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The importance of dose and schedule in cancer chemotherapy: epithelial ovarian cancer

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Selection of specific appropriate drugs has been facilitated by a series of randomised clinical trials confirmed by overview analysis. Hitherto these issues have dominated the debate over optimal chemotherapy management of advanced ovarian cancer. The impact of true dose escalation therapy is yet to be evaluated but appears to be worthy of examination in demonstrably chemosensitive disease.

Introduction

A meta-analysis was conducted by the Advanced Ovarian Trials Group (AOCTG)[1] in order to try to define the optimal first-line chemotherapy for patients with advanced epithelial ovarian cancer; in particular the role of platinum was investigated. Data from 45 different randomised trials were analysed and the results suggested the following.

(a) Platinum-based chemotherapy is superior to non-platinum regimens.
(b) Combination platinum-containing regimens are superior to treatment with single-agent cisplatin at the same dose.
(c) Cisplatin and carboplatin are equivalent in terms of their effect on survival.

In response to these conclusions the AOCTG initiated the International Collaborative Ovarian Neoplasm (ICON-2) trial for patients with advanced epithelial ovarian cancer. This trial was designed to assess the role of platinum-based combination chemotherapy and randomises patients to receive carboplatin or cyclophosphamide, doxorubicin and cisplatin (CAP) chemotherapy.

Controversy surrounds the inclusion of doxorubicin in platinum-based combination chemotherapy for first-line treatment of epithelial ovarian cancer. A second meta-analysis, the Ovarian Cancer Meta-Analysis Project (OCMP), addressed this issue, evaluating 1194 patients. A 7% survival benefit for CAP chemotherapy was demonstrated at 6 years compared to treatment with cyclophosphamide and cisplatin combination chemotherapy (CP).[2]

A'Hern and Gore performed an overview using data from both the AOCTG and the OCMP analyses[3] and also reported an improvement in survival in favour of doxorubicin (hazards ratio, 0.85; 95% confidence interval 0.76–0.95, $p = 0.003$). The size of the benefit was of a similar magnitude to that of platinum.

Standard combination chemotherapy for advanced epithelial ovarian cancer includes cisplatin at 75 mg/m^2 and cyclophosphamide 750 mg/m^2 or CAP chemotherapy at doses of cisplatin 50 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2. In the UK, standard therapy is still considered to be single-agent carboplatin or cisplatin, but this may change when the results of the ICON-2 study are known. In the US and most of Europe single-agent platinum is only considered in patients where the goal of treatment at the outset is purely palliative, i.e. the elderly. The activity of paclitaxel in platinum-refractory disease has led to trials of paclitaxel as first-line therapy. Several randomised trials are currently underway assessing the role of paclitaxel in combination with platinum. Preliminary results from one study performed by the Gynecological Oncology Group (GOG Protocol 111) in patients with sub-optimally debulked disease have been presented and suggest that cisplatin/paclitaxel is superior in terms of survival compared to standard therapy with cisplatin/cyclophosphamide.[4]

Evidence for a dose–response relationship in epithelial ovarian carcinoma

Initial evidence for a dose–response relationship in epithelial ovarian cancer comes from two sources:

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experimental *in vitro* models and retrospective dose-intensity analyses of clinical trials.

In vitro modelling

Kinetic modelling of the behaviour of tumour cells relies on basic assumptions with regard to the sensitivity and resistance of these cells to chemotherapy agents. These models ascribe mathematical relationships to the responses seen with cytotoxic agents in *in vitro* experiments. However, the models are limited by their inability to incorporate the behaviour of tumour cells as this relates to the cell cycle. Based on the Goldie–Coldman model of somatic mutation,[5] dose intensity is designed to overcome either intrinsic chemotherapy resistance or initial inadequate dose delivery. This may be achieved by either scheduling or overall dose, the actual dose being important for eradicating chemoresistant cells and the dose intensity for eradicating chemosensitive cells. *In vitro* model systems have implied that increasing the dose intensity of platinum or alkylating agents does not overcome resistance in cell lines or improve response in bulky disease. However small volume and chemotherapy-sensitive disease could potentially benefit from high dose-intensive regimens.[6] Ozols and colleagues suggest that the best results with dose-intensive regimes will be in patients with minimal residual disease after initial surgical debulking.[7]

Retrospective analyses of clinical trials

Retrospective analyses of dose intensity examine the relative or received dosage. Relative dose intensity is used to compare separate chemotherapy regimes with reference regimens. This method may, however, be subject to selection bias through the choice of the reference treatment.[8] The received dose intensity is the dose delivered as a function of time.

