 months, 29·3–43·6; HR 0·75, 95% CI 0·57–0·97; p=0·0027; figure 3B), but it did not differ significantly between treatment groups in patients with residual disease less than 1 cm (not reached *vs* not reached; HR 0·76, 95% CI 0·49–1·19; p=0·23; figure 3B). According to histological subtype, progression-free and overall survival of patients with serous or other histological subtypes was longer in the dose-dense regimen group than in the conventional regimen group (median progression-free survival 28·7 months, 95% CI 24·0–35·3 *vs* 17·5 months, 15·8–21·1; HR 0·70, 95% CI 0·57–0·86; p=0·0007; median overall survival 100·5 months, 65·2–∞ *vs* 61·2 months, 52·6–82·6; HR 0·76, 95% CI 0·59–0·97; p=0·0252; figure 3C, 3D). In patients with clear-cell or mucinous tumours, progression-free and overall survival did not differ significantly between treatment groups (median progression-free survival 18·7 months, 9·9–∞ *vs* 16·7 months, 8·5–∞; HR 1·06, 95% CI 0·63–1·76; p=0·84; median overall survival not reached *vs* 62·2 months, 19·0–∞; HR 0·92, 95% CI 0·53–1·61; p=0·776; figure 3C, 3D).

In the multivariate analysis, after adjustment for prognostic variables, treatment with the dose-dense regimen was associated with a significantly better progression-free and overall survival (table). Stage III or IV disease, residual disease at least 1 cm, and a poor performance status were associated with poor progression-free survival and overall survival (table). We did ad-hoc analyses to assess the effect of treatment delays, dose reductions, and dose intensity of carboplatin and paclitaxel. Dose reductions, treatment delays of chemotherapy, or lower relative dose intensity (<80%) of carboplatin were not independent prognostic factors for overall survival (data not shown). Only lower relative dose intensity (<80%) of paclitaxel was associated with a poor overall survival (HR 1·42, 95% CI 1·12–1·81; p=0·004) according to multivariate analysis.

Discussion

A combination of platinum and a taxane has been a cornerstone of treatment of epithelial ovarian, fallopian tube, and peritoneal cancer for more than 15 years. The addition of a third cytotoxic drug provides no benefit, including in both triplet combinations and sequential doublets.[6] However, improvements might be made through changes in scheduling, dose intensity, or delivery.[7] We have shown that a dose-dense regimen improves progression-free and overall survival after 5 years of follow-up. The long-term results of this study, in which each group received the same dose and schedule of carboplatin, reinforce this strategy as a potential standard of care (panel).

We did not assess long-term adverse events in the present study. In the original report,[2] anaemia was more common in the dose-dense regimen group versus the conventional regimen group (69% *vs* 44%), but other haematological toxic effects, grade 3 or 4 hypersensitivity reactions (1·9% *vs* 1·6%), and neurotoxicity (7% *vs* 6%) were not significantly different between groups.

Median overall survival in the optimally resected group (with residual disease <1 cm) who received the conventional regimen was better than that in previous trials done in Europe and the USA. This and other studies have shown that Asian patients with ovarian cancer have significantly better survival than do non-Hispanic white patients.[9,10] The study by duPont and colleagues[9] enrolled patients from South Korea and Japan in the Gynecologic Oncology Group 218 phase 3 study with advanced-stage ovarian cancer.[8] Overall survival was significantly higher in Asian patients when adjusted for age, stage, residual disease, performance status, and histology. Future studies should explore biological differences, environmental factors, socioeconomic factors, and response to treatment to clarify the racial and ethnic differences in survival.

