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Switching from standard to dose-dense chemotherapy in front-line treatment of advanced ovarian cancer: a retrospective study of feasibility and efficacy

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ABSTRACT

Background: Current standard neoadjuvant treatment for advanced ovarian cancer is 3-weekly platinum-based chemotherapy (CP3w). Patients unable to have interval debulking surgery (IDS) or with significant residual disease have a poor outcome to CP3w treatment. We investigated the outcome in patients who were switched to dose-dense chemotherapy.

Methods: We retrospectively analysed 30 patients treated at UCLH in 2009–2013, who switched to dose-dense chemotherapy after neoadjuvant CP3w, having achieved a poor response/progressed and unable to proceed to IDS (n=21), or had >1 cm residual disease after IDS (n=9). Treatment was 3-weekly carboplatin and weekly paclitaxel (n=23), or both drugs weekly (n=7). For comparison, we included 30 matched patients treated with CP3w followed by IDS (n=24, without or ≤1 cm residual disease; n=6, with >1 cm residual disease). Time to progression (TTP) and overall survival (OS) were measured from the date of diagnosis until progression (CT scan or CA-125) and death from any cause, respectively.

Results: Baseline characteristics were similar in both groups. The response rate to dose-dense chemotherapy was 70% (Gynecological Cancer Intergroup criteria). In the dose-dense group, 24 patients had tumour progression and 16 died; the corresponding numbers in the control group were 24 and 11. Median TTP was 15.8 months with dose-dense therapy, higher than expected for this patient group, and the same as in the control group (15.7 months) undergoing IDS, p=0.27. Median TTP in patients with residual disease postsurgery was 16.5 months (dose-dense) and 10.8 months (controls), p=0.02. TTP in dose-dense patients who did not have surgery was 10.4 months. Median OS was 31.3 (dose-dense) and 59.6 months (controls), p=0.06. Dose-dense chemotherapy was well tolerated: only three patients interrupted treatment due to toxicity.

Conclusion: Switching to dose-dense chemotherapy in patients who failed to respond to CT3w neoadjuvant chemotherapy appears to be an effective strategy and requires further investigation.

INTRODUCTION

Ovarian cancer is the fifth most common cause of cancer death in women in most European countries.[1] The standard treatment for patients with advanced (FIGO (International Federation of Gynecology and Obstetrics) stage IC–IV) disease is initial debulking surgery followed by 3-weekly carboplatin and paclitaxel combination chemotherapy.[2] In patients undergoing surgery, this approach leads to median progression-free survival (PFS) ranging from 15 to 25 months and median overall survival (OS) from 24 to 40 months. Patients with gross residual tumour after surgery tend to have lower PFS and their outcome is poor.[3–7] The outcome of patients not amenable to surgery upfront but treated with neoadjuvant chemotherapy followed by surgery is similar.[8 9]

Despite improvements in chemotherapy, the tumour response in some patients is not sufficient to undergo surgery, or significant residual disease remains after surgery. The prognosis of these patients is very poor due to early progression.[10–12] When this occurs, the aim of therapy changes from one of curative intent to palliation and management of a chronic disease, with the purpose of prolonging survival, maintaining or improving quality of life and good symptom control.

There is evidence from a Japanese randomised trial that delivering paclitaxel in a weekly 'dose-dense' schedule rather than every 3 weeks in first-line treatment of advanced ovarian cancer increases the tumour response rate and prolongs survival.[13] The mechanistic basis for these benefits is unclear but it has been postulated to involve Gompertzian models of chemotherapy regrowth and antiangiogenic mechanisms.[14 15] Most commonly, weekly paclitaxel (80 mg/m^2) is given with six cycles of 3-weekly carboplatin. This resulted in a 30% improvement in both PFS and OS compared with standard 3-weekly dose scheduling.[13 16] In

Key questions

What is already known about this subject?

- Current standard neoadjuvant treatment for advanced ovarian cancer is 3-weekly platinum-based chemotherapy followed by interval debulking surgery (IDS). However, the tumour response in some patients is not sufficient to undergo surgery or significant residual disease remains after surgery. The prognosis of these patients is very poor due to early progression. There is evidence that delivering paclitaxel in a weekly 'dose-dense' schedule rather than every 3 weeks in first-line treatment of advanced ovarian cancer increases the tumour response rate and prolongs survival.

What does this study add?

- We retrospectively analysed 30 patients, treated in our Institution, who switched to dose-dense chemotherapy after neoadjuvant 3-weekly platinum-based chemotherapy, having achieved a poor response/progressed and unable to proceed to IDS or had >1 cm residual disease after IDS. For comparison, we collected data on 30 patients who received standard 3-weekly neoadjuvant chemotherapy, IDS and then continued with 3-weekly postoperative chemotherapy.
- Although the dose-dense group had worse prognosis, we found similar median time to progression (TTP) in the two treatment groups, whereas median overall survival in the dose-dense group was longer than expected. In addition, patients in the dose group who had >1 cm residual disease after surgery showed significantly longer median TTP compared with controls with residual after surgery.

How might this impact on clinical practice?

- This retrospective analysis suggests that effective disease control can be achieved in some patients despite an initial poor response to 3-weekly induction chemotherapy. Weekly dose-dense chemotherapy might improve the tumour response rate and in some cases it allows debulking surgery to be performed. Dose-dense treatment is therefore a policy that merits further exploration in patients responding poorly to 3-weekly chemotherapy for ovarian cancer.

a subsequent subgroup analysis, a similar clinical benefit of dose-dense chemotherapy was seen in patients with significant residual disease after surgery.[13] The treatment was well tolerated but there was a greater degree of haematological toxicity, leading to discontinuation of regimen in 60% of patients in the dose-dense arm compared with 43% in the standard arm.[16 17]

Given these findings, we postulated that patients whose tumours respond poorly or progress during a standard front-line chemotherapy given every 3 weeks, or who have residual disease after interval surgery, might benefit from a switch to a dose-dense scheduling of paclitaxel or both drugs. We explored this treatment policy in a group of 30 women with advanced ovarian cancer treated at the UCL Hospitals, London.

