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Original Paper

Cisplatin (P), Vinblastine (V) and Bleomycin (B) Combination Chemotherapy in Recurrent or Advanced Granulosa(-Theca) Cell Tumours of the Ovary. An EORTC Gynaecological Cancer Cooperative Group Study

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The aim of this study was to investigate the clinical activity and toxicity of a modified PVB regimen (cisplatin, vinblastine and bleomycin) in patients with advanced or recurrent, pure granulosa cell tumours (GCTs) or mixed granulosa-theca cell tumours (GTCTs). The PVB regimen consisted of cisplatin (P) 20 mg/m^2 intravenous (i.v.) days 1–5, vinblastine (V) 0.15 mg/kg i.v. days 1–2 and bleomycin (B) 30 mg i.v. on day 2, and 15 mg on day 15, for 28 days. 38 eligible patients were entered in this trial. Prior to PVB all patients underwent surgery and 13 received postoperative radio- or other prior chemotherapy. The median number of PVB cycles was 4 in both groups. In the group of 25 patients who had received prior surgery only, 7 and 6 patients had complete and partial responses, respectively (response rate: 52%, 95% confidence limits: 31.3–72.2%). At a median follow-up of 39 months, 6 patients were alive with no evidence of disease, 6 were alive with disease, 12 died due to malignant disease and 1 died due to intercurrent disease. The median time to progression was 13.9 months. The median survival was 25.4 months. 3-year survival was 49% (95% confidence limits: 29–69%). In the group of 13 patients who had previously received postoperative radio- or chemotherapy, 5 complete and 5 partial responses were observed on PVB (response rate: 77%, 95% confidence limit: 46.2–95.0%). At a median follow-up of 50 months, 6 patients were still alive, only 1 without evidence of disease, 6 died due to malignant disease and 1 died due to intercurrent disease. The median time to progression was 19.3 months. The median duration of survival was 41.1 months. Accompanying toxicity was distributed in a similar pattern for both groups. Severe toxicity was mainly documented as haematological toxicity, nausea/vomiting and alopecia. Furthermore cisplatin-related peripheral neurotoxicity and mild/moderate signs of bleomycin-related pulmonary toxicity were observed. The present data confirm the therapeutic activity of the PVB regimen in advanced/recurrent GCTs. The response rate was moderately high compared with previous studies, with a median duration of response of 20 months for both groups. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: granulosa cell tumour, ovarian cancer, phase II trial, chemotherapy, cisplatin, vinblastine, bleomycin
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INTRODUCTION

GRANULOSA- AND theca-cell tumours are rare functional sex cord-stromal ovarian tumours. As a group they comprise only 2–3% of all ovarian malignancies. Pure thecomas are regarded as benign tumours but pure or mixed granulosa cell tumours (GCTs) should all be regarded as potentially malignant, although recurrence and metastasis may be slow [1–4]. In their review of 305 patients with granulosa- and theca-cell tumours, Björkholm and Pettersson [4] reported that none of the thecoma patients died but that 21% of those with GCT died from their disease.

The majority of GCTs present as FIGO stage I as the hormonal symptoms make an early diagnosis possible [2, 3]. When surgically treated the 5-year survival rate for stage I is 90%, but patients with advanced disease have a 5-year survival ranging from 0 to 22% [4–6].

In the majority of cases, the initial form of therapy is surgery [5]. The selection of patients for any postoperative treatment is controversial [7]. In patients with advanced disease, postoperative chemo-, or hormono- or radiotherapy should be considered. In those patients with recurrent or metastatic disease, therapy has not yet been standardised [5, 7].

Over the past decade, platinum-based combination chemotherapy has emerged as the most widely used postoperative treatment in GCTs. Although a number of responses have been reported in small series or case reports, the highest identified response rates were obtained with the PVB regimen (cisplatin, vinblastine and bleomycin), but toxicity was significant [7].

The European Organization for Research and Treatment of Cancer (EORTC) Gynaecological Cancer Co-operative Group initiated a prospective clinical trial to investigate the clinical activity of a modified PVB regimen and its additional toxicity in patients with poor prognosis GCTs. Adjustment of the regimen was achieved by reducing the cumulative doses of vinblastine and bleomycin per cycle and increasing the interval between successive cycles by a week compared with the original reported PVB [8, 9]. The early results have been published in abstract form [10].