In the stratification subgroup analyses, the greatest benefit was achieved in the group of patients with residual disease of 1 cm or more and who had serous or other histology (not clear-cell or mucinous). The improvement in median overall survival (33·5 to 51·2 months) was greater than the improvement in median progression-free survival (12·1 to 17·6 months) for patients with residual disease of 1 cm or more. The reason for this difference is unclear, although subsequent treatment could affect this outcome. The proportion of patients who received subsequent treatments (chemotherapy including platinum *vs* non-platinum chemotherapy) after discontinuation of the protocol treatment did not differ between both groups (data was not shown). However, we did not assess the patients who received subsequent treatment with weekly paclitaxel. The dose-dense regimen might have had a favourable effect in the optimally resected group: progression-free survival was longer in this group. More patients or more events will be needed to detect the effect on overall survival. We report no advantage for clear cell or mucinous histological types, suggesting that other

Panel: Research in context

Systematic review

We searched PubMed, the abstracts of major oncology congresses (American Society of Clinical Oncology and European Society for Medical Oncology), and ClinicalTrials.gov. We used MeSH and full-text search terms for advanced ovarian cancer, chemotherapy, and phase 3 clinical trials, limiting our results to English language articles and abstracts published or presented in the past 2 years. For PubMed, the search was: (advanced[All Fields] AND ("ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields] AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields])) AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields]) AND (Clinical Trial, Phase III[ptyp] AND ("2010/07/05"[PDAT] : "2013/07/05"[PDAT]) AND English[lang]). For conferences, the search was: "ovarian cancer" or "advanced ovarian cancer", manually limited to abstracts. The last search was done on July 5, 2013. We identified 14 results in PubMed. The most promising treatment was bevacizumab[8] combined with first-line chemotherapy of carboplatin and paclitaxel for advanced ovarian cancer. The use of bevacizumab during and up to 10 months after carboplatin and paclitaxel chemotherapy prolongs median progression-free survival by about 4 months.

Interpretation

Dose-dense carboplatin and paclitaxel is the most active treatment other than targeted treatment with bevacizumab for advanced ovarian cancer. Several confirmatory trials using the dose-dense regimen with or without bevacizumab are now ongoing in Europe and the USA. If these studies confirm the results of JGOG 3016, then it is likely that dose-dense chemotherapy will become an internationally accepted standard of care.

treatment strategies are needed. Both clear cell and mucinous tumours are distinct from high-grade serous cancer and can be classified as type I ovarian cancers, whereas type II tumours comprise the more common high-grade serous carcinomas.[11] A randomised clinical trial (JGOG 3017; University Hospital Medical Information Network in Japan number 000000499) is underway to compare carboplatin and paclitaxel with cisplatin and irinotecan. Standard chemotherapeutic drugs have only modest activity against clear-cell cancer. Greater benefits might be achieved with molecularly targeted treatments, such as sunitinib[12] or mTOR inhibitor.[13]

We calculated the carboplatin dose with the formulas of Calvert and Jellife without adjustment for serum creatinine concentrations. We used the enzymatic peroxidase-antiperoxidase method to estimate the glomerular filtration rate for measurement of serum creatinine. This method can result in an excessive dose of carboplatin and more severe myelotoxicities than the methods used in previous trials.[6,14] Several methods have been proposed to estimate the glomerular filtration rate more accurately,[15–17] but no global consensus exists as to the best method for assessment of renal function as the basis for determining the dose of carboplatin. For this reason, we did not use any adjustment methods to calculate the carboplatin dose. In our post-hoc prognostic analysis, the relative dose intensity of carboplatin was not associated with progression-free or overall survival (data not shown). Therefore, possible excessive doses of carboplatin probably have little effect on survival compared with the different dose schedules for paclitaxel.

The best doses and schedule for a dose-dense regimen of paclitaxel and carboplatin are still unclear. An Italian trial (MITO-7; NCT00660842) is assessing a different schedule of weekly carboplatin and a lower paclitaxel dose than our trial: weekly carboplatin (AUC 2 mg/mL per min) plus weekly paclitaxel (60 mg/m^2) compared with carboplatin (AUC 6 mg/mL per min, administered every 3 weeks) and paclitaxel (175 mg/m^2). The weekly regimen did not significantly improve progression-free survival compared with the conventional regimen (18·8 months *vs* 16·5 months; p=0·18), but was associated with better quality of life and fewer toxic effects.[18] Other ongoing studies—including the ICON8 trial (NCT01654146), the GOG 262 trial (NCT01167712), and the GOG 262 trial (NCT00951496)—are assessing different schedules and doses in an effort to establish the best dose-dense regimen.

Dose-dense treatment offers a potential new standard of care for first-line chemotherapy for patients with advanced epithelial ovarian cancer. Ongoing studies will clarify the best dose, schedule, and route of administration.