PATIENTS AND METHODS

We reviewed the medical records of 30 consecutive patients treated at UCL Hospitals between 2009 and 2013 who switched to dose-dense chemotherapy during first-line 3-weekly chemotherapy for ovarian cancer. Patients switched mostly to weekly paclitaxel with 3-weekly carboplatin, but in some cases both drugs were given weekly. This change occurred after they were deemed to have had a poor initial response to chemotherapy and were unsuitable for interval debulking surgery (IDS), or after surgery if significant residual disease remained (>1 cm). We excluded patients who began chemotherapy on a dose-dense regimen.

In addition, we collected data on 30 patients treated during the same period who received standard 3-weekly neoadjuvant chemotherapy, IDS and then continued with 3-weekly postoperative chemotherapy. These were selected to have similar characteristics to those in the dose-dense group, for example, age, tumour type and stage at diagnosis. We chose this group as a comparator because they had responded to standard chemotherapy and underwent IDS for advanced ovarian cancer (the majority with no residual tumour after surgery), and hence were considered to be a group with better prognosis and reflecting the standard practice population.

The study design is summarised in figure 1.

Demographic factors, treatment and response data (imaging and serum CA-125) were obtained from medical records.

Treatment

Standard 3-weekly chemotherapy was with carboplatin alone (C3w), or more commonly in combination with paclitaxel (CP3w). Carboplatin was administered at a dose of AUC 5 based on the Calvert formula[18] using an EDTA glomerular filtration rate or AUC 6 based on a calculated creatinine clearance. Paclitaxel was administered at the dose of 175 mg/m^2.

Dose-dense paclitaxel 80 mg/m^2 was given continuously each week with 3-weekly carboplatin (CPw) in most cases but some patients received weekly paclitaxel with weekly carboplatin, given at an AUC 2 (CwPw)

Statistical methods

Data on response to chemotherapy were calculated using the Gynecological Cancer Intergroup response criteria,[19] using both serum CA-125 and radiological criteria. Radiological data were obtained from reports in the case notes. For example, complete response (CR) was considered to be the disappearance of all known disease on CT scan and return of serum CA-125 levels to normal values (≤35 IU/mL) for at least 4 weeks. Partial response (PR) was considered to be a 30% decrease in the sum of the longest diameter of target lesions (evaluated by CT scan) in patients with measurable disease, or a 50% decrease in serum levels of CA-125 (confirmed with repeat serum CA-125 level after an interval of no less than 4 weeks). Progressive disease (PD) was considered to be appearance of new lesions, or more than 30% increase in the sum of the longest diameter of target lesions (evaluated by CT scan) in measurable disease or increase in serum levels of CA-125 more than twofold the nadir value in non-measurable disease. All the remaining cases were considered stable disease (SD).

