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A randomised comparison of treosulfan and carboplatin in patients with ovarian cancer: A study by the Scottish Gynaecological Cancer Trials Group (SGCTG)

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ARTICLE INFO

Article history:
Received 10 August 2005
Received in revised form 2 September 2005
Accepted 6 September 2005
Available online 6 December 2005

Keywords:
Advanced
Ovarian
Cancer
Treosulfan
Carboplatin
Randomised
Clinical
Trial
Unfit

ABSTRACT

The management of older and unfit women with advanced ovarian cancer requires post-operative chemotherapy but many of these patients are not suitable for high-dose cisplatin-based regimes. Carboplatin has been an easier alternative and can be given in the ambulatory setting. Historical data suggests that oral alkylating agents to be just effective with similar efficacy. In this study we have compared platinum-based carboplatin to the alkylating agent treosulfan in a population unfit to receive high-dose cisplatin. The trial randomised patients to either intravenous carboplatin or treosulfan as single agent. The trial was stopped prematurely after the interim analysis showed improved survival and response rates in the carboplatin arm. We conclude that carboplatin is a safe and effective drug in a population that is unfit for high-dose cisplatin. Treosulfan showed limited activity but may be considered along with other oral drugs in limited circumstances. With the exception of myelosuppression, toxicity was mild in both arms. Carboplatin remains the gold standard in this older and less fit group of patients.

1. Introduction

The mainstay of treatment of epithelial ovarian carcinoma remains optimal surgery with a total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, thorough inspection of the abdominal and pelvic contents particularly including under the diaphragm, the taking of peritoneal washings and where indicated lymph node sampling [1,2]. Patients with high-risk stage 1 disease and more advanced disease will receive follow-up chemotherapy. Over the past two decades we have evolved from alkylating agents to platinum-based regimes and more recently platinum/taxane combinations. In

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doi:10.1016/j.ejca.2005.09.022

certain parts of the world, the addition of anthracyclines to platinum has been considered an essential part of the treatment and most recently novel couplings with newer drugs such as topotecan and gemcitabine have been explored.

However there remains a category of patients who are either elderly and often of relatively poor performance status or who have concurrent significant major medical problems which preclude the use of platinum drugs and/or taxanes. They may be unable to tolerate high fluid loads required for platinum hydration or may be unable to tolerate the high-dose steroids as pre-medication for taxol. In the West of Scotland, the associated increased co-morbidity from smoking related disorders, such as chronic obstructive airways disease, ischaemic heart disease, and cerebrovascular disease, significantly reduces the number of patients who may be eligible for the above treatments. For these patients alternative treatment schedules must be considered.

The role of alkylating agents in the management of epithelial ovarian cancer is longstanding [3–5]. These drugs have been available for over thirty years and have traditionally been associated with response rates of around 20–30%. Treosulfan is a bi-functional alkylating agent which is claimed to have greater anti-tumour activity than other drugs such as melphalan, chlorambucil, cyclophosphamide and thiotepa. The introduction of cisplatin in the early 1980s, usually combined with an alkylating agent such as cyclophosphamide, became the gold standard treatment [6,7] and remained so until the GOG-111 and Intergroup OVO-10 studies showed the superiority of cisplatin and taxol compared to cisplatin and cyclophosphamide [8,9]. It was anticipated that this new combination would eliminate the need for alkylating agent therapy. In spite of this, there remained few centres that continued to use alkylating agents either in unfit elderly patients or for relapsed disease in poor performance status patients. Furthermore, there has been a longstanding interest in Germany, where cisplatin and treosulfan [10,11] have been combined with response rates in excess of 70%. More recently, the standard of care has been carboplatin and paclitaxel [12–14], with several major combination studies confirming equivalence of this regime over cisplatin and paclitaxel, not withstanding the controversies over how to interpret ICON 3 [15]. Most specialists however, still use a platinum/taxane combination for younger fitter patients with stage 2–4 epithelial ovarian cancer.