Contributors

NK, MY, SI, FT, HM, EK, TS, and KO had the idea for, and designed, the study with the Japanese Gynecologic Oncology Group. MY was the coordinating principal investigator. NK, FT, and HM analysed and interpreted the results. NK wrote the first draft. KO was responsible for the overall planning and conduct of the study. NK, MY, SI, EK, DA, TJ, SK, FT, TS, and KO enrolled patients and collected data. 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.

Conflicts of interest

SI has received honoraria from Bristol-Myers Squibb. NK has received honorara from Nippon Kayaku. NK and DA have received grants from Nippon Kayaku. The other authors declare that they have no conflicts of interest.

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ORIGINAL RESEARCH

Analysis of the antitumor activity of gemcitabine and carboplatin against ovarian clear-cell carcinoma using the DNA damage marker γH2AX

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Background: Differences in the incidence and type of DNA damage induced by antitumor agents for ovarian clear-cell carcinoma (CCC) were determined in two CCC cell lines, using γH2AX.

Materials and methods: The antitumor activity of gemcitabine (GEM) and carboplatin (CBDCA) were examined using cultured cell lines of CCC (OVISE and RMG-I). Each cell line was treated with GEM and CBDCA, the cells were collected, fixed, and then reacted with anti-γH2AX antibody. γH2AX and nuclear DNA were then simultaneously detected by flow cytometry using fluorescein isothiocyanate and propidium iodide, respectively, to determine the amounts of γH2AX formed in each cell-cycle phase.

Results: After administration of GEM, both cell lines showed DNA damage and cell-cycle arrest in the S and G_2/M phases, and increased apoptosis. Similarly, with CBDCA, OVISE showed S- and G_2/M-phase arrest, while RMG-I showed G_2/M-phase arrest.

Conclusion: The mechanism of action of GEM and CBDCA in CCC cell lines was elucidated using γH2AX as a DNA damage marker. Our findings suggested that concomitant use of GEM plus CBDCA may be effective in the treatment of CCC.

Keywords: γH2AX, clear-cell carcinoma, ovarian cancer, DNA damage, apoptosis, gemcitabine, carboplatin

Introduction

Ovarian clear-cell carcinoma (CCC), a subtype of epithelial ovarian cancer, is relatively less sensitive to chemotherapy, and is therefore classified as a refractory ovarian cancer.[1] It has been shown that a combination of carboplatin (CBDCA) and paclitaxel (PTX), a standard therapy for ovarian cancer,[2,3] is effective against serous adenocarcinoma and endometrioid adenocarcinoma, with a response rate of approximately 75%, while CCC shows lower response rates, ranging from 18% to 50%.[4] The incidence of CCC has been increasing and is now estimated to be 23% in Japan, while that in Europe is reported to be 5%–6%. No treatment has been established yet for this histological subtype of ovarian cancer. Histopathology remains the gold standard for classifying epithelial ovarian cancer into subgroups; however, there is emerging evidence indicating differences in the genetic and molecular profiles among these cancers. On the other hand, there is no international consensus regarding the necessity of establishing treatment strategies based on the histological subtype. Current chemotherapeutic options for ovarian cancer include drugs inducing DNA damage (eg, cisplatin and CBDCA), microtubule inhibitors (eg, PTX), topoisomerase inhibitors (eg, polyethylene glycolated liposomal

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doxorubicin, topotecan, irinotecan), and antimetabolites (eg, gemcitabine [GEM] and 5-fluorouracil).

Recently, it has become apparent that phosphorylation of histone H2AX, one of the variants of the nucleosome core histone H2A, can serve as a sensitive and reliable marker of DNA damage (Figure 1A). More specifically, DNA damage, particularly that involving the formation of DNA double-strand breaks, induces phosphorylation of histone H2AX on Ser-139; phosphorylated H2AX is termed γH2AX (Figure 1B).[5] Dot γH2AX, detectable using γH2AX-specific antibody, is considered to be a specific marker of DNA damage. Therefore, DNA damage can be detected by immunocytochemistry.[6]

We reported previously that γH2AX is a useful marker for the evaluation of DNA damage and apoptosis.[7] In this study, we focused on γH2AX as a marker of DNA damage to examine the cellular effects of GEM and CBDCA on CCC in terms of cell-cycle arrest, DNA damage, and induction of apoptosis. In addition, chemotherapeutic regimens that are likely to be effective in the treatment of CCC are discussed.