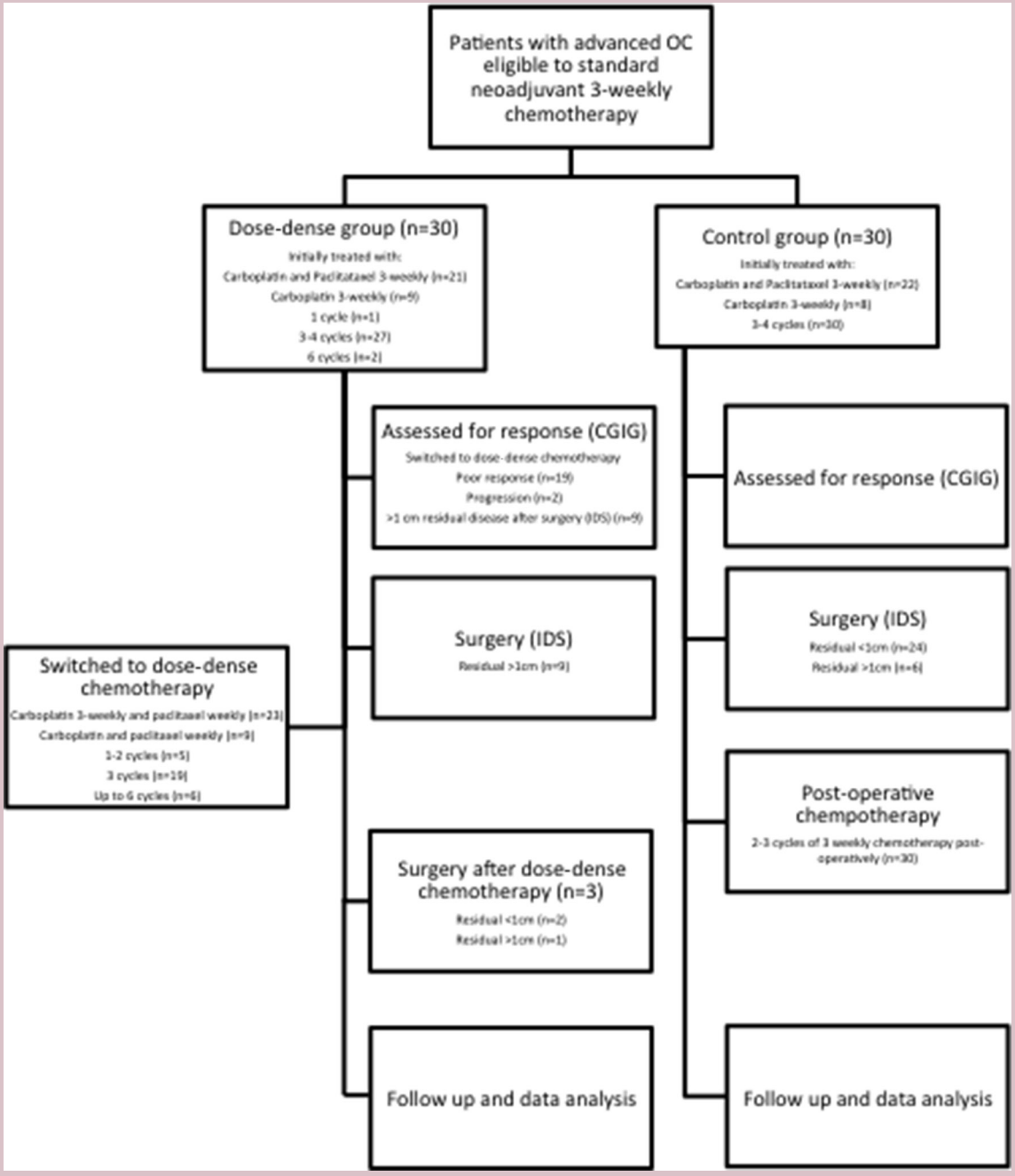

Figure 1 Consort-like flow chart of the study.

Haematological toxicities were graded according to Common Terminology Criteria for Adverse Events(CTCAE) of the National Cancer Institute and National Institutes of Health, version 4.0, May 2009. Data on non-haematologic toxicities were not consistently available, and so not collected.

Time to progression (TTP) was measured from the date of diagnosis until PD and OS was measured until death from any cause (all patients who died had recorded progression previously). Both were analysed using Kaplan-Meier curves and multivariable Cox regression modelling to compare the dose-dense group with controls, and allowing for baseline factors such as age, tumour type, stage and CA-125.

RESULTS

Patients' characteristics

Baseline characteristics are shown in table 1. Mean age at diagnosis was 67.5 years (range 28–83). Among dose-dense patients, all tumours were high-grade (G3) carcinoma and most had serous histology (n=26, 86.7%). A high proportion of patients had FIGO stage IV disease (14 patients, 46.7%); the rest had stage 3C (16 patients, 53.3%). In seven patients CA-125 data were not available.

Initial treatment and surgery

Details of treatment are provided in table 1. In the dose-dense group, most patients were treated initially with the combination of carboplatin and paclitaxel (CP3w)

Table 1 Baseline characteristics and treatment details (number of patients with percentages in brackets, except for age, CA-125 and number of cycles)

	Dose-dense group (n=30)%	Control group (n=30)%	p Value*
Age at diagnosis, years			
Median (range)	67.5 (28–83)	68.5 (37–81)	0.72
Tumour type			
Ovarian	22 (73.3)	17 (56.7)	0.28
PPC/fallopian tube	8 (26.7)	13 (43.3)	
Histology			
Serous	26 (86.7)	29 (96.7)	0.48
Endometrioid	1 (3.3)	1 (3.3)	
Mucinous	1 (3.3)	0	
Undifferentiated	2 (6.7)	0	
Grade			
Grade 3	30 (100)	30 (100)	
Stage (FIGO)			
IIIC	16 (53.3)	15 (50)	0.99
IV	14 (46.7)	15 (50)	
CA-125 at diagnosis, units/mL			
Median (range)	1287 (119–9937)†	950 (87–9000)	0.29
Initial treatment type			
CP3w	21 (70)	22 (73.3)	0.99
C3w	9 (30)	8 (26.7)	0.88
Median no of cycles (range)	3 (1–6)	3 (3–4)	
Reason for switching to dose-dense chemotherapy			
Progression	2 (6.7)		
Poor response	19 (63.3)		
Residual after surgery	9 (30)		
Dose-dense chemotherapy type			
CPw	23 (76.7)		
CwPw	7 (23.3)		
Median no of cycles (range)	3 (1–6)		
Surgery			
Yes	12 (40)	30 (100)	
No	18 (60)		
Surgery before dose-dense chemo	9 (75)		
Surgery after dose-dense chemo	3 (25)		
Residual disease after surgery			
≤1 cm	2 (6.7)	24 (80)	
>1 cm	10 (66.7)	6 (20)	<0.001
No of further lines of chemotherapy, median (range)	1 (1–4)	2 (1–4)	0.40

*Wilcoxon two-sample test for age, CA-125 and number of cycles; Fisher's exact test for all others
†For 23 patients who had CA-125 measurements
CP3w, carboplatin and paclitaxel 3-weekly; C3w, carboplatin 3-weekly; CPw, carboplatin 3-weekly and paclitaxel weekly; CwPw, carboplatin and paclitaxel weekly; PPC, Primary Peritoneal Cancer.

(n=21, 70%) but nine patients (30%) received single agent carboplatin (C3w). Most patients switched to dose-dense therapy after three (n=23, 76.7%) or four cycles (n=4, 13.3%) of chemotherapy. In one patient, the switch was made after the first cycle of standard therapy due to tumour progression, and two patients received a total of six cycles before switching. All patients were assessed for response at the end of initial three to four cycles of chemotherapy.

Twenty-one patients (70%) had a poor response to initial treatment and were considered unsuitable for IDS and because of this switched to dose-dense chemotherapy; of these, two patients switched because of tumour progression during the first three to four cycles of chemotherapy.

Nine patients (30%) switched to dose-dense chemotherapy after surgery, due to significant residual disease.

Three patients in the dose-dense group underwent surgery after the completion of the dose-dense chemotherapy, having initially been considered unsuitable for surgery. Optimal debulking with no residual disease was achieved in two, whereas the other still had significant residual disease after surgery. Therefore, a total of 12 (40%) dose-dense patients underwent debulking surgery.