The introduction of carboplatin in the mid 1980s confirmed that it was a useful drug in ovarian cancer but for many years it was felt to be inferior to cisplatin [16]. A subsequent overview and meta-analysis in the 1990s showed equivalence of carboplatin to cisplatin [17]. One key element in using carboplatin is that optimal effect is seen when patients achieve significant myelosuppression [18]. Carboplatin is an easier analogue than cisplatin to use since it can be given as an outpatient or day-case and requires only a short infusion without the need for hydration and significantly reduces the risk of renal damage, oto-toxicity and neuropathy. Its principal dose limiting toxicity is myelosuppression. Thus it has increasingly replaced cisplatin particularly in the older and relatively unfit patients and furthermore, using the Calvert formula, dosing of carboplatin can be matched to renal function although one caveat is that the formula may be less reliable in older patients.

In the West of Scotland, patients with poor performance status (PS) who are unfit for high-dose cisplatin were treated previously in a variety of ways, receiving carboplatin or alkylating agents or other combinations. Based on extensive experience and data from Germany which suggested that treosulfan had higher response rates and duration of response compared to other alkylating agents, it was felt that it was timely to mount a trial to compare treosulfan with carboplatin. Treosulfan is a bi-functional alkylating agent and claimed to have slightly different properties from the other class agents. The doses chosen for the treosulfan were selected from the German practice [19]. The choice of AUC 6 every four weeks for carboplatin reflected a cautious dose in view of this relatively high-risk and poor PS group. Both of these drugs can be given as a day-case with short infusions and relatively low toxicity, myelosuppression being the major side-effect and dose limiting treatment of both drugs. It is important to remember that at the time of study development, there was a feeling that response rates with carboplatin would be inferior to those seen with cisplatin and that treosulfan might have greater activity than other alkylating agents; in particular it was unclear whether or not, in an elderly or frail patient population, the administration of carboplatin would carry any real benefit compared to an alkylating agent such as treosulfan.

There has been only one study comparing single agent platinum drugs with an alkylating agent. The North Thames Co-operative Group [20] reported on a study comparing cisplatin 120 mg vs. cyclophosphamide 2 g four weekly and found not only was there a significant difference in median survival (19 months compared to 12 months), but also a longer duration of complete clinical response (18 months vs. 8 months) in favour of cisplatin. Their trial suggested that the difference in median survival between an alkylating agent and single agent platinum may be about 50%. The difference in median progression-free survival may be larger because crossover between the arms was permitted for patients not obtaining a response, although no data on this end-point are presented. A randomised clinical trial was therefore devised to compare treosulfan and carboplatin in patients unfit to receive high-dose cisplatin therapy (i.e., greater than 75 mg/m^2). This study was powered to detect a 50% difference in median progression-free survival; although differences smaller than 50% in this end-point would probably be clinically important to detect. However, it was felt that, given the lack of work in this group of patients, a trial to detect a difference of this magnitude would provide useful information and, moreover, was the sort of difference that may plausibly exist. Given this background, it was felt justifiable to proceed to a randomised clinical trial in this sub-group of patients.

2. Patients and methods

Patients with histologically proven epithelial ovarian cancer, planned to be treated with chemotherapy, were eligible for inclusion in this study. Patients were excluded if they were fit enough to receive cisplatin either as a single agent or in

combination at a dose $\geqslant$75 mg/m^2, and it was anticipated that they would be entered into the Scottish Gynaecological Cancer Trials Group (SGCTG) active first-line ovarian trial. Inclusion criteria included histologically proven epithelial ovarian cancer; age over 18, no upper age limit was applied; and performance status (PS) up to PS3 was permitted. Optimal debulking surgery was advocated but in those patients in whom a lesser initial surgical procedure was carried out, interval debulking surgery was recommended for those showing evidence of response after 3 cycles [21]. The minimum allowable creatinine clearance was 30 ml/min calculated using the Cockcroft and Gault formula. The study was initially set up by the SCGTG but subsequently other UK centres joined. Written informed consent was obtained from all patients and the protocol was submitted to the local ethical committees.