PATIENTS AND METHODS

38 patients with advanced or recurrent GCT of the ovary were entered into a prospective clinical trial conducted by the Gynaecological Cancer Co-operative Group of the European Organization for Research and Treatment of Cancer (EORTC/GCCG). All patients were treated with PVB combination chemotherapy. The dosage and schedule of administration of chemotherapy consisted of: cisplatin (P), 20 mg/m^2 on days 1–5 by intravenous (i.v.) infusion over a 3-h period with (pre)hydration with normal saline; vinblastine (V), 0.15 mg/kg i.v. push on days 1 and 2, but prior irradiated patients were administered a reduced dose of vinblastine: 0.10 mg/kg i.v. push on days 1 and 2; bleomycin (B), 30 mg on day 2 by continuous i.v. infusion and 15 mg by i.v. push or intramuscular on day 15. This regimen was repeated at 28-day intervals. In the absence of disease progression, the desired minimum of 4 cycles was administered.

Before each course of chemotherapy, patients underwent a complete blood count and chemical survey. Nadir counts were performed during and between the administration of successive chemotherapy cycles. Pulmonary function and renal function were monitored closely by chest X-ray, pulmonary function test (vital capacity (VC) and forced expiratory volume in the first second (FEV_1)), creatinine clearance and urinalysis before every cycle. Computed tomography (CT) scanning and ultrasound were used to measure indicator lesions before the first and third cycles and after the last cycle. Bone scan and audiogram were performed before starting PVB treatment and repeated if indicated. After chemotherapy patients were followed up every 3 months.

Inclusion criteria were histologically confirmed GCT of the ovary, either advanced (FIGO stage III/IV) or recurrent. Radical surgery was not possible and radiotherapy was not appropriate. All patients were informed of the treatment and the involved risks and gave their formal consent according to the local custom. Patients were considered clinically assessable for response if they had a tumour mass detectable by physical examination, CT-scanning or ultrasound before the PVB chemotherapy had started. Selected indicator lesions should be measurable or evaluable. Treatment response was assessed according to World Health Organisation (WHO) criteria [11]. In case of clinical response, surgical evaluation after the fourth cycle was recommended. Early death or early toxic death was defined as a death occurring within the first 8 weeks due to tumour progression or drug toxicity.

RESULTS

From December 1984 to June 1991, 53 patients were registered in the trial. Follow-up was not sufficient in 4 patients. 10 other patients were considered ineligible, 4 with incorrect histological diagnosis (adenocarcinoma 1, lymphoma 1, small cell carcinoma of the ovary 2) and 6 with ineligible staging (FIGO stage IIb 3, no measurable lesions 3). One eligible patient did not receive any treatment. During the premedication for cisplatin she suffered a pulmonary embolism and consequently chemotherapy was not administered. The patient died 10 days after registration; no autopsy was performed.

The present analyses are based on 38 eligible patients who started the protocol treatment (Table 1). Prior to PVB all patients underwent at least one surgical procedure and 13 received postoperative radio- or chemotherapy.

*Group 1—no prior post operative radio- or chemotherapy (*n = *25)*

In the first group, consisting of 25 patients who had received prior surgery only, the WHO performance status was 0 for 17, I for 6 and II for 2 patients. Age varied between 19 and 68 years with a median of 51 years. Histology types (according to the WHO criteria) included pure GCTs in 23 patients and mixed GTCTs in 2 patients. The median number of PVB cycles was 4 and 18 patients received the required minimum of 4 courses. Of these patients, 6 received additional cycles of chemotherapy: patient 22 received 5 complete cycles of PVB and was surgically evaluated as having progressive disease. She underwent tumour debulking and continued with 4 cycles of doxorubicin/cyclophosphamide resulting in a clinically complete response; the other 5 patients received additional chemotherapy cycles 3–12 months after cessation of PVB treatment: patient 10 underwent debulking surgery and was subsequently treated with 4 cycles of cisplatin/cyclophosphamide but disease progressed; patient 5 received 6 courses of cisplatin/bleomycin/VP16 and had a clinically complete response, but shortly after disease relapsed and she was subsequently treated with chlorambucil/prednisone; patient 6 underwent laparotomy followed by 3

Table 1. *Clinical data and outcome of* 38 *patients with advanced/recurrent granulosa cell tumours treated with PVB*