In the control group, the majority of patients (n=22, 73.3%) were treated with carboplatin AUC 5–6 and paclitaxel 175 mg/m^2 (CP3w); eight patients (26.7%) were treated with the same dose of single agent carboplatin. All patients underwent IDS after a PR to neoadjuvant chemotherapy. In 80% of patients (n=24) this resulted in optimal debulking with ≤1 cm of residual; six patients (20%) had >1 cm residual disease after surgery. Patients received a median of 3 (range 2–3) cycles of postoperative chemotherapy. Two patients in this group received bevacizumab which was continued as maintenance therapy for up to 1 year.

Dose-dense treatment

The majority of patients in the dose-dense group switched to CPw (n=23, 76.7%); seven patients switched to CwPw. Most of patients received three cycles of dose-dense chemotherapy (n=19, 63.3%), five patients received less than one to two cycles (16.6%) and six patients (20%) received up to six cycles. Response was assessed at the end of the dose-dense chemotherapy. Six patients were not assessable for response. Out of the 24 evaluable patients, 5 patients (20.8%) achieved a CR, 13 patients (54.2%) a PR, 3 (12.5%) had SD, and 3 (12.5%) had disease progression during the chemotherapy. Additionally, four patients received bevacizumab as part of their dose-dense treatment and as maintenance therapy for up to 1 year of administration.

Survival analysis

The median follow-up was 42 months among all patients (censoring those who were alive); 37 and 42 months in the dose-dense control groups, respectively. This slightly longer follow-up might contribute towards a difference in survival times in favour of controls, however the median follow-up among patients who were still alive was similar, 37 and 38 months.

The median TTP was similar between patients in the dose-dense group and controls: 15.8 and 15.7 months (table 2 and figure 2), p=0.38. The OS in the dose-dense group was 31.3 months, lower than in controls, 59.6 months (p=0.06).

The effect of several clinical factors (such as debulking surgery or not, residual disease after surgery, type of initial chemotherapy and number of cycles of initial chemotherapy) on TTP and OS are shown in table 2 and figures 3–4. TTP was significantly higher among the dose-dense group who had >1 cm residual disease after surgery (16.5 months), compared with controls with residual after surgery (10.8 months), p=0.005. There were no other clear differences in TTP or OS between dose-dense patients and controls, according to the factors examined (table 2, figures 3–4).

In the dose-dense group, patients who had surgery had a longer TTP than those who did not have surgery: 17.0 vs 10.4 months (p=0.09, unadjusted HR 0.46, 95% CI 0.19 to 1.12; and adjusted HR 0.34, 95% CI 0.07 to 1.59). The difference was greater for OS: 43.2 vs 21.1 months (p=0.046, unadjusted HR 0.31, 95% CI 0.10 to 0.98; and adjusted HR 0.18, 95% CI 0.02 to 1.26). There was also some evidence that the median OS was higher for patients who initially had CP3w versus C3w (43.2 vs 22.7 months), unadjusted HR=0.25, 95% CI 0.08 to 0.72, p=0.01; adjusted HR=0.29, 95% CI 0.05 to 1.78, p=0.18. Patients who had CPw as dose-dense therapy had higher median OS than CwPw (43.2 vs 21.1 months); unadjusted HR 0.48, 95% CI 0.17 to 1.32, p=0.15; adjusted HR 0.16, 95% CI 0.03 to 0.90, p=0.04 (including also type of initial chemotherapy).

Toxicity of dose-dense therapy

Detailed data on haematological toxicities are reported in table 3. Grade 3 or 4 neutropenia was the most common treatment-related adverse event, seen in 50% of patients. No cases of febrile neutropenia were observed. Grade 2 anaemia was seen in 36.7% of patients. Interestingly, only three patients interrupted treatment due to toxicity. In most cases, toxicities were easily managed with treatment delays (n=13, 43.3%) or dose reductions (n=17, 56.7%).

DISCUSSION

We instituted a change of treatment schedule policy starting dose-dense therapy in patients who responded poorly to neoadjuvant chemotherapy who were not able to undergo IDS or who had a poor surgical result from IDS. These patients have short median TTP, and a very poor prognosis, with a median OS usually not exceeding 16 months.[3 4 7 10] Similar findings are observed in patients who do not have optimal debulking at IDS, but most continue on the same regimen of chemotherapy postoperatively.[20 21] There are no clear guidelines about how best to manage this group of women who have a poor prognosis, and we

Table 2 TTP and OS according to several factors

		Dose dense, n=30	Controls, n=30	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
		Median, months (95% CI)			
All patients					
TTP		15.8 (10.4 to 17.3)	15.7 (11.7 to 21.8)	1.29 (0.73 to 2.29)	1.67 (0.84 to 3.34),
Events (n)		24	24	p=0.38	p=0.14
OS		31.3 (19.7 to ne)	59.6 (34.0 to ne)	2.08 (0.94 to 4.62)	2.35 (0.96 to 5.74)
Events (n)		16	11	p=0.06	p=0.06
Debulking surgery					
Yes	TTP	17.0 (11.3 to 29.3)	15.7 (11.7 to 21.8)	0.84 (0.38 to 1.89)	1.03 (0.36 to 2.95)
	OS	43.2 (24.0 to ne)		1.08 (0.33 to 3.53)	1.73 (0.36 to 8.38)
No	TTP	10.4 (8.5 to 17.3)	-		
	OS	21.1 (10.8 to 31.3)	-		
Residual disease					
≤1 cm	TTP	Only 2 patients	18.0 (13.7 to 24.4)		
	OS		59.6 (28.8 to ne)		
>1 cm	TTP	16.5 (11.3 to 29.3)	10.8 (4.5 to 14.0)	0.10 (0.02 to 0.49)	0.02 (<0.01 to 0.34)
	OS	43.2 (24.0 to ne)	Not reached	1.15 (0.21 to 6.31)	1.50 (0.09 to 24.1)
Type of initial chemotherapy					
CP3w	TTP	16.1 (10.3 to 18.6)	14.6 (10.1 to 18.5)	0.95 (0.48 to 1.87)	1.08 (0.45 to 2.57)
	OS	43.2 (21.1 to ne)	Not reached	1.35 (0.47 to 3.89)	1.75 (0.54 to 5.67)
C3w	TTP	15.0 (4.0 to 24.2)	23.1 (5.8, ne)	3.12 (0.91 to 10.70)	6.87 (0.82 to 57.6)
	OS	22.7 (5.1 to 30.6)	53.7 (12.1 to 59.6)	7.11 (1.43 to 35.4)	4.21 (0.45 to 39.3)
Cycles of initial chemotherapy (n)					
≤3	TTP	15.8 (10.4 to 22.0)	15.6 (10.8 to 21.8)	1.10 (0.59 to 2.06)	1.69 (0.79 to 3.65)
	OS	30.6 (17.2 to ne)	47.8 (34.0 to ne)	1.88 (0.80 to 4.42)	1.98 (0.74 to 5.31)
≥4	TTP	15.9 (8.5 to 18.6)	15.9 (13.7 to ne)	(only 11 patients)	
	OS	34.7 (9.9 to ne)	Not reached		
Type of dose-dense chemotherapy					
CPw	TTP	15.8 (10.4 to 24.2)			
	OS	43.2 (22.7 to ne)			
	TTP	15.9 (5.4 to 17.3)			
	OS	21.1 (10.8 to 34.7)			
Cycles of dose-dense chemotherapy (n)					
≤3	TTP	15.8 (10.4 to 17.3)			
	OS	21.1 (19.7 to ne)			
≥4	TTP	15.9 (6.6 to 24.2)			
	OS	21.1 (13.9 to 34.7)			