The chosen treosulfan dose was 7 g/m^2 administered intravenously. The dose was selected as a result of the previous experience from Germany and from the company literature [22]. Higher doses have been used but this was thought to represent a safe and usable dose and would permit dose escalation. For patients receiving carboplatin an initial dose of AUC-6 was selected. The dose was determined by a calculated creatinine clearance using the Cockroft and Gault formula. These doses were given by intravenous infusion every four weeks with a maximum of six cycles prescribed. Interval debulking between the third and fourth cycles was recommended for those who had initial suboptimally debulked disease and showed signs of response. Dose escalations were permitted if on day 21 of cycle 1 or 2 platelets were $>100\times10^9$/l and WBC $>3.0\times10^9$/l. Carboplatin was to be increased by 10% over the previous cycle, and treosulfan was to be increased from 7 to 7.5 g/m^2 on the first escalation. If a second escalation was possible, then the dose was to be increased to 8 g/m^2. No dose escalations were permitted beyond the third cycle (i.e., there were a maximum of two planned dose escalations). With regard to dose delays and reductions, if on the day of treatment platelets $<100\times10^9$/l or WBC $<3.0\times10^9$/l, then chemotherapy was to be delayed for 1 week and dose reduced by 20%. If chemotherapy was delayed for longer than two weeks because of myelosuppression, protocol treatment was to be discontinued. At this point the investigator could choose to continue the same chemotherapy at a dose and frequency as appropriate. No dose escalations were permitted after a dose reduction. Although there is low probability of nausea and vomiting with treosulfan, dexamethasone and standard antiemetics were prescribed for both arms. It was felt that antiemetic omission would prejudice the quality of life analysis, since this was considered to be one of the key outcome determinates.

2.1. Clinical assessments

Prior to entry, patients underwent full clinical examination and the size and extent of disease was documented using chest X-ray, ultrasound of abdomen and/or abdomino-pelvic CT/MRI scan. The following were also measured at the start of treatment: a full blood count with differential, biochemical profile, CA-125, and creatinine clearance level (Cockcroft and Gault). These laboratory measurements were all repeated with each course of treatment. During treatment, response was assessed by the same imaging techniques used at baseline after cycles 3, 6 and, if appropriate 9. Toxicities were documented using NCI CTG Expanded Common Toxicity Criteria. Each patient was followed up 3 monthly for the first 2 years post-chemotherapy, 6 monthly to 5 years and annually thereafter. A pelvic examination was to be carried out at each follow-up visit; the ultrasound/CT/MRU was to be repeated if CA-125 began to rise and/or progressive disease was clinically suspected. The HAD scale and Rotterdam Symptom Check List were to be completed prior to each course of chemotherapy and at each follow-up visit; they were not required beyond disease progression.

2.2. Statistics

The primary end point for the study was time to disease progression (defined as time from randomisation to disease progression or cancer death). It was estimated that the median time to progression with treosulfan would be approximately 40 weeks. An improvement of 50% in median progression time with carboplatin was viewed as clinically important. In order to have an 80% chance of detecting such a difference (at the 5% level of statistical significance) 190 progressions/cancer deaths would have to be observed. In order to achieve this target within a reasonable follow-up time, the aim was to recruit 300 patients. A total of 3 analyses of the primary efficacy variable were planned after 63, 127 and 190 patients had progressed. The *P*-values employed at each of these analyses were 0.0006, 0.0151 and 0.0472 [23]. The power of this procedure is virtually the same as if no interim analyses were planned. A Data Monitoring Committee (DMC) was set up to review the results of the interim analyses and consisted of an independent clinician and an independent statistician. Patients were randomised by telephoning the West of Scotland Clinical Trials Unit where eligibility criteria were checked. Patients were allocated to treatment according to a computer generated randomisation list after stratification according to performance status (0, 1, 2 or 3), bulk of residual disease (<2 or >2 cm), disease stage (IC, II, III or IV) and treatment centre. Time to progression and survival were compared between the treatment arms using Cox's proportional hazards model. The randomisation stratification factors were included in the model. Kaplan–Meier estimates were used to draw the survival curves. Pearson's χ^2 test (unadjusted) and logistic regression were used to compare response rates; and the Mann–Whitney *U* test was used to compare the severity of toxicity between the two arms. The analysis was conducted on an intention-to-treat basis.