Levin and Hryniuk have retrospectively analysed the relationship between dose intensity of single agent or combination chemotherapy regimens, clinical response and survival in epithelial ovarian cancer.[9,10] Relative dose intensity was calculated as a fraction of the dosage of each drug compared to that contained in the standard regimen of cyclophosphamide, hexamethylamine, doxorubicin and cisplatin (CHAP). These authors reported a statistically significant relationship between response rate and relative dose intensity of the cisplatin when given either as a single agent ($p < 0.05$) or in combination chemotherapy regimes ($p < 0.02$). Lack of data prevented extrapolation of this result to suggest a plateau in the dose–response relationship. The authors were limited by insufficient data to explore a dose intensity of greater than 27 mg/m^2/week for single-agent cisplatin, and of greater than 25 mg/m^2/week for combination chemotherapy regimens. In addition, the authors reported that the dose–response relationship for cyclophosphamide as a single agent was of borderline statistical significance ($p = 0.06$) and was not statistically significant in the context of combination regimes. They commented that their analysis was limited by the narrow range of dose intensities of cyclophosphamide. Similarly there were insufficient data to analyse doxorubicin for its dose–response relationship as a single agent, although it was of borderline significance when part of combination regimes ($p = 0.05$). Torri and colleagues undertook a weighted regression analysis of randomised clinical trials of first-line chemotherapy in patients with advanced epithelial ovarian cancer, published between 1975 and 1989. The dose intensity for each drug in these regimens was compared to that which gives an arbitrary but fixed response rate for that agent.[11] They reported a positive relationship between dose intensity and response for platinum, doxorubicin and cyclophosphamide as well as a positive relationship with survival for platinum and doxorubicin. In order to eliminate potential bias, intra- as opposed to inter-trial comparisons were made. The authors noted that few studies include treatment arms that differ greatly in their dose intensity, and investigating dose–response relationships beyond narrow ranges of dose intensity is therefore not possible.

Two studies have examined the relationship between outcome and received dose intensity. Repetto and colleagues studied 198 patients entered into two prospective randomised trials of platinum-based first-line chemotherapy for stage III–IV disease. The majority of patients received more than 76% of the planned dose intensity; relative total drug dose as such did not affect progression-free or overall survival.[12] Sweetenham and colleagues[13] analysed mean received dose intensity in 19 patients with advanced ovarian carcinoma undergoing high-dose chemotherapy with cisplatin 120 mg/m^2 and cyclophosphamide 1000 mg/m^2 every 3 weeks for six cycles. The dose intensity relative to the CHAP regimen[9] was 1.14 and the average received relative dose intensity was 0.90. Increasing duration of therapy has not been shown to be of benefit in two prospective randomised trials of combination chemotherapy with cisplatin, doxorubicin and cyclophosphamide.[14,15]

Randomised comparisons of dose intensity

Several randomised trials have prospectively addressed dose intensity of individual drugs given in the context of combination regimens in epithelial ovarian cancer. Interest has focused on the platinum compounds (cisplatin and carboplatin), alkylating agents (cyclophosphamide and ifosfamide), anthracyclines (doxorubicin and epirubicin), and the first of the taxanes, paclitaxel.

Five prospective randomised trials have been reported examining the issue of standard-dose vs higher-dose chemotherapy as first-line treatment of epithelial ovarian cancer. The GOG randomised 485 patients with suboptimally debulked (≥ 1 cm) stage III or any stage IV epithelial ovarian cancer to receive four cycles of cisplatin 100 mg/m^2 and cyclophosphamide 1000 mg/m^2 every 3 weeks for four cycles or cisplatin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for eight cycles. The received dose intensity ratio was 0.91:0.46, i.e. 2:1, while the total dose was constant in the two arms.[16] The response, median progression-free interval and survival rates were similar but toxicity, grade 3–4 pancytopenia and emesis were greater in the high-dose arm. The Milan trial compared cisplatin 50 mg weekly for nine cycles with cisplatin at 75 mg/m^2 every 3 weeks for six cycles, in 306 patients with stage III–IV epithelial ovarian cancer. The dose intensity ratio was again 2:1 and the same total dose remained constant.[17] Pathological complete remission rates, median progression-free intervals and survival were similar but toxicity, particularly ototoxicity, was significantly worse in the dose-intense group. The Italian Oncology Group for Clinical Research (GOIRC)[18] reported an earlier randomised trial of 101 patients with stage III–IV epithelial ovarian cancer, comparing cisplatin 100 mg/m^2 weekly with a 5-week interval between the third and fourth cycles with cisplatin 100 mg/m^2 every 3 weeks for six cycles. Both arms were then followed by four cycles of doxorubicin and cyclophosphamide chemotherapy. The cisplatin relative dose intensity was 54.5:33.3 (1.6:1) and again the total dose of cisplatin was the same. The overall reported response rates and survival were similar but the authors describe a trend for increased survival at 4 years of 31% vs 13% with increasing relative dose intensity.