*Allowing for age, tumour type, stage and CA-125
CP3w, carboplatin and paclitaxel 3-weekly; C3w, carboplatin 3-weekly; CPw, carboplatin 3-weekly and paclitaxel weekly; CwPw, carboplatin and paclitaxel weekly; OS, overall survival; ne, not estimable; TTP, time to progression.

hypothesised that in this group dose-dense chemotherapy may reduce resistance to chemotherapy.

In this retrospective analysis, we showed that switching to a weekly schedule is feasible and might benefit patients in this poor prognosis group. On switching to dose-dense chemotherapy after a poor response to 3-weekly induction chemotherapy, or suboptimal surgery, the overall CR rate at the end of weekly treatment was 20.8%, and 54.2% of patients had a partial tumour response. The median TTP and OS were 15.8 and 31.3 months, respectively, longer than expected from previously published reports in this population, where they typically are about 10 and 16 months, respectively.[3 4 7 10] Only three patients developed tumour progression during weekly treatment. Haematological toxicity was acceptable, consistent with previous reports that show CPw and CwPw are tolerable in most women.[13 22 23]

The median TTP in the dose-dense group with residual disease after attempted IDS was significantly higher than the corresponding control patients treated with standard 3-weekly chemotherapy (16.5 vs 10.8 months, respectively; p=0.005). The median number of 'post switch' chemotherapy cycles was three, but the extended duration of treatment in a few patients may have contributed to a

