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First-line therapy for ovarian cancer with carboplatin followed by paclitaxel–gemcitabine (SCOTROC5): A feasibility study and comparative analysis of the SCOTROC series

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ARTICLE INFO

Article history:
Received 5 March 2010
Accepted 11 March 2010
Available online 13 April 2010

Keywords:
Carboplatin
Paclitaxel
Gemcitabine
Sequential therapy
Ovarian cancer

ABSTRACT

Background: We have conducted a series of four feasibility studies in stage Ic–IV ovarian cancer exploring six sequential first-line schedules with the same entry criteria in a total of 339 patients. Here we present the results of the sixth study, and an analysis of the overall series.

Methods: In this trial patients received 4 cycles of carboplatin AUC 7 every 3 weeks, followed by 4 cycles of concurrent paclitaxel 175 mg/m^2 (day 1) and gemcitabine 1000 mg/m^2 (days 1 and 8) every 3 weeks. The primary end-point of the trial was feasibility of administering all cycles of planned chemotherapy to >60% of patients.

Results: Fifty-four patients were recruited to the trial between June 05 and June 06. A total of 40 (74.1%) patients received all 8 cycles of treatment. Reasons for early discontinuation included toxicity ($n = 8$) and disease progression ($n = 4$). The overall response rate was 73.7%, and the median progression free survival (PFS) was 14.2 months with a median follow-up of 24 months. A comparative analysis of all six regimens from the SCOTROC series suggests that the sequential schedule in which paclitaxel was given weekly (median PFS 19.5 m) is most effective.[1]

Conclusion: The sequential schedule explored in this trial is feasible, but comparative efficacy analysis suggests that trials involving weekly paclitaxel should be prioritised for further study.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.03.006

1. Introduction

The standard of care for advanced epithelial ovarian cancer is cytoreductive surgery and carboplatin–paclitaxel chemotherapy based on the results of GOG-111 and OV-10, which demonstrated a survival advantage for cisplatin–paclitaxel over cisplatin–cyclophosphamide,[2,3] and three trials which have shown equivalent efficacy and better tolerability of carboplatin versus cisplatin.[4–6] However, prognosis remains poor with median progression free survival (PFS) for patients with advanced disease of approximately 18 months, and 5-year overall survival (OS) of 30–40%.

One strategy to improve outcomes is to combine a third active cytotoxic agent with carboplatin and paclitaxel. Despite encouraging improvements in response rates, Phase III trials comparing triplet regimens with carboplatin–paclitaxel have failed to demonstrate improvements in survival and were associated with significant increases in toxicity.[7,8] It is conceivable, however, that a sequential approach to the addition of a third drug may be more effective as well as being better tolerated. There is also the potential of antagonism between the two most important agents (paclitaxel and carboplatin), as suggested by lack of additional benefit from the paclitaxel–platinum combination versus single agent platinum in two studies – ICON3 and GOG-132,[9,10] and this can be avoided if the two agents are scheduled to be given sequentially rather than concurrently.

Based on this paradigm, in a series of three Phase II studies, we previously explored the feasibility of five sequential regimes, beginning with single agent carboplatin and then adding gemcitabine or irinotecan to paclitaxel, or substituting paclitaxel with docetaxel.[1,11,12] In one of these, SCOTROC 2C, we explored the addition of gemcitabine to carboplatin and paclitaxel, where 4 cycles of carboplatin (AUC 7; q3 weeks) were followed by 4 cycles of concurrent weekly paclitaxel (70 mg/m^2; d1,8,15 q3 weeks) and gemcitabine (1000 mg/m^2; d1,8 q3 weeks).[1] Efficacy data were encouraging (median PFS 19.5 months), although grade 3 dyspnoea was observed in 5.8% of patients during the weekly paclitaxel–gemcitabine phase. Pulmonary toxicity associated with weekly regimes incorporating gemcitabine and a taxane has also been reported in non-small cell lung cancer.[13,14] In the current trial we assessed the feasibility and efficacy of this regime with the paclitaxel administered 3-weekly rather than weekly. We also re-assessed the incidence of pulmonary toxicity, and whether it could be ameliorated by this change in scheduling during the paclitaxel-gemcitabine phase.