Conversely, two randomised trials with both a dose intensity and total dose advantage for higher doses of cisplatin report survival advantages for the high-dose arms. Kaye and colleagues[19] reported early closure of their trial after an interim analysis of the first 165 patients comparing cisplatin 100 mg/m^2 and cyclophosphamide 750 mg/m^2 every 3 weeks for six cycles with cisplatin 50 mg/m^2 and cyclophosphamide 750 mg/m^2 every 3 weeks for six cycles. The relative dose intensity ratio and total dose between the two arms was 2:1 and the authors reported an overall survival advantage of 114 weeks in the high-dose arm compared with 69 weeks in the conventional-dose arm. The incidence of neurotoxicity and nephrotoxicity was greater in the high-dose arm. An earlier, smaller trial reported from Hong Kong[20] compared cisplatin 120 mg/m^2 and cyclophosphamide 600 mg/m^2 with cisplatin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 in 28 evaluable patients. With a relative dose intensity ratio and total dose ratio of 2:1 between the two arms, the authors reported a 3-year actuarial survival of 60% in the high-dose arm and 30% in the standard-dose arm. However, once again there were significant toxicities associated with the higher dose.

In summary, it appears that both relative dose intensity and total dose are important contributors to improved response and survival. This improvement is modest and has an associated significant morbidity.

Phase II trials investigating dose intensity

Platinum agents

Standard-dose carboplatin and cisplatin give similar long-term survival rates;[21] but the former is less toxic, particularly with regard to neuro-, nephro- and ototoxicity, although it is more myelosuppressive, mainly causing thrombocytopenia. It therefore has the potential for dose escalation with haemopoietic growth factors, bone marrow or peripheral blood stem cell support. Several trials have reported responses in patients retreated with high-dose platinum agents after failure or relapse following initial treatment at conventional dose, implying potential for a further cytotoxic effect on residual chemosensitive tumour cells.[22–24] Response rates in the range of 30% are reported but sometimes with excessive toxicity;[25] overall the response rates are similar to standard platinum-containing combination regimes.

Jodrell and colleagues,[26] using the Calvert formula,[27] analysed data from 989 patients entered into clinical trials of single-agent carboplatin in previously untreated patients with advanced stage ovarian cancer (stage III–IV) or those with relapsed disease. Regression analysis demonstrated that the area under the curve (AUC) for carboplatin, prior treatment and performance status were predictors

of tumour response and toxicity (thrombocytopenia and leucopenia). Higher response rates were reported with increments in the AUC, the relationship was non-linear, and the authors reported that increasing the carboplatin AUC above 5–7 mg/ml/min did not improve the likelihood of response but did increase myelotoxicity. Two randomised trials are underway in order to prospectively address this issue: the London Gynaecological Oncology Group (LGOG)[28] is comparing single-agent carboplatin AUC 6 with carboplatin AUC 12 in previously untreated patients (stage I_c–III), and the Danish Ovarian Cancer Group is comparing two dose levels of carboplatin AUC 4 and AUC 8 each with cyclophosphamide 500 mg/m^2 in previously untreated patients with stage II–IV epithelial ovarian cancer.[7]

Combinations of cisplatin and carboplatin

The dose-limiting toxicities of the two platinum compounds are different and several groups have explored the possibility of combining cisplatin and carboplatin in order to intensify the dose of platinum. Two phase II studies[29,30] have assessed the combination of carboplatin 300 mg/m^2 and cisplatin 100 mg/m^2 in 73 patients with no prior therapy, in two slightly different schedules. Pathological complete response rates were both reported as 22%, at the expense of treatment delays in up to 45% of cycles and ototoxicity in 39% of patients. A third study evaluated carboplatin AUC 11 on day 1 combined with cisplatin 30–50 mg/m^2 on day 2 in 26 patients with stage IV disease. The overall response rate was 65% with a median disease-free survival of 9 months, with one early death and significant emesis, neuro- and ototoxicity at the higher cisplatin dose.[31] Fanning and colleagues[32] explored a schedule of cisplatin 70 mg/m^2 on day 1 and carboplatin 100 mg/m^2 on day 8 every 28 days for five cycles in 30 patients. They reported a 44% pathological response rate associated with grade 3–4 peripheral neuropathy, ototoxicity and thrombocytopenia. It appears that the toxicities encountered with cisplatin–carboplatin combinations make the delivery of such regimens impractical.