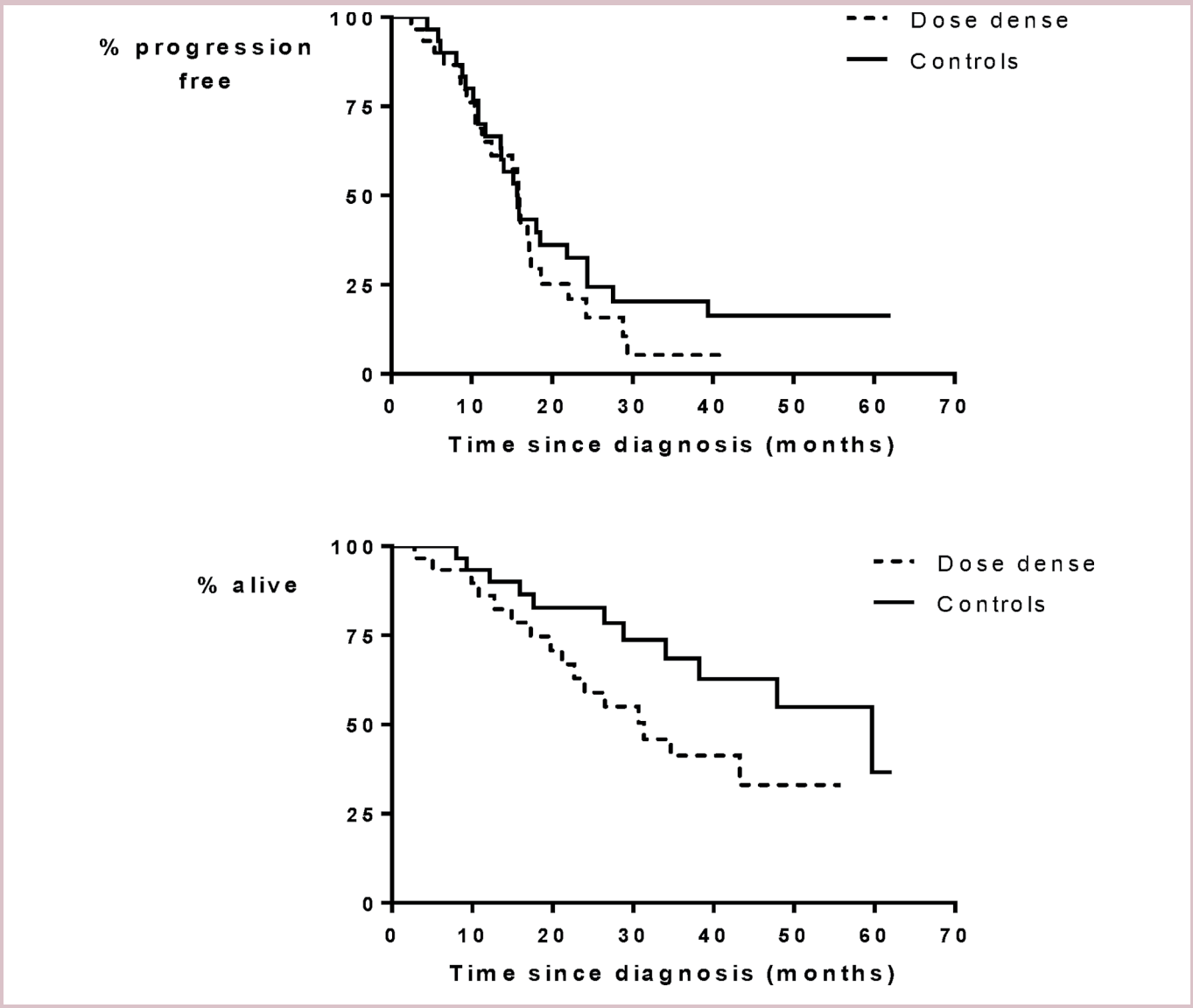

Figure 2 Time to progression (upper) and overall survival (lower) for patients switched to dose-dense chemotherapy and controls.

longer TTP in this group. OS is dependent on stage and histology and the completeness of surgical debulking and a median OS of 31.3 months in these patients is encouraging. For example, in previously published randomised trials of initial surgery with complete resection of disease followed by chemotherapy the median survival was 99.1 months.[7] Whereas, patients entered into a neoadjuvant versus primary surgery trial, the survival of women undergoing complete surgical debulking ranged from a median of 38 months in the IDS group to 45 months in the same population who had primary surgery.[8] The median OS in the dose-dense group also compares favourably with the median survival of 59.6 months seen in the case–control group where 80% of the patients had no residual disease following IDS. It is similar to the median OS of 25–26 months reported by Vergote *et al*[8] in patients with macroscopic residual disease (>1 cm) irrespective of the timing of surgery. In our previously reported case series of patients receiving 3-weekly chemotherapy, the median OS was 22.5 months in patients undergoing suboptimal surgery and 7.8 months in those who never had surgery.[24] However, our findings are based on a single-centre study and the results were compared with a non-randomised matched control group who responded to neoadjuvant chemotherapy. Both factors may confound or bias the results we have reported. However, within patients, we observed a change in response in some patients when switched to a dose-dense schedule and recommend that further prospective studies are performed.

The strategy of switching the scheduling of chemotherapy in poorly responding patients has been explored by others[25] but there have been no randomised trials comparing a switch to a dose-dense strategy with continuation of the same treatment regimen. We used a historical case–control series from our institution to help put our findings into the context of our standard practice. There

