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×10⁹ per L or more, platelet count 100×10⁹ 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 1·0×10⁹ cells per L (amended from 1·5×10⁹ cells per L on April 11, 2005, because of frequent occurrence of delaying) or more and a platelet count of 75×10⁹ 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 0·5×10⁹ cells per L or more and a platelet count of 50×10⁹ per L (amended from 75×10⁹ 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 0·5×10⁹ cells per L persisted for 7 days or more, the platelet count was less than 10×10⁹ per L, the platelet count was between 10×10⁹ per L and 50×10⁹ 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

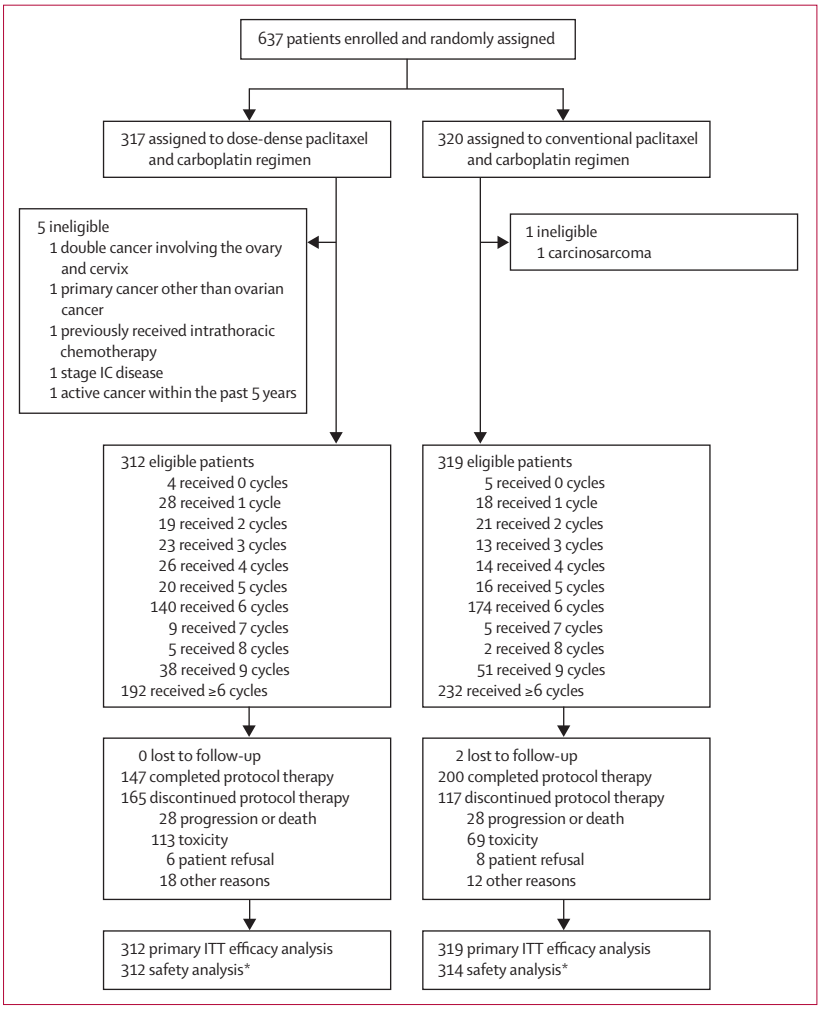

Figure 1: **Trial profile**
ITT=intention-to-treat. *Analysis of safety includes all randomised women who had received at least one cycle of treatment (one ineligible patient in each group did not receive treatment).

	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.