2. Patients and methods

2.1. Patients

The trial was conducted with ethical approval from the local and national IRBs, and informed consent of patients. Women aged 18 or older with histologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube carcinomas were eligible. Patients with peritoneal carcinomatosis of 'uncertain' origin were also eligible, provided that the tumour was not mucin-secreting, and histology did not suggest a lung, gastrointestinal or biliary tract primary. Patients had to have International Federation of Gynaecology and Obstetrics stages Ic–IV disease, no prior chemotherapy, be within 8 weeks of initial surgery, Eastern Cooperative Oncology Group performance status of 0–2, and able to comply with follow-up requirements. Adequate liver bilirubin $\leqslant$ upper limit of normal (ULN), aspartate aminotransferase/alanine aminotransferase $\leqslant 1.5 \times$ ULN, or alkaline phosphatase $\leqslant 3 \times$ ULN), renal (creatinine $\leqslant 1.25 \times$ ULN), and bone marrow (neutrophils $\geqslant 1.5 \times 10^9$/l, platelets $\geqslant 100 \times 10^9$/l, and haemoglobin $\geqslant$ 9.0 g/l) functions were required. Patients were excluded if they had borderline ovarian malignancies, ruptured capsule as the only evidence of stage Ic, carcinosarcoma, previous malignancy (except for in situ cervical cancer or non-melanoma skin cancer), concurrent severe or uncontrolled co-morbid medical conditions, history of prior serious allergic reactions, or symptomatic peripheral neuropathy.

2.2. Treatment plan

The chemotherapy regimen consisted of 4 cycles of carboplatin (area under the curve of 7 mg·min/ml calculated using the Calvert formula and using ^{51}Cr-EDTA GFR) given 3-weekly, followed by 4 cycles of paclitaxel 175 mg/m^2 on day 1, and gemcitabine 1000 mg/m^2 on days 1 and 8 at 3-week intervals. Carboplatin was given as a 1 h infusion in 500 ml 5% glucose, and paclitaxel as a 3 h infusion in 250 ml 5% glucose, followed by gemcitabine as a 30 min infusion in 250 ml 0.9% saline, with standard anti-emetics. After completing carboplatin therapy, interval debulking surgery was permitted for patients sub-optimally debulked at their first operation. Full doses of carboplatin were given if neutrophils were $\geqslant 1.5 \times 10^9$/l OR total white cell count $\geqslant 3.0 \times 10^9$/l and platelets were $\geqslant 100 \times 10^9$/l on the day of treatment. If, on the day of treatment, neutrophil and platelet levels were not within these ranges, carboplatin was delayed until haematological recovery. A delay of >2 weeks necessitated withdrawal from study treatment. If recovery occurred between 1 and 2 weeks, or prolonged neutropenia, neutropenic sepsis, or complicated grade 4 thrombocytopenia was observed, the subsequent dose of carboplatin was reduced by 1 AUC level (minimum of AUC 5, after which patient withdrawn from the study). During paclitaxel/gemcitabine treatment full doses of both drugs were given if neutrophils on day 1 were $\geqslant 1.5 \times 10^9$/1 and platelets were $\geqslant 100 \times 10^9$/l. If these levels were not reached on day 1, treatment was delayed for up to 2 weeks before withdrawal from study. If blood counts recovered between 1 and 2 weeks or if neutropenic sepsis or complicated grade 4 thrombocytopenia occurred, the subsequent doses of gemcitabine were reduced by 20%. If grade 3/4 mucositis (at physician's discretion if grade 2), or $\geqslant$grade 2 skin toxicity occurred, treatment was delayed. If the toxicity persisted, paclitaxel doses could be reduced to 135 mg/m^2 for the subsequent cycles, before withdrawal of the patient from the study. On treatment day 8, full dose of gemcitabine was given if neutrophils were $\geqslant 1.0 \times 10^9$/l and platelets were $\geqslant 100 \times 10^9$/l. If these levels were not reached on day 8, the day 8 dose of gemcitabine was omitted on that cycle, and all subsequent doses of gemcitabine (d1 and 8) reduced by 20%. If this recurred on a subsequent cycle, gemcitabine was again omitted and paclitaxel