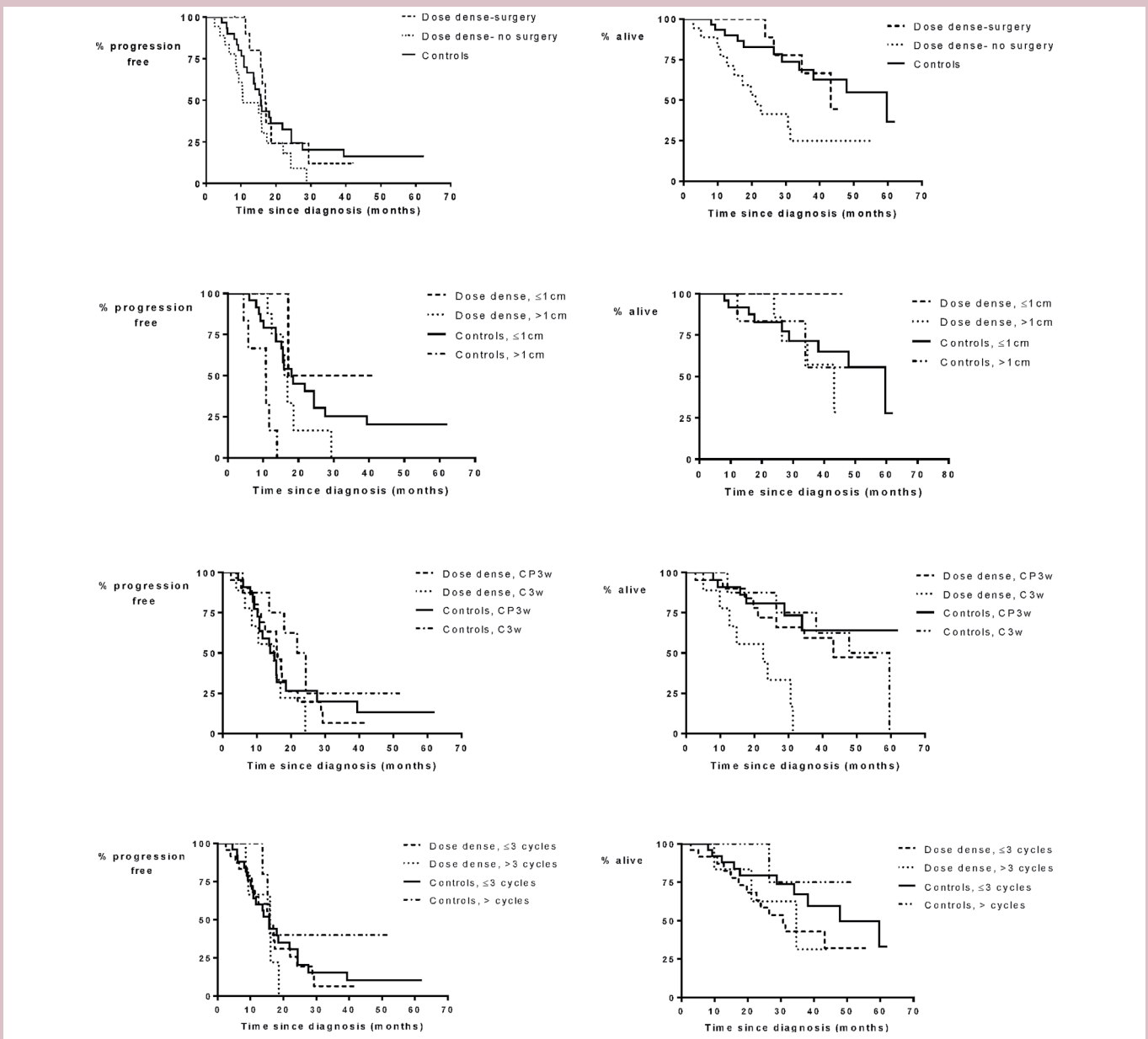

Figure 3 Time to progression and overall survival for patients according to four factors (in order, top to bottom): debulking surgery or not, residual disease after surgery, type of initial chemotherapy and number of cycles of initial chemotherapy. CP3w, carboplatin and paclitaxel 3-weekly; C3w, carboplatin 3-weekly.

is no clear guidance about how best to manage patients who have significant tumour residuum after IDS or those unable to proceed to surgery after three to four cycles of neoadjuvant chemotherapy. Standard practice is generally to continue with 3-weekly treatment. Some would advocate adding bevacizumab, extrapolating the evidence reported in the ICON7 trial that bevacizumab is more effective in patients with bulky residual disease or in those who have not undergone surgery.[26] Following the results of the Japanese dose-dense paclitaxel trial (JGOG 3016), some clinicians now use a dose-dense regimen for patients with newly diagnosed advanced OC, including those who are appropriate for IDS. However, this approach should not be considered a standard regimen until more reliable evidence is obtained.

Our retrospective analysis suggests that effective disease control can be achieved in some patients despite an initial poor response to 3-weekly induction chemotherapy. Weekly dose-dense chemotherapy might improve the tumour response rate and in some cases it allows debulking surgery to be performed. Dose-dense treatment is therefore a policy that merits further exploration in patients responding poorly to 3-weekly chemotherapy for ovarian cancer.

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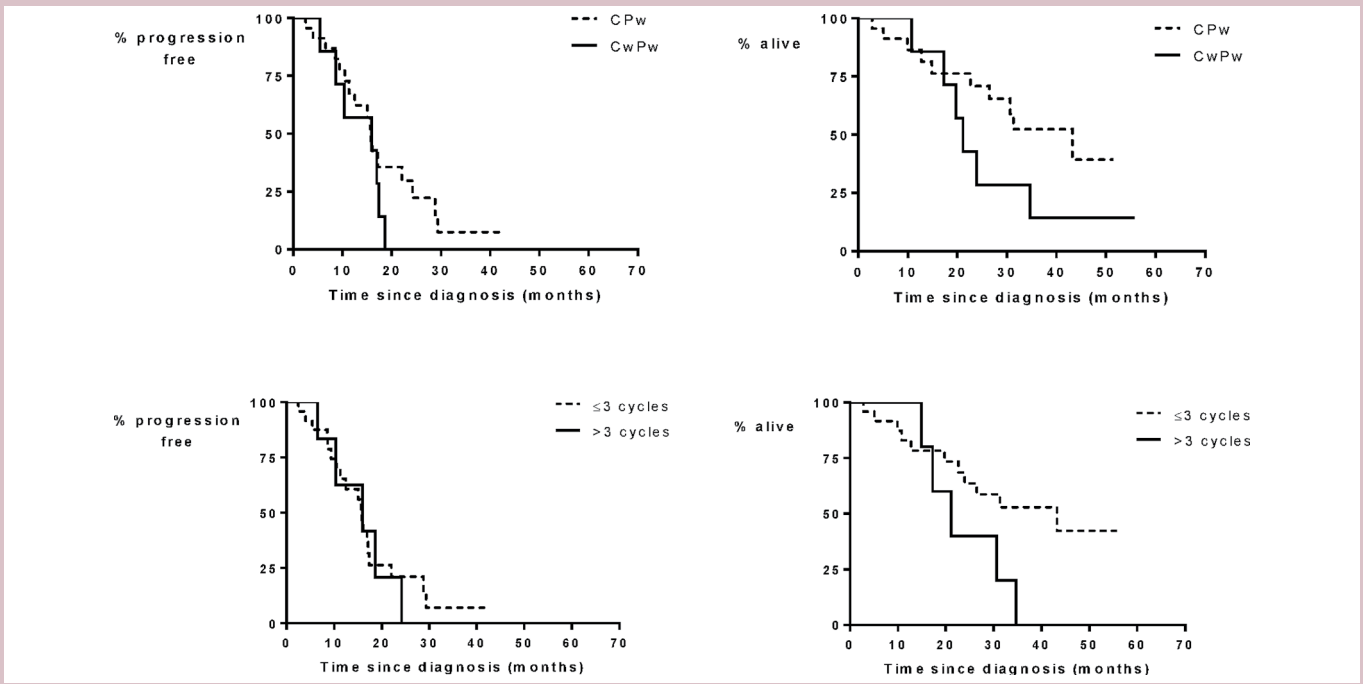

Figure 4 Time to progression and overall survival for patients who had dose-dense chemotherapy, according to two factors (in order, top to bottom): type of dose-dense chemotherapy and number of cycles of dose-dense chemotherapy. CPw, carboplatin 3-weekly and paclitaxel weekly; CwPw, carboplatin and paclitaxel weekly.

Contributors RK, MMC and JAL initially conceived the study. AM extracted and interpreted data. AH did the statistical calculations. AM, JAL and AH wrote the first paper draft. RK, MMC, FR, DL, MW, NMD, TM and AO reviewed it critically. All authors contributed to and approved the final version of the manuscript.

Competing interests None declared.