3. Results

3.1. Patient characteristics

A total of 204 patients, 102 in each arm, were entered into this trial during the 44 months enrolment period with an average of 4.6 patients per month. The trial opened in November 1994 and closed in July 1998. At the second interim

analysis, 120 patients had progressed and the P-value for the comparison of time to progression between the two arms was $P < 0.001$; on the basis of this and full interim analysis report, the DMC recommended study closure. The median follow-up for living patients at the interim analysis was 13 months; the median follow-up at this analysis is 37 months. Patients were entered from 13 different institutions, with 70% coming from the 4 leading centres. Six patients (4 carboplatin, 2 treosulfan) were deemed ineligible for the study but all were included using the intention to treat principle; three patients were ineligible because of lack of confirmatory pathology, one had a carcino-sarcoma and two had insufficient renal function. Patient characteristics were very well balanced in this study, and are shown in Table 1.

Table 1 – Pre-treatment characteristics

	Study treatment arm			
	Carboplatin ($n = 102$)		Treosulfan ($n = 102$)	
	%	Number	%	Number
Performance status				
0	10	10	8	8
1	46	47	46	47
2	34	35	36	37
3	10	10	10	10
Residual disease				
⩽2 cm	33	34	33	34
>2 cm	67	68	67	68
Stage				
Ic	3	3	3	3
II	7	7	5	5
III	72	73	74	75
IV	19	19	19	19
Differentiation				
Well	6	6	7	7
Moderate	28	29	20	20
Poor/Undiff	56	57	57	58
Unknown	10	10	17	17
Histology				
Serous	27	27	30	31
Mucinous	3	3	5	5
Clear cell	3	3	0	0
Endometrioid	8	8	6	6
Anaplastic	18	18	22	22
Papillary	21	21	16	16
Other/not known	22	22	22	22
Debulking surgery				
None	2	2	1	1
Biopsy only	34	35	25	26
Less than optimal	40	41	54	55
TAH + BSO + omentectomy	24	24	20	20
Age				
Median	73		73	
Inter-quartile range	69–76		67–76	
Range	54–90		45–86	
GFR (ml/min)				
Median	49		53	
Inter-quartile range	38–62		44–69	
Range	23–125		30–153	

GFR, Glomerular Filtration Rate.

3.2. *Treatment delivery*

Six cycles were recommended and the majority of carboplatin patients (68%) were able to complete the six cycles while only 35% of the treosulfan patients completed their six cycles. The reasons for stopping were as follows: 21 and 48 patients on carboplatin and treosulfan, respectively, stopped treatment because of progression; and 2 and 11, respectively, stopped treatment because of excessive toxicity, which was all haematological and mainly involving thrombocytopenia. The number of patients experiencing treatment delays was similar in each arm with 40 out of 504 episodes in the carboplatin arm; and 58 out of 424 in the treosulfan arm. Thrombocytopaenia was more often quoted as reason for delay for treosulfan than carboplatin (23 vs. 2 delays). A dose intensification was planned for each arm with two possible dose escalations on cycles 2 and 3; 53% of patients on carboplatin and 45% of patients on treosulfan achieved at least one dose escalation; the corresponding figures for two dose escalations were 26% and 16% respectively. A dose reduction was required for about a quarter of the patients in each arm; again thrombocytopenia was quoted as a reason more commonly in the treosulfan arm (14 vs. 3 reductions). The median dose intensity on the carboplatin arm was 90% (range 41–131%); and on the treosulfan arm the equivalent figures were 91% (50–103%). The dose intensity was computed as a percentage of the intended dose intensity (including the two dose escalations) over the cycles received. Some patients who stopped protocol therapy early without progressing started alternative first-line therapy. Six patients on the treosulfan arm were switched to carboplatin, and one patient starting on carboplatin was switched to chlorambucil. Treatment beyond six cycles was carried out in 5 patients, 3 with carboplatin and 2 with treosulfan.