doses reduced to 135 mg/m^2 in the subsequent cycles. If this recurred, the patient was withdrawn from the trial. Treatment was also stopped if grade 3/4 neurotoxicity or ototoxicity occurred. If hypersensitivity reactions to paclitaxel were observed, the infusion was stopped, treated accordingly and restarted after recovery at the discretion of the attending physician. Treatment was withheld if the patient developed unexplained pulmonary symptoms, or intrapulmonary infiltrates were observed radiologically, until the pathogenesis could be determined. If this was considered to be drug-related, the patient did not receive further therapy.

2.3. Clinical assessments

At baseline and before each cycle of therapy, a physical examination was performed, and toxicity, performance status, and weight were assessed. The FBC and biochemical profile were repeated at baseline, on day 1 of each cycle of carboplatin and weekly during paclitaxel and gemcitabine therapy. Chest X-rays were performed at baseline, prior to each cycle of paclitaxel–gemcitabine, and during carboplatin cycles only if disease was evident at baseline or if clinically indicated.

Clinical response was determined using CT scans in patients with measurable disease at the start of chemotherapy. Scans were performed at baseline, after 4 cycles of carboplatin (both before and after surgery if interval debulking was performed) and once all 8 cycles of chemotherapy were completed. Modified Southwest Oncology Group solid tumour response criteria were used. CA125 levels were measured before each cycle of chemotherapy and during follow-up. CA125 response was assessed using internationally agreed conventions.[15]

All patients were followed up 2 monthly for 2 years, 3-monthly in the third year, 4-monthly in the fourth year and 6-monthly until progressive disease or death.

2.4. Statistical considerations

This was a single stage one arm multi-centre Phase II feasibility study designed to assess whether the experimental regimen was feasible as determined by the proportion of patients completing all 8 cycles of chemotherapy. Fifty-four patients were required to test the null hypothesis that the completion rate is $\leqslant$60% against the alternative that it is >60%. Based on a one-sided significance level set at 5% and a power of 95% for a true completion rate of 80%, and the premise that >80% is clearly an acceptable study completion rate, 60–80% is a 'grey area', and $\leqslant$60% is clearly unacceptable. Protocol-defined secondary end-points were: toxicities, clinical and CA-125 response rates, PFS and OS. PFS was measured from the date of randomisation to progression or death from any cause (whichever came first), and OS from the date of randomisation to death. Kaplan–Meier methods were used to generate survival curves and estimate PFS and OS rates. Cox regression techniques were used to compare hazard ratios (HRs) between feasibility studies[1,11,12] and SCOTROC1[16] which included similar patients, adjusting for registration performance status, bulk of residual disease and stage.

3. Results

3.1. Patient characteristics

Between June 2005 and June 2006, 54 patients from seven UK centres were enrolled into the study. The median age of patients was 60 years, and the majority had stage III (74%), grade 3 (63%), serous papillary adenocarcinomas (70%), and were of good performance status (PS < 2; 94%; Table 1). Two patients who commenced therapy, despite fulfilling initially diagnostic criteria for inclusion, were subsequently withdrawn due to the clinical suspicion that they had non-ovarian primaries (Fig. 1), but were included in the subsequent analyses of toxicity, feasibility and efficacy based on the intention-to-treat principle.