Patient No.	Age (years)	FIGO stage	Prior radio- or chemotherapy	Number of cycles	Response	Duration of response (months)	Status + survival from the start of PVB (months)
1.	31	R		8	CR	66	AWED 99 +
2.	47	R (GTCT)		4	PR	11	AWED 38 +
3.		R		4	PD		DOD 18
4.	62	R		6	PR	19	AWED 39 +
5.	68	R		4	CR	14	DOD 27
6.	60	R		4	PR	16	DOD 59
7.	68	R (GTCT)		3	SD		AWED 24 +
8.	42	R		5	PR	4	DOD 10
9.	32	III		4	CR	81	AWNED 81 +
10.	37	III		4	SD		DOD 12
11.	58	R		2	Early death*		Died 2
12.	67	R		3	PD		DOD 3
13.	19	IV		2	PD		AWED 2 +
14.	61	III		3	PD		DOD 5
15.		R		1	ID		DOD 10
16.	21	IV		3	PD		DOD 4
17.	50	R		5	CR	70	AWNED 70 +
18.	19	R		4	CR	16	AWED 38 +
19.	38	R		4	CR	55	AWNED 55 +
20.		IIIa		4	PR	7	DOD 7
21.	52	R		5	CR	74	AWNED 74 +
22.	59	R		5	PD		AWNED 69 +
23.	58	R		4	SD		DOD 13
24.	27	IV		4	SD		DOD 11
25.	66	R		5	PR	24	AWNED 24 +
26.	54	R	VAC	4	CR	19	AWED 74 +
27.	52	R	RT	4	PR	13	DOD 16
28.	64	R	RT	4	PR	32	DOD 34
29.	62	R	RT	4	PR	12	DOD 78
30.	44	R	RT	4	SD		AWED 41 +
31.	62	R	RT	1	ID		DOD 33
32.	68	R	RT	4	PR	22	DOD 40
33.	74	R	RT	2	Early death†		Died 1
34.	65	R	RT	4	CR	13	AWED 18 +
35.	66	R	RT + i.p. C	4	PR	31	AWED 63 +
36.	44	R	RT	4	CR	30	AWED 55 +
37.	54	R	RT	6	CR	43	AWNED 43 +
38.	56	R (GTCT)	RT + C	4	CR	12	DOD 17

*Intra-abdominal haemorrhage. †Cardiovascular accident. AWED, alive with evidence of disease; AWNED, alive with no evidence of disease; i.p., intraperitoneal; C, cyclophosphamide; CR, complete response; DOD, died of disease; GTCT, granulosa-theca cell tumour; ID, insufficient data; PD, progressive disease; PR, partial response; R, recurrence; RT, radiotherapy; SD, stable disease; VAC, vincristine/actinomycin/cyclophosphamide.

courses of etoposide/ifosfamide/cisplatin and the remaining 2 patients (4 and 7) received chemotherapy consisting of carboplatin/etoposide. After chemotherapy another 3 patients (1, 2 and 25) underwent debulking surgery.

Side-effects due to the PVB regimen were documented using WHO toxicity criteria (Table 2). A total of 21 patients had at least one type of grade III or IV chemotherapy toxicity. Severe toxicity was mainly observed as general chemotherapy-related side-effects such as haematological toxicity, nausea/vomiting and alopecia. During PVB treatment leucopenia and/or anaemia were reported in all patients, 33% of which had additional thrombocytopenia. Grade III or IV haematological toxicity was reported in 17 patients. According to the protocol the doses of cisplatin and vinblastine were reduced, treatment was delayed in 6 patients and 5 patients received blood transfusions. The median leucocyte count nadir was 1.6×10^9/l (range 0.2–5.2), the platelet count nadir was 160 $\times 10^9$/l (range 50–366) and the nadir haemoglobin was 5.2 mmol/l (range: 2.8–6.6).

14 patients experienced infections with different grades of myelosuppression (leucopenia and/or thrombocytopenia). In 2 patients a grade III infection was documented. Patient 7 suffered from an *E. coli* sepsis during the first PVB cycle, white blood cell count (WBC) ranged from 0.3 to 9.2×10^9/l. Cisplatin was not administered on days 4 and 5 because of accompanying severe cardiac insufficiency despite mannitol, furosemide and digoxine. Consequently the full dose of cisplatin was administered on the first day of the following 2 PVB cycles and the dose of vinblastine was reduced by 33% because of a nadir platelet count less than 50%. The patient went off-study due to excessive toxicity having a clinical stable disease and she received carboplatin and etoposide combination chemotherapy 1 year later. The other patient (pt 19) suffered from transient renal impairment due to acute

Table 2. Side-effects due to treatment (worst value of WHO grade)

Side-effect $n = 38$	0	1	2	3	4	Unknown	Group 1 ($n = 25$) Grade 3/4	Group 2 ($n = 13$) Grade 3/4
Nausea/vomiting	1	8	14	15	0	0	36%	46%
Diarrhoea	22	10	4	2	0	0	4%	8%
Mucositis	29	6	3	0	0	0	0	0
Liver	32	2	0	0	0	4	0	0
Haemorrhage	38	0	0	0	0	0	0	0
Pulmonary	33	3	2	0	0	0	0	0
Neutropenic fever	23	6	9	0	0	0	0	0
Allergy	36	1	0	1	0	0	4%	0
Hair	7	2	15	13	0	0	32%	38%
Infection	24	5	7	2	0	0	8%	0
Neurotoxicity, stage of consciousness	35	1	1	0	1	0	0	8%
Neurotoxicity, peripheral	17	14	5	1	1	0	4%	8%
White blood cell count	3	3	7	21	4	1	60%	77%
Platelet count	24	5	8	1	0	1	0	8%
Haemoglobin	2	14	11	5	4	2	28%	15%

pyelonephritis during the second cycle. After treatment the creatinine clearance increased from 50 to 80 ml/min and serum creatinine decreased from 538 to 102 μmol/l. Thereafter the dose of cisplatin was reduced by 25% for the remaining 2 cycles.