3.3. *Clinical/radiological response and time to progression and survival*

Seventy-one patients on the carboplatin arm and 78 patients on the treosulfan arm were assessable for response (Table 2). The response rate on the carboplatin arm was 49% patients as compared to 29% on the treosulfan arm. Comparing the overall response (CR/PR) rate between the two arms (49% vs. 29%,

Table 2 – Clinical/radiological response evaluation

	Study treatment arm			
	Carboplatin ($n = 71$)		Treosulfan ($n = 78$)	
	%	Number	%	Number
Response				
CR	24	17	10	8
PR	25	18	18	14
Stable	15	11	22	17
Progression	28	20	45	35
Unevaluable	7	5	5	4

95% confidence interval (CI) for the difference: 5–35%) using Pearson's χ^2 test (unadjusted) gives $P = 0.008$. When a logistic regression model was fitted containing all the pre-treatment stratification factors as covariates this gave $P = 0.009$ for the study arm comparison. Similarly a significant benefit in time to progression was seen with carboplatin arm (Fig. 1). The median time to progression on the carboplatin arm was 10 months (95% CI 9–12 months). The median time to progression on the treosulfan arm was 5 months (95% CI 4–6 months). When a Cox model was fitted containing all the pre-treatment stratification factors as covariates this gave an estimated relative progression rate (treosulfan/carboplatin) of 1.77 (95% CI 1.30–2.42, $P < 0.001$). On the carboplatin arm, 80 patients progressed or died from their disease as compared to 90 on the treosulfan arm. The median follow-up for living patients on both arms is 37 months with 90% of patients followed up for more than 24 months. Seventy-eight patients died on the carboplatin arm and 91 patients on the treosulfan arm; 89% of deaths were ascribed to malignant disease. The median survival time on the carboplatin arm was 15 months (95% CI 10–21 months). The median survival time on the treosulfan arm was 12 months (95% CI 9–15 months). When a Cox model was fitted containing all the pre-treatment stratification factors as covariates this gave an estimated relative death rate (treosulfan/carboplatin) of 1.77 (95% confidence interval 1.04–1.94, $P < 0.026$) (Fig. 2).

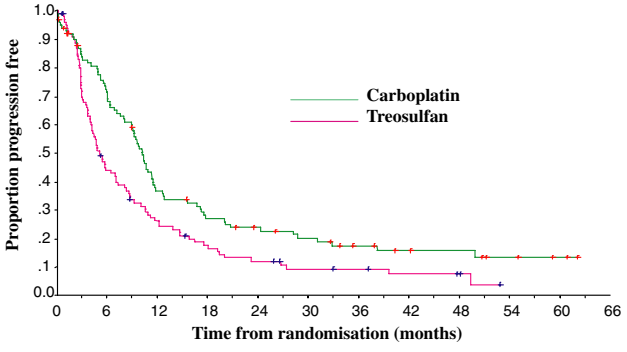

Fig. 1 – Time to progression.

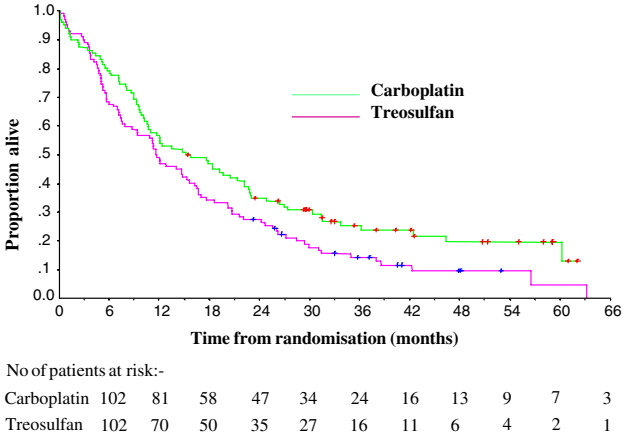

Fig. 2 – Overall survival.