3.2. Chemotherapy administration and completion rates

Forty patients (74.1%; 90% confidence interval [CI]: 63–84%) on the study completed all 8 cycles of chemotherapy, confirming feasibility of the regimen. The progress of patients through the trial is shown in Fig. 1. Of the 14 patients who did not complete treatment, 8 were due to toxicity, 4 due to disease

Table 1 – Baseline patient characteristics (*n* = 54).

	n	%
Age (years)		
Median (range)	60	(36–72)
FIGO stage		
Ic	1	1.9
II	6	11.1
III	40	74.1
IV	7	13.0
Grade		
1	2	3.7
2	10	18.5
3	34	63.0
NK	8	14.8
Histology		
Serous/papillary	38	70.4
Endometroid	4	7.4
Mucinous	1	1.9
Clear cell	2	3.7
Adenocarcinoma NOS	6	11.1
Other	3	5.6
Residual disease		
None or microscopic	17	31.5
$\leqslant$2 cm	11	20.4
>2 cm	19	35.2
Not classified	7	13.0
Performance status		
0	29	53.7
1	22	40.7
2	3	5.6
CA-125 >35 prior to chemotherapy		
No	12	22.2
Yes	42	77.8

FIGO = International Federation of Gynecologic Oncology; CA-125 = cancer antigen 125.

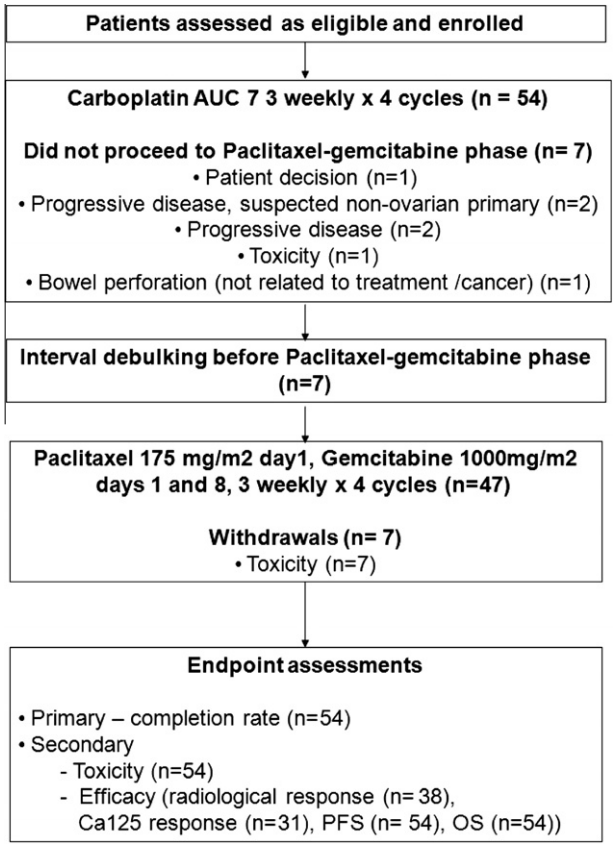


Fig. 1 – Patient journey through trial.

progression (of whom two were suspected subsequently to have non-ovarian primary tumours), 1 patient developed a bowel perforation unrelated to treatment and was taken off trial, while 1 patient withdrew consent. Overall 68.5% of patients had one or more dose reductions or omissions, and 88.9% had dose delays.

Despite this, patients completed 211 (97.7%) of 216 planned cycles of carboplatin chemotherapy, and the median carboplatin dose intensity delivered was 87% of that planned. Furthermore, the 47 patients who went on to start paclitaxel–gemcitabine completed 178 (94.7%) of 188 planned cycles of chemotherapy, and the overall median dose intensity achieved for paclitaxel and gemcitabine were 99% and 80%, respectively, of that planned.

The predominant reason for carboplatin and gemcitabine omissions and delays was neutropaenia. Paclitaxel doses were reduced in 13 cycles in 12 patients, predominantly due to neuropathy in 6, haematological toxicity in 5 and one patient experienced a grade 3 ALT elevation.

3.3. *Toxicity*

Table 2 summarises the incidence of haematological and non-haematological toxicities. Grades 3–4 neutropaenia was the commonest haematological toxicity reported during both carboplatin and paclitaxel–gemcitabine phases of the study, and observed in 51.8% and 48.9% of patients, with 1 patient experiencing an episode of neutropaenic sepsis during carboplatin chemotherapy. In contrast grade 3/4 anaemia (13% carboplatin; 4.3% paclitaxel–gemcitabine) and thrombocytopaenia (20.4% carboplatin; 4.2% paclitaxel–gemcitabine) were more common during the carboplatin phase (Table 2). One patient with thrombocytopaenia associated bleeding required a platelet transfusion on cycle 4 of carboplatin.