Alkylating agents

Osborne and colleagues[33] gave two cycles of cyclophosphamide 7 g/m^2 to 20 patients and reported three complete responses and 11 partial responses. Subsequently, patients received conventional-dose cisplatin and the overall complete response rate was 25%. The median duration of response was only 14 months with a median survival of 20 months. Similarly, others investigating high-dose alkylating-agent chemotherapy after conventional induction have reported median durations of remission of approximately one year, not dissimilar to those achieved with conventional-dose chemotherapy, even though the pathological complete remission rate has been reported to be as high as 45%.[34]

Ifosfamide has been demonstrated to be active in advanced epithelial ovarian cancer, with response rates in the range of 33%–79% in previously untreated patients.[35] Gallagher and colleagues[36] assessed dose-escalating the combination of carboplatin 200 mg/m^2 plus ifosfamide 2.5 g/m^2 to carboplatin 400 mg/m^2 plus ifosfamide 5 g/m^2 given 4-weekly. Four patients (31%) responded of the 13 with recurrent disease and seven patients (78%) responded among nine previously untreated patients. Perren and colleagues[37] compared three cycles of ifosfamide 5 g/m^2 followed by three cycles of carboplatin 400 mg/m^2 with six cycles of carboplatin alone, every 4 weeks, in 152 patients with stage III disease. After three cycles of treatment 29% of patients had responded in the combined-treatment arm and 63% in the carboplatin-alone arm. Sixteen of 35 patients who did not respond to ifosfamide subsequently responded to carboplatin. The total dose ratio for carboplatin was 2:1 between the two arms and it appears that carboplatin was able to salvage ifosfamide-refractory patients.

Anthracyclines

The response rate for single-agent doxorubicin used as front-line chemotherapy is 22%–50%,[38–41] and epirubicin has been reported to produce responses in 12 out of 27 patients (44%).[42] Dose–response for anthracyclines has never been fully assessed but the EORTC Gynaecological Cancer Co-operative Group investigated high-dose epirubicin in a phase I/II dose escalation trial.[43] Fifty-one eligible patients, divided according to response to first-line cisplatin-containing combination chemotherapy, received epirubicin at 150 mg/m^2 escalating to 180 mg/m^2. The authors reported two partial remissions in 13 patients who had progressed whilst on cisplatin chemotherapy, two partial remissions in 15 patients with persistent disease after cisplatin chemotherapy, and one complete remission and six partial remissions in 23 patients who had an initial response to cisplatin chemotherapy, for an overall response rate of 27%. Toxicities included grade 3 alopecia in 74%, grade 3 nausea and vomiting in 29% and grade 3 mucositis in 24% of patients.

Table 1. Response rate to paclitaxel therapy for relapsed/refractory epithelial ovarian cancer

Dose	Ref.	Responders/evaluable	Response rate
	55	141/652	
	56	0/13	
	57	10/65	19% (232/1211)
135 mg/m^2	58	25/100	
	48	29/195	
	59	22/140	
	60	5/46	
	61	6/19	
175 mg/m^2	56	7/25	
	45	6/43	24% (66/274)
	48	37/187	
	62	6/30	44% (42/95)
250 mg/m^2	63	5/21	
	64	21/44	

Table 2. Duration of response following paclitaxel therapy (135 mg/m^2) for relapsed/refractory epithelial ovarian cancer

Ref.	*n*	Duration of response (mo)
55	652	7.1
57	65	6.4
45	3	4.5
62 *	19	5$^+$
48 $^+$	391	8.5
59	140	9.8

* 175 mg/m^2, $^+$ 175 and 135 mg/m^2.