3.4. *CA-125 evaluation*

Rustin's CA-125 response criteria were used [24]. However, patients unevaluable for CA-125 response according to the above criteria, but who progressed within 6 weeks and had an elevated CA-125 level taken within 9 days before starting chemotherapy, were also been classified as non-responders. Eighty-seven patients on carboplatin and 78 patients on treosulfan were evaluable for CA-125 response (Table 3). Comparing the response rate between the two arms (61% vs. 37%, 95% CI for difference 8–38%) using Pearson's χ^2 test (unadjusted) gives $P = 0.002$. When a logistic regression model was fitted containing all the pre-treatment stratification factors as covariates, this gave $P < 0.001$ for the study arm comparison. Salvage treatment after progression was offered, and most of the treosulfan patients received carboplatin whereas the carboplatin treated patients had a variety of treatments. Of the 57 patients on treosulfan who went on to carboplatin as salvage therapy, 53 received it as first-line salvage, and 1 had CR, 11 had PR, 7 were stable, 9 progressed and 25 were not assessed or unevaluable. Of the 17 patients on carboplatin who went on to treosulfan as salvage therapy, 15 received it as first-line salvage, of these none had CR, 1 had PR, 4 were stable, 4 progressed and 10 were not assessed or unevaluable.

Toxicity in this study was generally mild, as was intended to be for a group of less fit patients where severe toxicity would not have been acceptable. As expected, the main side-effects and events were seen in the bone marrow where levels of neutropaenia and anaemia were more severe in the carboplatin arm (Table 4); these comparisons were dominated by the observations on cycles 1 and 2 where blood counts were taken on day 21. The use of growth factors was not encouraged in this study. Of the other events, alopoecia, nausea, vomiting, fatigue, abdominal pain, constipation, diarrhoea and dyspepsia were not serious and no statistically significant difference could be demonstrated between the two arms.

3.5. *Quality of life*

Quality of life (QOL) data was one of the secondary endpoints of the study, and requested strictly in the protocol, unfortunately only a small proportion of patients had this measured as per protocol. The data were limited in quality and further analysis

Table 3 – CA-125 response evaluation

	Study treatment arm			
	Carboplatin ($n = 87$)		Treosulfan ($n = 78$)	
	%	Number	%	Number
Responders	61	53	37	29
Non-responders (Rustin criteria)	29	25	54	42
Non-responders (unevaluable on Rustin criteria, but progressed <6 weeks and had elevated baseline CA-125)	10	9	9	7

Table 4 – Haematological toxicity: worst recorded grades over all cycles received

	Grade	Study treatment arm			
		Carboplatin (n = 96)		Treosulfan (n = 97)	
		%	Number	%	Number
Neutropenia	0–2	80	77	83	81
(P = 0.007)	3–4	20	19	17	16
Leucopenia	0–2	92	86	85	82
(P = 0.80)	3–4	8	8	15	15
Thrombo-cytopenia	0–2	84	80	85	82
(P = 0.15)	3–4	16	16	15	15
Anaemia	0–2	83	80	96	93
(P < 0.001)	3–4	17	16	4	4

was not carried out. This was disappointing but perhaps reflects the difficulties in getting QOL scores in this population as much as the apparent lack of motivation by the clinicians.

4. Discussion

This trial carried out by the SGCTG was set up to compare an intravenous alkylating agent treosulfan with the platinum analogue carboplatin. Previous experience suggested cisplatin to be the platinum drug of choice and at the time of initiating the study, carboplatin was thought to be a less active analogue in ovarian cancer compared to cisplatin; and treosulfan a superior alkylating agent compared to other alkylating drugs like cyclophosphamide and chlorambucil. Both drugs have the advantage of being able to be given as short infusions as a day-case and with relatively mild patient morbidity. Both drugs are suitable for patients with significant medical co-morbidity which would preclude entering studies or receiving treatment with high-dose platinum. There is a paucity of trials comparing first-line platinum vs. an alkylating agent, especially in elderly/frail patients with poor PS with ovarian cancer. In light of this, we set out to determine if there was any evidence for substantial benefit for the use of carboplatin as compared to treosulfan in this population.