No grade 4 non-haematological toxicities were observed during carboplatin therapy, and the most common grade 3 toxicities in >5% of patients were fatigue (5.6%) and nausea (9.3%). With paclitaxel–gemcitabine the commonest non-haematological toxicities (grade 3) in >5% was sensory neuropathy (6.4%). There was a single episode of grade 4 dyspnoea during paclitaxel–gemcitabine chemotherapy. The patient had a history of asthma, and was admitted with a 3-d history

Table 2 – Haematological (grade 3-4) and non-haematological toxicities (worst grade over treatment cycles).

Toxicity	Grade	Carboplatin		Paclitaxel–gemcitabine	
		n	%	*n*	%
Haematological					
Neutropaenia	3	18	33.3	22	46.8
	4	10	18.5	1	2.1
White blood cells	3	11	20.4	7	14.9
	4	0	0	0	0
Platelets	3	4	7.4	1	2.1
	4	7	13	1	2.1
Haemoglobin	3	5	9.3	0	0
	4	2	3.7	2	4.3
Non-haematological					
Alopecia	2	0	0	42	89.4
Fatigue	2	22	40.7	20	42.6
	3	3	5.6	2	4.3
Nausea	2	9	16.7	8	17
	3	5	9.3	0	0
Vomiting	2	5	9.3	6	12.8
	3	2	3.7	0	0
Sensory neuropathy	2	0	0	8	17
	3	0	0	3	6.4
Stomatitis	2	3	5.6	3	6.4
	3	1	1.9	0	0
Diarrhoea	2	2	3.7	4	8.5
	3	2	3.7	0	0
Constipation	2	13	24.1	10	21.3
	3	1	1.9	0	0
Oedema	2	3	5.6	4	8.5
	3	1	1.9	1	2.1
Hot flashes	2	3	5.6	2	4.3
Rash	2	0	0	3	6.4
	3	0	0	1	2.1
Arthralgia	2	0	0	17	36.2
	3	0	0	1	2.1
Dyspnoea	2	10	18.5	11	23.4
	4	0	0	1	2.1
Headache	2	4	7.4	1	2.1
Infection	2	4	7.4	6	12.8
(non-neutropaenic)	3	2	3.7	0	0
Dyspepsia	2	3	5.6	0	0
Pain	2	2	2.7	4	8.5
	3	0	0	1	2.1
Myalgia	2	1	1.9	9	19.1
	3	1	1.9	0	0

of dyspnoea associated with fine interstitial nodules on chest X-ray. She was treated with intravenous antibiotics, steroids, and subcutaneous low-molecular weight heparin, and made a full recovery. Clinically the dyspnoea was thought to be gemcitabine related, and the patient continued on paclitaxel alone. Due to concerns regarding potential pneumonitis associated with the paclitaxel–gemcitabine phase when both were administered weekly in the previous SCOTROC2C trial,[1] patients underwent regular chest X-rays during chemotherapy. No significant abnormalities suggestive of chemotherapy induced pneumonitis were reported except in the patient with dyspnoea discussed above, and no other patients discontinued treatment due to dyspnoea.

3.4. *Efficacy*

At baseline 38 patients were assessable for response radiologically, 31 by Ca-125, and 43 overall by either method. Of these 3 patients achieved a radiological complete response, 18 a partial response, 10 stable disease and 2 progressed with carboplatin chemotherapy. Five were unevaluable for response (Table 3). Seven patients underwent debulking surgery after the carboplatin phase with microscopic residual disease in 2, $\leqslant$2 cm in 3, >2 cm residual in 1 and not recorded for 1 patient. At the end of all chemotherapy a total of 15 patients had achieved a radiological complete response, 13 a partial response, and 2 had progressed, giving an overall radiological response rate of 73.7% (28/38). The Ca125 response rate in evaluable patients was 90.3% (28/31), and the overall response rate was 76.7% (33/43), by either method.