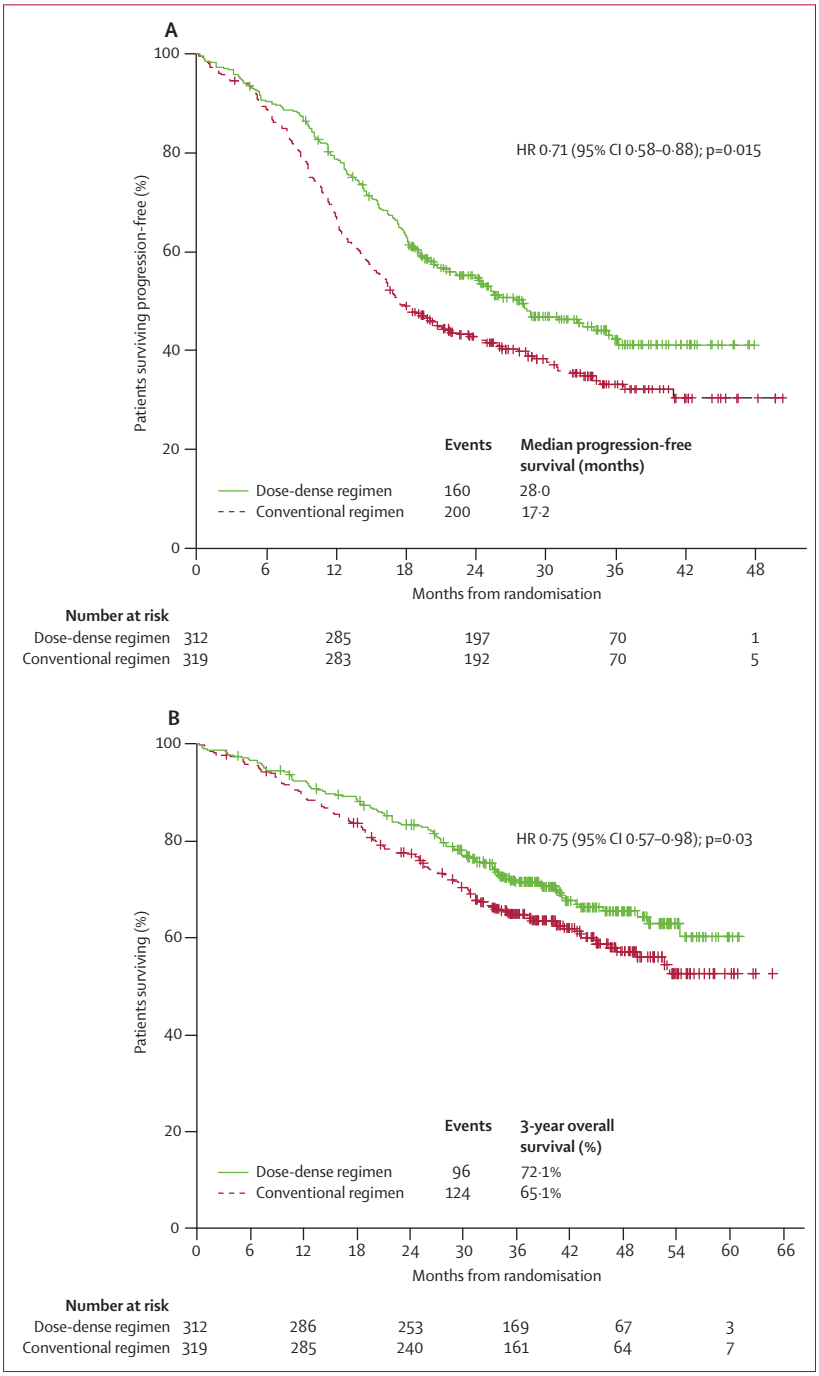

Figure 2: **Progression-free survival (A) and overall survival (B) in 631 eligible patients**
HR=hazard ratio.

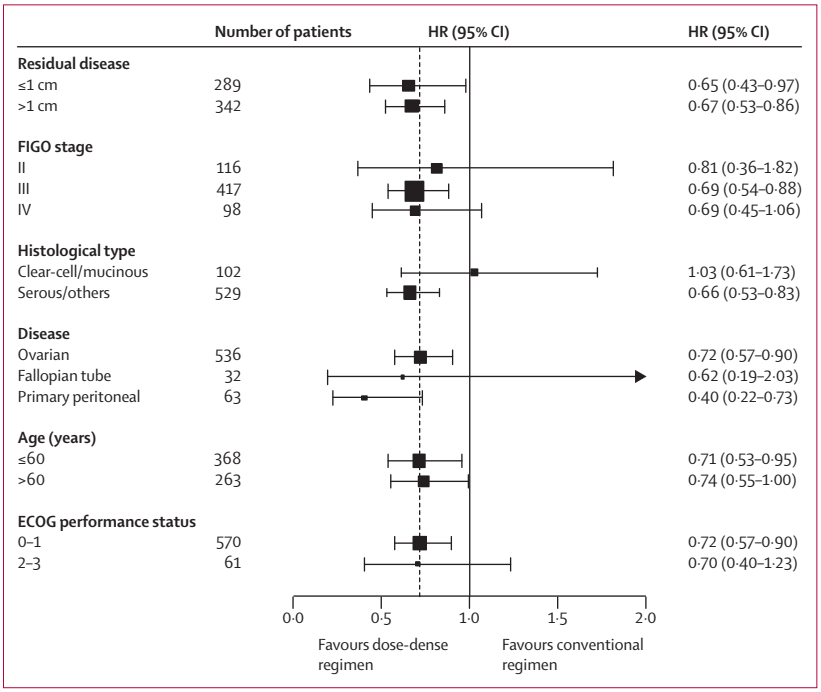

Figure 3: **Progression-free survival according to baseline characteristics**
FIGO=International Federation of Gynecology and Obstetrics. ECOG=Eastern Cooperative Oncology Group. The hazard ratios (HRs; 95% CIs) are for patients assigned to conventional paclitaxel and carboplatin, compared with those 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.[16]

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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