The trial was discontinued prematurely at the request of the Data Monitoring Committee when a large, highly statistically significant difference in time to progression emerged in favour of the carboplatin arm. The median time to progression on the carboplatin arm was 10 months compared with a disappointing 5 months for the treosulfan arm. Carboplatin achieved a response rate of 49% in comparison to 29% for the treosulfan arm and in addition, there were significantly more complete responders in the carboplatin arm. More patients in the treosulfan arm discontinued their treatment due to progressive disease. Treosulfan did show a 29% response rate, which is around the expected rate for alkylating agents [4,5], thus confirming that this class of drug has limited activity in epithelial ovarian cancer. Nevertheless, the superiority of a platinum analogue was demonstrated in this study. A median time to progression of 10 months with carboplatin is poor in comparison to that seen with combinations of cisplatin/cyclophosphamide as in the GOG-111 and OVO-10 trials [8,9], where 12–13 months progression-free survival was seen. The median survival of 15 months is considerably poorer than that for the cisplatin/cyclophosphamide combination of 25 months or the cisplatin/taxol combination of 35–38 months as seen in the two major international studies [8,9]. However, we are dealing with a much less healthy population with a high concomitant co-morbidity. It must be remembered that these patients were not fit for entry into the concurrently recruiting SGCTG trials or other studies with platinum/taxane combinations. The overall median of Glomerular Filtration Rate (GFR) of around 50, the median age of 73 and the fact that 45% of the patients were of performance status 2 or 3 all effectively indicate the relatively poor physical health of this group. Toxicity in the study was generally relatively mild and alopoecia, nausea and vomiting, which are commonly considered as distressing side-effects, were of low incidence. Myelosuppression was the major side-effect affecting treatment delivery, with thrombocytopenia being particularly problematic in the treosulfan arm. While the dose intensity achieved in each arm was very similar, the number of cycles of treosulfan delivered was markedly reduced and is probably reflected in the number of patients progressing on treatment.

In conclusion, this study has shown that in a group of patients unfit for high-dose cisplatin chemotherapy, carboplatin is a significantly more active drug that treosulfan. Although moderate activity was seen in the patients receiving treosulfan, the study was closed prematurely because of the superiority and advantage of the platinum analogue. Toxicity in both arms was reasonable although myelosuppression leading to treatment delay/termination was slightly less in the carboplatin arm. On the basis of this study, we can not recommend that alkylating agents be used as first-line treatment for epithelial ovarian cancer. Carboplatin remains an acceptable alternative in patients unfit to receive high-dose cisplatin and modest, but acceptable, anti-tumour activity is seen, despite the relatively poor performance status and significant core morbidity in this group of patients. Where do we go from here? The optimal dosing and scheduling of carboplatin is still in debate. A follow-up study is being undertaken by the SGCTG group of investigators, which will address the question of whether a flat dose of carboplatin is adequate or whether further improvement can be seen by dose escalation (SCOTROC 4 protocol). Other issues that could also be addressed include the use of erythropoetins to reduce the incidence of anaemia, a common problem in this group of patients, to lead to increased quality of life and survival. In the meantime, we have shown that for this elderly and poor PS group of patients, single agent carboplatin can be safely recommended as first-line therapy.

Conflict of interest statement

None declared.

Acknowledgements

We thank all our collaborators who entered patients into this trial from the following centres who participated in the trial.

Beatson Oncology Centre, Glasgow: T. Habeshaw, R.P. Symonds, S.B. Kaye, A. Hay, J. Paul, N. Reed. Glasgow Royal Infirmary: J.H. Kennedy, M. Soukop. Stobhill Hospital, Glasgow: J.A. Davis. Aberdeen Royal Infirmary: D. Parkin, T. Sarkar. Airedale General Hospital: M. Crawford. University Hospital, Birmingham: C. Poole. Weston Park Hospital, Sheffield: R. Coleman. Belfast City Hospital: R. Atkinson, J. Price. Ninewells Hospital Dundee: I. Duncan, P. Windsor. Bristol Oncology Centre, Bristol: J. Graham, J. Murdoch. Norfolk and Norwich Hospital, Norwich: J. Ostrowski. Mount Vernon Hospital, Middlesex: G. Rustin. Royal Shrewsbury Hospital, Shrewsbury: S. Awwad.

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