Since patients who progressed on carboplatin did not proceed to the paclitaxel–gemcitabine phase, it was not possible to assess the relative cross-resistance of the paclitaxel–gemcitabine component relative to carboplatin. Disease progression during the paclitaxel–gemcitabine phase occurred towards the end of treatment, and did not lead to any early discontinuations of therapy.

As of May 2008, the median follow-up on the trial was 24 months (range 5–30), and 37 (68.5%) patients had progressed of whom 19 (35%) had died, all due to ovarian cancer. The median PFS was 14.2 months (95%: CI: 10.9–17.5 months, Fig. 2), and progression free rate at 8-months was 89% (90% CI: 82–96%). Although median OS has not yet been reached, 62% (90% CI: 48–73%) of patients were alive at 2 years.

Table 3 – Radiological Response assessments.

	Post-carboplatin[a]		Overall[a]	
	n	%	*n*	%
CR	3	7.9	15	39.5
PR	18	47.4	13	34.2
CR + PR	21	55.3	28	73.7
SD	10	26.3	8	21.1
PD	2	5.3	2	5.3
Non-evaluable	5[b]	13.2	0	0

CR = complete response; PR = partial response; PD = progressive disease; SD = stable disease.

[a] Compared to baseline scan.

[b] Non-evaluable after carboplatin therapy (4 = no scan, 1 = non-measurable disease).