Taxanes

In patients previously treated with platinum-based regimens the response rate to 135 mg/m^2 of paclitaxel is 19% and there is a suggestion of a dose–response relationship, with 44% of patients treated at 250 mg/m^2 responding (Table 1). However, the duration of response as measured from the start of treatment is 4–7 months in most studies (Table 2). Cumulative data from two studies show that for patients who relapse within 6 months of completing their previous therapy 29% respond, whereas for those who relapse at an interval of greater than 6 months the response rate is 42%.[44,45] There are very few data on the activity of single-agent paclitaxel in previously untreated patients with epithelial ovarian cancer. A single-arm study from Sweden and a randomised study from the GOG in which one arm uses single-agent paclitaxel remain unreported. A preliminary analysis from a third study by the LGOG suggests that the response rate to paclitaxel is perhaps slightly lower than might be expected: 32% in the first 28 patients analysed.[46] This result is interesting because if paclitaxel/platinum-based combinations prove to be the most effective treatment for epithelial ovarian cancer then it is possible that there is synergy between these two drugs. Only one study of paclitaxel-based chemotherapy as first-line treatment in epithelial ovarian cancer has been reported, and this report is only a preliminary analysis. The study was performed by the Gynaecology Oncology Group in suboptimally debulked patients who were randomised to receive a combination of paclitaxel 135 mg/m^2 over 24 h plus cisplatin 75 mg/m^2 or cyclophosphamide 750 mg/m^2 plus cisplatin 75 mg/m^2. A statistically significant survival advantage for the paclitaxel combination was reported, median survival 37.5 months against 24.4 months (p = 0.001).[4] It seems that paclitaxel can be given at a dose of 225–250 mg/m^2 without haemopoetic growth factor support but that beyond this figure haemopoetic growth factors are necessary. At 300 mg/m^2 15% of patients develop ≥ grade 3 peripheral neuropathy and 17% have significant myalgia/arthralgia.[47]

Thirty-four European and Canadian centres[48] reported their experience in treating 407 patients randomised in a bifactorial design to receive either 175 mg/m^2 or 135 mg/m^2 of paclitaxel over either 24 h or 3 h. Response was slightly higher at the 175 mg/m^2 dose (20%) than at 135 mg/m^2 (15%), but this was not statistically significant (p = 0.2). The authors reported a modest increase in progression-free survival at the 175 mg/m^2 dose (19 weeks vs 14 weeks: p = 0.02).

Dose escalation studies of paclitaxel combined with other agents are underway. One study of paclitaxel given at 200 mg/m^2 and cisplatin at 75 mg/m^2 suggests that neuropathy may well be a problem. Several studies have investigated the combination of paclitaxel and carboplatin and it appears that granulocyte-colony stimulating factor (G-CSF) is not required for combinations of paclitaxel 135 mg/m^2 and carboplatin given at AUC 6,[49] but if carboplatin is given at AUC 9, then G-CSF is required.[50] One study has been able to deliver paclitaxel 175 mg/m^2 and carboplatin AUC 6 with only 14% of patients developing > grade 3 myelosuppression, while another suggests that the maximum tolerated dose without G-CSF is a combination of paclitaxel 135 mg/m^2 and carboplatin AUC 7.5.[51] Many of these investigators are finding that far from pacli-

taxel having an additive myelosuppressive effect on carboplatin, it may afford a level of protection against carboplatin-induced thrombocytopenia. Following on from their investigations into sequencing of high-dose chemotherapy in ovarian cancer, the Memorial Sloan-Kettering Cancer Center group[52] have added paclitaxel to cyclophosphamide with G-CSF prior to high-dose carboplatin and peripheral blood stem cell (PBSC) rescue. The dose-limiting toxicity of paclitaxel combined with G-CSF was neuropathy not myelotoxicity at 300 mg/m^2.[53] Furthermore this group has utilised G-CSF support in a Phase I dose-escalation study assessing the activity of a combination of paclitaxel, cisplatin and cyclophosphamide.[54]

High-dose chemotherapy with bone marrow/ peripheral stem cell support.

Hematopoietic growth factors accelerate haematological recovery after standard-dose chemotherapy and may allow an increase in the total dose and dose intensity of chemotherapeutic agents when the dose-limiting toxicity is haematological.[65] They can also be used to mobilise PBSCs, which may be harvested and reinfused to facilitate haematological recovery after high-dose myeloablative chemotherapy.