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Table 3 Toxicities of dose-dense treatment

Toxicity—haematological	All cases (n=30)%
Neutropenia	
Grade 1	0 (0)
Grade 2	3 (10)
Grade 3	11 (36.7)
Grade 4	4 (13.3)
Not reported	12 (40)
Anaemia	
Grade 1	2 (6.7)
Grade 2	11 (36.7)
Grade 3	3 (10)
Grade 4	0 (0)
Not reported	14 (53.3)
Thrombocytopenia	
Grade 1	4 (13.3)
Grade 2	5 (16.7)
Grade 3	1 (3.3)
Grade 4	0 (0)
Not reported	20 (66.7)
Treatment interrupted for toxicity	3 (10)
Delays for toxicities	13 (43.3)
Required dose reductions	17 (56.7)

Because of rounding off, the sum of percentages does not always equal 100.

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REFERENCES

1. Trent Cancer Registry. *Overview of Ovarian Cancer in England: Incidence, Mortality and Survival*, 2012.
2. du Bois A, Quinn M, Thigpen T, *et al*. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). *Ann Oncol* 2005;16:viii7–12.
3. du Bois A, Lück HJ, Meier W, *et al*. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003;95:1320–9.
4. McGuire WP, Hoskins WJ, Brady MF, *et al*. Cyclophosphamide and cisplatin versus paclitaxel and cisplatin: a phase III randomized trial in patients with suboptimal stage III/IV ovarian cancer (from the Gynecologic Oncology Group). *Semin Oncol* 1996;23(Suppl 12):40–7.
5. Muggia FM, Braly PS, Brady MF, *et al*. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. *J Clin Oncol* 2000;18:106–15.
6. Piccart MJ, Bertelsen K, James K, *et al*. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 2000;92:699–708.
7. du Bois A, Reuss A, Pujade-Lauraine E, *et al*; Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft

Gynaekologische Onkologie Studiengruppe Ovarialkarzino. *Cancer* 2009;115:1234–1244.
8. Vergote I, Tropé CG, Amant F, *et al*. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010;363:943–53.
9. Kehoe S, Hook J, Nankivell M, *et al*. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 2015;386:249–57.
10. Wimberger P, Lehmann N, Kimmig R, *et al*; Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group. Prognostic factors for complete debulking in advanced ovarian cancer and its impact on survival. An exploratory analysis of a prospectively randomized phase III study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR). *Gynecol Oncol* 2007;106:69–74.
11. da Costa Miranda V, de Souza Fêde ÂB, Dos Anjos CH, *et al*. Neoadjuvant chemotherapy with six cycles of carboplatin and paclitaxel in advanced ovarian cancer patients unsuitable for primary surgery: Safety and effectiveness. *Gynecol Oncol* 2014;132:287–91.
12. Hong SH, Lee S, Kim HG, *et al*. Phase II study of gemcitabine and vinorelbine as second- or third-line therapy in patients with primary refractory or platinum-resistant recurrent ovarian and primary peritoneal cancer by the Korean Cancer Study Group (KCSG)_KCSG GY10-10. *Gynecol Oncol* 2015;136:212–7.
13. Katsumata N, Yasuda M, Isonishi S, *et al*. 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. *Lancet Oncol* 2013;14:1020–6.
14. Fennelly D, Aghajanian C, Shapiro F, *et al*. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. *J Clin Oncol* 1997;15:187–92.
15. Norton L, Simon R, Brereton HD, *et al*. Predicting the course of Gompertzian growth. *Nature* 1976;264:542–5.
16. Katsumata N, Yasuda M, Takahashi F, *et al*. 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. *Lancet* 2009;374:1331–8.
17. Harano K, Terauchi F, Katsumata N, *et al*. Quality-of-life outcomes from a randomized phase III trial of dose-dense weekly paclitaxel and carboplatin compared with conventional paclitaxel and carboplatin as a first-line treatment for stage II-IV ovarian cancer: Japanese Gynecologic Oncology Group Trial (JGOG3016). *Ann Oncol* 2014;25:251–7.
18. Donahue A, McCune JS, Faucette S, *et al*. Measured versus estimated glomerular filtration rate in the Calvert equation: influence on carboplatin dosing. *Cancer Chemother Pharmacol* 2001;47:373–9.
19. Rustin GJ, Vergote I, Eisenhauer E, *et al*. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *Int J Gynecol Cancer* 2011;21:419–23.
20. Aletti GD, Dowdy SC, Gostout BS, *et al*. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. *Obstet Gynecol* 2006;107:77–85.
21. Rosen B, Laframboise S, Ferguson S, *et al*. The impacts of neoadjuvant chemotherapy and of debulking surgery on survival from advanced ovarian cancer. *Gynecol Oncol* 2014;134:462–7.
22. van der Burg ME, de Wit R, van Putten WL, *et al*. Weekly cisplatin and daily oral etoposide is highly effective in platinum pretreated ovarian cancer. *Br J Cancer* 2002;86:19–25.
23. van der Burg ME, Vergote I, Onstenk W, *et al*. Long-term results of weekly paclitaxel carboplatin induction therapy: an effective and well-tolerated treatment in patients with platinum-resistant ovarian cancer. *Eur J Cancer* 2013;49:1254–63.
24. Saha A, Varughese M, Gallagher CJ, *et al*. Primary chemotherapy for inoperable ovarian, fallopian tube, or primary peritoneal cancer with or without delayed debulking surgery. *Int J Gynecol Cancer* 2012;22:566–72.
25. Marchetti C, Bellati F, Musella A, *et al*. Thinking twice before abandoning first-line chemotherapy in ovarian cancer: report of two cases and literature review. Passing from tri-weekly to weekly regimens. *Int J Clin Oncol* 2012;17:385–9.
26. Oza AM, Cook AD, Pfisterer J, *et al*. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015;16:928–36.

Switching from standard to dose-dense chemotherapy in front-line treatment of advanced ovarian cancer: a retrospective study of feasibility and efficacy

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