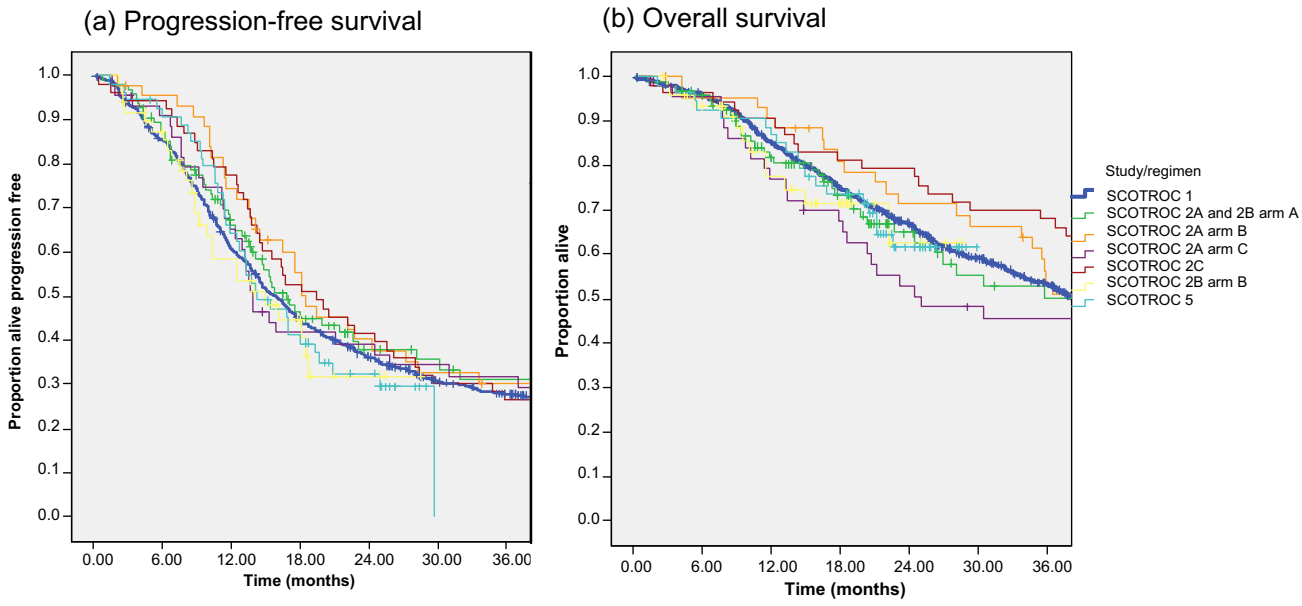
4. Discussion

The aim of this study of sequential chemotherapy, incorporating a 3-weekly cycle of paclitaxel, was to evaluate its feasibility, toxicity and efficacy, as compared to our previous experience in phase II trials of sequential chemotherapy involving weekly taxane regimes.[1,12] Forty patients (74.1%; 90% CI: 63–84%) on the study completed all 8 cycles of chemotherapy, confirming feasibility of the regimen, based on a definition of a >60% completion rate. This was based on an 80% completion rate for all 6 cycles of carboplatin–taxane in SCOTROC1, conducted by us in a similar patient group.[16] This is further supported by the ability to deliver 87%, 99% and 80% of the planned dose-intensities of carboplatin, paclitaxel and gemcitabine, respectively, overall in the current study, which is similar to those observed in ICON5-GOG182.[8]

Our results are also in keeping with those of Friedlander et al., who conducted a similar sequential study of 4 cycles of 3-weekly carboplatin followed by 4 cycles of 3-weekly paclitaxel–gemcitabine.[17] The key differences in that trial were that paclitaxel was administered on day 8 instead of day 1, and carboplatin at AUC 6 instead of AUC7, the primary endpoint was PFS and only patients with stages IIC–IV disease were eligible. The completion rate for all 8 cycles of chemotherapy in that study was 82.9%, with a median PFS of 13.8 months. As in the current study, myelosuppression was the predominant dose-limiting toxicity, and suggests that limiting neutropaenia is not ameliorated by administering paclitaxel on day 8 instead of day 1.

In the current trial, 23.4% of patients had grade 2 dyspnoea during paclitaxel–gemcitabine, which was similar to that during the carboplatin phase (18.5%). No patient developed grade 3 dyspnoea, with only one patient (2.1%) experiencing grade 4 dyspnoea with paclitaxel–gemcitabine. This is in contrast to rates of grade 2, 3 and 4 dyspnoea reported with weekly paclitaxel–gemcitabine (9.8%, 5.8% and 0%), weekly docetaxel–gemcitabine (40%, 5.7% and 2.9%), 3-weekly docetaxel with weekly-gemcitabine (35.7%, 4.8% ad 0%) and 3-weekly docetaxel without gemcitabine (10.8%, 0% and 0%), respectively.[1,11,12] Our results confirm that the risk of serious (grades 3–4) pulmonary toxicity using these sequential schedules is small, and is not changed by administering paclitaxel 3 weekly with gemcitabine given weekly, compared to the weekly taxane combinations.

To assess the justification for further first-line trials using sequential chemotherapy regimens, we performed a comparative analysis of our experience in 4 trials (SCOTROC 2a–c and SCOTROC 5) with this approach.[1,11,12] Fig. 2 shows a summary of the PFS and OS of patients treated on all six arms of the first-line Phase II ovarian chemotherapy trials conducted by the Scottish Gynecological Clinical Trials Group, with similar entry and follow-up criteria.[1,11,12] It also includes data from the original Phase III SCOTROC1 trial in which patients received carboplatin with either paclitaxel or docetaxel.[16] SCOTROC 2a–c were conducted contemporaneously between 2000 and 2002 by the same subgroup of investigators and a total