Early trials assessing the feasability of delivering high doses of chemotherapy followed by haematological rescue with ABMT in patients with solid tumours included patients with relapsed or refractory epithelial ovarian cancer. Investigators have utilised myeloablative drugs and not always agents with known efficacy in epithelial ovarian cancer[67] (Tables 3–5). The wide variety of regimens used and the heterogeneous patient populations studied mean it is difficult to draw meaningful comparisons and conclusions. Overall response rates of > 60% are reported in mixed patient populations that include patients with relapsed and refractory disease, but at the cost of significant morbidity. Dauplat and colleagues reported on 14 patients who underwent tumour debulking followed by cisplatin-based chemotherapy. At second-look surgery there was microscopic disease in five patients and macroscopic disease in nine. Subsequently these patients were treated with melphalan 140 mg/m^2 followed by autologous bone marrow transplantation (ABMT). Five patients (37.5%) were reported to be disease-free and four alive with disease at 30–60 months.[69] In another study, 11 patients with persistent disease after first-line chemotherapy were treated with cyclophosphamide 7.0 g/m^2 and etoposide 0.9–1.0 g/m^2 followed by ABMT. Six complete remissions were reported in eight patients with residual disease ≤ 2 cm at the start of high-dose chemotherapy; none of the three patients with macroscopic disease > 2 cm responded. Viens and colleagues have used high-dose melphalan and ABMT as consolidation for patients who had responded to cisplatin-based chemotherapy as assessed by second-look surgery. Updated results[66,74] have reported a 69% overall response rate; however the authors comment that the responses were of short duration (median duration 6 months). These results appear to be equivalent to those obtained with standard therapeutic strategies.

Encouraged by the initial high response rates in relapsed and refractory disease and the potential for amelioration of the haematological toxicities of high-dose chemotherapy with colony-stimulating factors and PBSC, there is evidence to support investigation of consolidation therapy for patients with favourable characteristics such as microscopic disease after primary surgery and disease sensitive to platinum-based chemotherapy. Murakami and colleagues[91] reported their results from 42 patients, with stage I_c–IV epithelial ovarian cancer, after primary cytoreductive surgery treated with high-dose CAP (cisplatin 100–150 mg/m^2, doxorubicin 80–100 mg/m^2, cyclophosphamide 1600–2400 mg/m^2) followed by ABMT. They have reported a large difference between the results obtained in patients with good as opposed to bad prognostic features; a 78% 5-year disease-free survival for 23 patients with no residual disease after surgery and a 26% 5-year disease-free survival in 19 patients with macroscopic residual disease.

More recently, there has been a move to deliver high-dose chemotherapy with reduced intervals between treatments, based on kinetic modelling.[102] Two groups have reported, in abstract form, high response rates, 87% and 81% respectively,[92,93] in chemotherapy-naive patients treated with dose-intensive high-dose platinum-based regimens supported with PBSC rescue.

Trials of dose intensification utilising recombinant human growth factors: granulocyte macrophage-colony stimulating factor and interleukin-3

Dose escalation studies of carboplatin with or without cyclophosphamide have met with mixed success in reducing nadir thrombocytopenia or plate-

Table 3. High-dose chemotherapy and ABMT/PBSC/CSF support in relapsed/refractory epithelial ovarian cancer

Ref.	No. evaluable pts	Regimen	CR (*n*)	PR (*n*)	ORR (%)	Median response duration (mo)
		ABMT				
67	2	Cyclo/Etop	1		50	12+, 16+
68	2	Cyclo/Etop	1		50	10+, 10+
69	14	Mel	ND	ND	ND	ND
70	11	Cyclo/Etop	6		80	15
71	5	Cyclo/MTZ or Mel	2	2	66	3, 9, 9, 13
72	1	Cyclo/TBI	1		100	19+
73	11	Carbo	1	5	55	ND
74	35	Mel	ND	ND	ND	8–54
75	3	Ifos/Carbo/Etop	2		66	ND
76	6	Cyclo/MTZ/Carbo	4	1	83	ND
77	11	Mel				
78	31	Mel (18); Cyclo/Carbo (13)	ND	ND	ND	ND
79	16	VM-26/Ifos/Carbo	2	7	56	ND
80	8	Cyclo/Etop/Carbo				
81	8	Carbo/Ifos	5	2	88	6
82	32	Cyclo/Cis(ip)/Thio	ND	ND	> 60	
83	6	MTZ/Cyclo/Carbo	5	1	100	7–30+
		PBSC				
84	6	Carbo/GM-CSF/PBSC	3	1	66	7.5, 8, 11
		GM-CSF				
85	8	Ifos/Etop		4	50	ND
86	34	Carbo	2	11	38	ND

BCNU = Carmustine, Bus = busulphan, Carbo = carboplatin, Cis = cisplatin, Cyclo = cyclophosphamide, Doxo = doxorubicin, Etop = etoposide, Ifos = ifosfamide, Mel = melphalan, MTZ = mitozantrone, RT = radiotherapy, TBI = total body irradiation, Thio = thiotepa. CR = complete response, PR = partial response, ORR = overall response rate, mo = months, ip = intraperitoneal.