Materials and methods

Cell culture

We used two CCC cell lines (OVISE and RMG-I) obtained from the Health Science Research Resources Bank (Osaka, Japan). OVISE was established from a patient with metastatic disease after completion of six cycles of a platinum-based combination therapy, and was cultured in dishes (BD, Franklin Lakes, NJ, USA) containing Roswell Park Memorial Institute 1640 medium (Sigma-Aldrich, St Louis, MO, USA) supplemented with 10% fetal bovine serum. RMG-I was established from a chemotherapy-naïve patient with ascites, and was reported to show primary platinum resistance.[8] RMG-I was grown in dishes (BD) in Ham F-12 medium supplemented with 10% fetal bovine serum. For both cell lines, the medium was supplemented with 100 U/mL penicillin and 100 μg/mL streptomycin (Meiji Seika, Tokyo, Japan). All cell lines were maintained at 37°C in a humidified atmosphere of 5% CO_2 in air.

Drug

GEM was dissolved in dimethyl sulfoxide (Sigma-Aldrich); the final concentration of dimethyl sulfoxide in the culture medium never exceeded 0.1% (w/v). CBDCA was dissolved in phosphate-buffered saline (PBS). The concentrations of GEM and CBDCA were set to correspond to the blood concentration at a standard clinical dose. Clinical maximum drug concentration and minimum effective concentrations of GEM and CBDCA are 25 μg/mL and 5 ng/mL, and 55 μg/mL and 10 μg/mL, respectively.

Immunohistochemistry

Both the cells floating in the medium and the cells that remained attached after trypsinization were collected and fixed with 1% methanol-free formaldehyde (Polysciences,

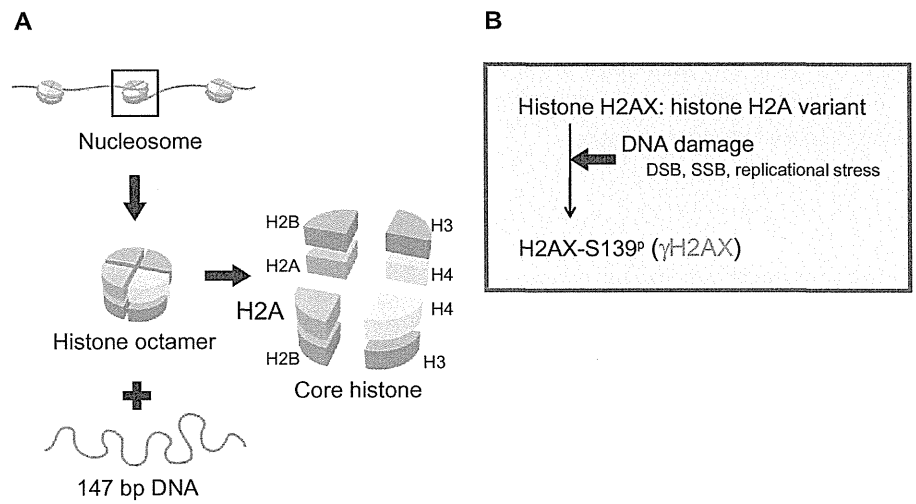

Figure 1 (**A**) Nucleosomes, units of chromatin, consist of core histones wrapped in 146 bp of DNA and linker DNA. Core histones are octamers designated as H2A, H2B, H3, and H4. Not all nucleosomes include typical histone octamers containing H2A, H2B, H3, and H4. In some parts of the chromosome, specific histones are replaced by histone variants that are slightly different histones involved in the local chromosome function. Histone H2AX is a variant of histone H2A. H2AX is known to be highly concentrated in areas of DNA damage. (**B**) When DNA damage occurs, serine 139 of histone H2AX in the chromatin on both sides of the damaged site is phosphorylated. Phosphorylated histone H2AX is referred to as γH2AX.
Abbreviations: DNA, deoxyribonucleic acid; DSB, double strand break; SSB, single strand break.