Study arm	Chemotherapy	Progression free survival Hazard Ratio	80% Confidence interval	1-sided p-value	Overall survival Hazard Ratio	80% Confidence interval	1-sided p-value
SCOTROC1 [16]	carboplatin AUC5 + paclitaxel 175mg/m^2 (d1 q21 x6) OR carboplatin AUC6 + docetaxel 75 mg/m^2 (d1 q21 x6)	1.00	-	-	1	-	-
SCOTROC 2A arm A [12] and SCOTROC 2B arm A [11]	carboplatin AUC7 (d1 q21 x4) then docetaxel 100mg/m^2 (d1 q21 x4)	0.85	0.71 - 1.01	0.11	0.99	0.8 - 1.23	0.48
SCOTROC 2A arm B [12]	carboplatin AUC7 (d1 q21 x4) then docetaxel 75mg/m^2 (d8 q21 x4)+ gemcitabine 1250mg/m^2 (d1,8 q21 x4)	0.80	0.63 -1.01	0.11	1.07	0.84 -1.36	0.63
SCOTROC 2A arm C [12]	carboplatin AUC7 (d1 q21 x4) then docetaxel 25mg/m^2 (d1,8,15 q21 x4)+ gemcitabine 800mg/m^2 (d1,8,15 q21 x4)	0.95	0.76 -1.19	0.39	1.32	1.03 -1.68	0.92
SCOTROC 2B arm B [11]	carboplatin AUC7 (d1 q21 x4) then docetaxel 60mg/m^2 (d1 q21 x4)+ irinotecan 200mg/m^2 (d1 q21 x4)	1.00	0.77 -1.29	0.49	1.04	0.71 - 1.52	0.55
SCOTROC 2C [1]	carboplatin AUC7 (d1 q21 x4) then paclitaxel 70mg/m^2 (d1,8,15 q21 x4)+ gemcitabine 1000mg/m^2 (d1,8 q21 x4)	0.83	0.67 -1.03	0.13	0.77	0.61 - 0.97	0.07
SCOTROC5 current study	carboplatin AUC7 (d1 q21 x4) then paclitaxel 175mg/m^2 (d1 q21 x4)+ gemcitabine 1000mg/m^2 (d1,8 q21 x4)	1.08	0.89 -1.36	0.66	1.15	0.84 - 1.56	0.72

*Hazard ratios based on cox-regression analyses after controlling for tumour stage, residual disease and performance status

Fig. 2 – Kaplan–Meier plots and Cox regression comparisons of progression-free and overall survival in the SCOTROC trials.

of 282 patients were treated. Although these studies were not designed for formal statistical comparisons, the results from the previous large Phase III SCOTROC1 trial with over 1000 patients, which showed a similar survival of patients treated with 3-weekly carboplatin–paclitaxel and carboplatin–docetaxel, provides a historical basis for making a comparison of the Phase II regimens.[16] Using a hazard ratio (HR) of 0.75 relative to SCOTROC1 (corresponding to a 33% increase in median progression-free or overall survival) only SCOTROC2C with concurrent weekly paclitaxel (70 mg/m^2; d1,8,15 q3 weeks) and gemcitabine (1000 mg/m^2; d1,8 q3 weeks) has HRs compatible with this figure for both PFS and OS relative to SCOTROC1 (Fig. 2).[1] For all other regimens 0.75 is excluded by the lower limit of the 80% confidence interval either for PFS or OS (Fig. 2). In the context of ICON5-GOG182, this suggests that the superiority in PFS observed in SCOTROC2C may have been due to the use of weekly paclitaxel, in a sequential manner rather than the addition of gemcitabine.[1,8,11,12]

A recent Japanese study has demonstrated a remarkable survival benefit from weekly paclitaxel with 3-weekly carboplatin (median PFS 27.9 months) versus 3-weekly carboplatin-paclitaxel (median PFS 17.1 months, $p = 0.0014$) as first-line chemotherapy for ovarian cancer.[18] As in our series the weekly schedule separates the concurrent administration of carboplatin and paclitaxel, reducing the potential of antagonism between the two drugs.[19]

The Japanese trial is the first randomised study to seriously challenge the standard 3-weekly regimen of concurrent carboplatin–paclitaxel. A large international trial ICON8 is currently planned, and if the survival benefit of weekly paclitaxel is confirmed, this would herald a major change in practice in ovarian cancer.

Sources of funding

The study and data management costs of this trial were partly met by a grant from Eli Lilly and Company. R.A. is funded by a Clinician Scientist Fellowship from Cancer Research UK. C.G. is supported by NHS Education for Scotland and the Charon Fund. Data analysis was conducted in the West of Scotland Clinical Trials Unit, which is supported by Cancer Research UK. Edinburgh early phase clinical trials are also supported by Cancer Research UK.

Role of funding source

Eli Lilly had the opportunity to comment on the manuscript, but were not involved in the interpretation of the results or writing of the manuscript.

Conflict of interest statement

None declared.

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