Table 4. High-dose chemotherapy and ABMT/PBSC/CSF support in mixed patient groups with advanced epithelial ovarian cancer

Ref.	No. evaluable pts	Regimen	CR (*n*)	PR (*n*)	ORR (%)	Median response duration (mo)
		ABMT				
87	7	Cyclo/Thio (14) Cyclo/Thio/Carbo (8)	3	1	57	8.5
88	17	Mel (10) Mel/Cyclo (14) Cyclo/Etop/Carbo (3) Mel/Etop/Carbo (3) Bus/Mel (1)	5	4	52	Consolidation 27 (2–41)
89	34	Cyclo/RT (17) +Mel/RT (3) +Carbo (14) Cyclo/Mel/Carbo (3)	ND	ND	ND	ND

BCNU = Carmustine, Bus = busulphan, Carbo = carboplatin, Cis = cisplatin, Cyclo = cyclophosphamide, Doxo = doxorubicin, Etop = etoposide, Ifos = ifosfamide, Mel = melphalan, MTZ = mitozantrone, RT = radiotherapy, TBI = total body irradiation, Thio = thiotepa. CR = complete response, PR = partial response, ORR = overall response rate, mo = months, ip = intraperitoneal.

Table 5. High-dose chemotherapy and ABMT/PBSC/CSF support in first-line chemotherapy for epithelial ovarian cancer

Ref.	No. evaluable pts	Regimen	CR (*n*)	PR (*n*)	ORR (%)	Median response duration (mo)
		ABMT				
90	1	BCNU/Ifos/Carbo/VP-16	ND	ND	ND	ND
91	42	Cyclo/Doxo/Cis				
	23	(no residual)	ND	ND	ND	77.7% 5 yr DFS
	19	(macro residual)	ND	ND	ND	26.3% 5 yr DFS
		PBSC				
92	15	Cyclo/G-CSF, then Carbo/PBSC	2	11	87	ND
		ABMT & PBSC				
93	11	Cis/Cyclo, then Cis/Etop/Carbo	6	3	81	ND
94	4	Cis/Etop/Carbo	ND	ND	ND	ND
		GM-CSF				
95	22	Carbo/GM-CSF ± Cyclo	ND	ND	ND	ND
96	19	Carbo/Cyclo/GM-CSF, then ip Cis/STS	ND	ND	ND	ND
97	5	Cyclo/GM-CSF, then Carbo/Cyclo/GM-CSF/PBSC	3		60	4, 1, 7
98	18	Ifos/Carbo/GM-CSF	7	4	61	ND
99	8	Cis/Cyclo/GM-CSF	6		75	ND
		G-CSF				
100	21	Carbo/Cyclo/G-CSF	4	9	52	ND
101	21	Carbo/G-CSF				

BCNU = Carmustine, Bus = busulphan, Carbo = carboplatin, Cis = cisplatin, Cyclo = cyclophosphamide, Doxo = doxorubicin, Etop = etoposide, Ifos = ifosfamide, Mel = melphalan, MTZ = mitozantrone, RT = radiotherapy, TBI = total body irradiation, Thio = thiotepa. CR = complete response, PR = partial response, ORR = overall response rate, DFS = disease-free survival. mo = months, ip = intraperitoneal.

let transfusions in clinical trials.[103–105] Calvert and colleagues administered escalating doses of carboplatin, AUC 5–9, every 2 weeks to 21 patients with stage I_c–IV epithelial ovarian cancer with additional G-CSF support.[101] The dose-limiting toxicity was thrombocytopenia at AUC 9. At the time of reporting 18 of the 21 patients had had an objective response. Reed and colleagues were able to deliver carboplatin 800 mg/m^2 every 5 weeks with granulocyte macrophage-colony stimulating factor (GM-CSF), commencing 72 h after the carboplatin, continuing for 7 days after reaching the leukocyte nadir, in escalating doses of 3–10 μg/kg/day in 27 patients with refractory ovarian cancer. They were able to demonstrate a reduction in episodes of febrile neutropenia compared with historical controls.[76] Further dose escalation is possible by rescheduling of GM-CSF[106] but more effective amelioration of thrombocytopenia is achieved by utilising PBSC with GM-CSF.[87,107]

Edmonson and colleagues treated 36 patients with advanced cancer with cyclophosphamide 1.0 g/m^2 and escalating doses of carboplatin 225–700 mg/m^2 followed by GM-CSF at 10 μg/kg every 12 h subcutaneously. The authors report prevention of first-cycle thrombocytopenia up to a carboplatin dose level of 700 mg/m^2. Five patients were reported as suffering atrial fibrillation whilst receiving GM-CSF.[106] Shea and colleagues attempted to deliver carboplatin 1200 mg/m^2 with GM-CSF 10 μg/kg/d every 4 weeks in 18 patients with advanced solid tumours. Severe neutropenia and thrombocytopenia complicated the first 20 courses and subsequently PBSCs were added, leading to a significant reduction in neutropenia, thrombocytopenia and platelet transfusions. Eleven of 16 assessable patients responded.[107]

Interleukin-3 (IL-3) promotes proliferation, survival and differentiation of multipotential stem and progenitor cells of haematological cell lines,[108] and

as such a more pronounced effect on thrombopoiesis may be expected. The activity of IL-3 in megakaryopoiesis has included patients with ovarian cancer. Seventeen patients with recurrent platinum-sensitive ovarian cancer were treated with escalating doses of IL-3 in one of two cycles of carboplatin 350 mg/m^2 given every 28 days. Increasing the dosage of IL-3 did not affect neutrophil or platelet nadir counts.[109] Fifteen patients with recurrent ovarian cancer were treated with carboplatin 800 mg/m^2 and IL-3 5 μg/kg/d subcutaneously from the second cycle onwards. IL-3 reduced the period of thrombocytopenia and neutropenia and reduced the need for platelet transfusions. Ten of the 14 patients were reported to have responded to carboplatin.[105]

Growth factors have also been studied in chemotherapy-naive patients with advanced epithelial ovarian cancer. In a double-blind placebo-controlled GM-CSF dose-finding study de Vries and colleagues treated 15 patients with stage III–IV disease with carboplatin 300 mg/m^2, cyclophosphamide 750 mg/m^2 and GM-CSF every 4 weeks for six cycles. GM-CSF significantly reduced the incidence of neutropenia and raised platelet counts on days 15 and 22.[104] Twenty chemotherapy-naive patients with epithelial ovarian cancer were treated with carboplatin 300 mg/m^2 and cyclophosphamide 600 mg/m^2 every 4 weeks for six cycles, with escalating doses of IL-3 after cycles 1, 3 and 5.[110] The authors reported a significant reduction in delay of chemotherapy due to insufficient bone marrow recovery. Speyer and colleagues[111] utilised escalating doses of IL-3 in 18 untreated patients in combination with cyclophosphamide 600 mg/m^2 and carboplatin 400 mg/m^2 given every 4 weeks for six cycles. IL-3 administered after chemotherapy reduced platelet and neutrophil nadir counts. Seventeen patients with newly diagnosed stage I_c–IV epithelial ovarian cancer were treated with carboplatin 300 mg/m^2 and cyclophosphamide 750 mg/m^2 plus rIL-3, with planned dose escalation of the carboplatin if no postponement of the first three cycles of chemotherapy had occurred. A dose of 5 μg/kg/d permitted the delivery of this combination in 62% of cycles given every 3 weeks and a significant reduction in platelet nadir counts was reported.[112]

Bartsch and colleagues treated 21 patients with ovarian cancer with carboplatin 300 mg/m^2, epirubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2. After cycle 1 escalating doses of IL-3 alone or with GM-CSF were added. There was no evidence for improved marrow recovery for the two agents compared with either agent alone amongst 15 evaluable patients.[113] Other growth factors of interest include PIXY, stem cell factor and IL-6. The latter has been reported to be constitutively produced by ovarian epithelial cells, to stimulate production of bone marrow cells, and has been associated with cisplatin resistance by ovarian carcinoma cells.[114,115]

Novel approaches to therapy for ovarian cancer include targeting IL-6 antioligosense nucleotides to abrogate growth.[116]

Conclusion

Retrospective studies have highlighted a potential dose–response curve for platinum agents. However, randomised trials have not conclusively proved a survival advantage for dose-intensive platinum-based regimens. There are not enough data on dose-intensifying other drugs commonly used to treat epithelial ovarian cancer to assess their impact on survival. High-dose chemotherapy regimens result in high response rates, but at the cost of significant morbidity and mortality, and there are no randomised studies to allow any assessment of the impact of this approach on survival. The inclusion of ABMT, PBSC and recombinant human growth factors have ameliorated some of the haematological toxicities of dose-intensive regimens, but other dose-limiting toxicities emerge with further dose escalation. There appears to be little or no place for high-dose chemotherapy as salvage treatment for refractory disease, although it could have a role in patients who relapse after a long treatment-free interval, i.e. with potentially chemosensitive disease. Most importantly this approach could have a role as consolidation therapy following response to first-line treatment.

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