Cisplatin-related peripheral neurotoxicity was mild/moderate in 15 patients, but severe in 1 patient. This patient (pt 4) gradually developed grade III sensory polyneuropathy during the last cycle. No cisplatin-related nephrotoxicity was reported. Only grade I/II signs of bleomycin-related pulmonary toxicity were been detected in 3 patients. Bleomycin was stopped due to mild respiratory insufficiency and interstitial pulmonary abnormalities observed on X-ray.

Pre- and post-treatment evaluations were assessed clinically using CT or ultrasound, and surgically in 15, 3, and 7 patients, respectively. The response rate (CR + PR) was 13/25 (52%, 95% confidence limits: 31.3–72.2%), 7 patients had complete and 6 partial responses, 4 patients had stable disease, 6 developed progressive disease during PVB treatment; 1 died early and 1 went off-study after 1 cycle. The median duration of response was 20.1 months (Figure 1).

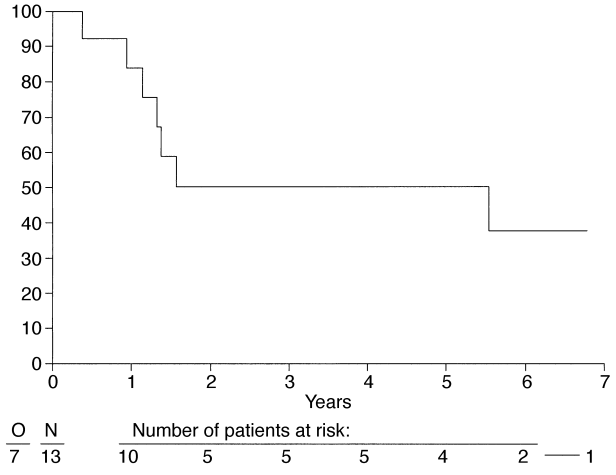

Figure 1. Duration of response for partial response (PR) + complete response (CR) from group 1. O, number of observed events; N, number of patents at risk.

When last traced, 12 patients were still alive (median follow-up: 39 months), 6 with no evidence of disease and 6 with disease. Of the 13 patients who died, 12 died due to malignant disease and 1 died due to intercurrent disease shortly after starting PVB treatment. The patient, a 58-year-old (pt 11), received 2 PVB cycles but accompanying morbidity required an adaptation of the PVB regimen. The patient was not given bleomycin during the first cycle because of the development of a paralytic ileus and consequently in the second cycle the dose of vinblastine was reduced. Fifty days after starting treatment she died of massive intra-abdominal haemorrhage having a normal platelet count (ranging from 185 to 366×10^9/l). Anticoagulants, prescribed because of thrombosis in the Hickman line, were thought to be the iatrogenic cause of death.

The median time to progression of these 25 patients was 13.9 months (Figure 2a). The median duration of survival was 25.4 months (Figure 2b). The 1- and 3-year survival and their 95% confidence intervals were 67% (48–86%) and 49% (29–69%), respectively.

*Group 2—received previous postoperative radio- or chemotherapy (*n = *13)*

In the second group, consisting of 13 patients who had received postoperative radio- and/or chemotherapy, the WHO performance status was 0 for 3, I for 9 and II for 1 patients. The median age was 62 years (range: 44–74 years). 12 patients had pure GCTs and 1 had a mixed GTCT. The median number of PVB cycles was 4 and 11 patients were administered the required minimum of 4 courses.

Side-effects due to the PVB regimen were documented using WHO toxicity criteria. All patients had at least one type of grade III or IV chemotherapy toxicity. Severe toxicity was again mainly observed as general chemotherapy-related side-effects but 1 patient suffered from severe neurotoxicity. This patient (pt 31) developed neurological problems 10 days after starting the first cycle of PVB. She suffered from severe cisplatin-related peripheral neurotoxicity and she had cerebral dysfunction (motoric aphasia, hemiparesis right, coma) caused by a cardiovascular event in the left hemisphere which was illustrated on CT-scan. The platelet count was normal ranging from 108 to 338 $\times$ 10^9/l. During PVB treatment,

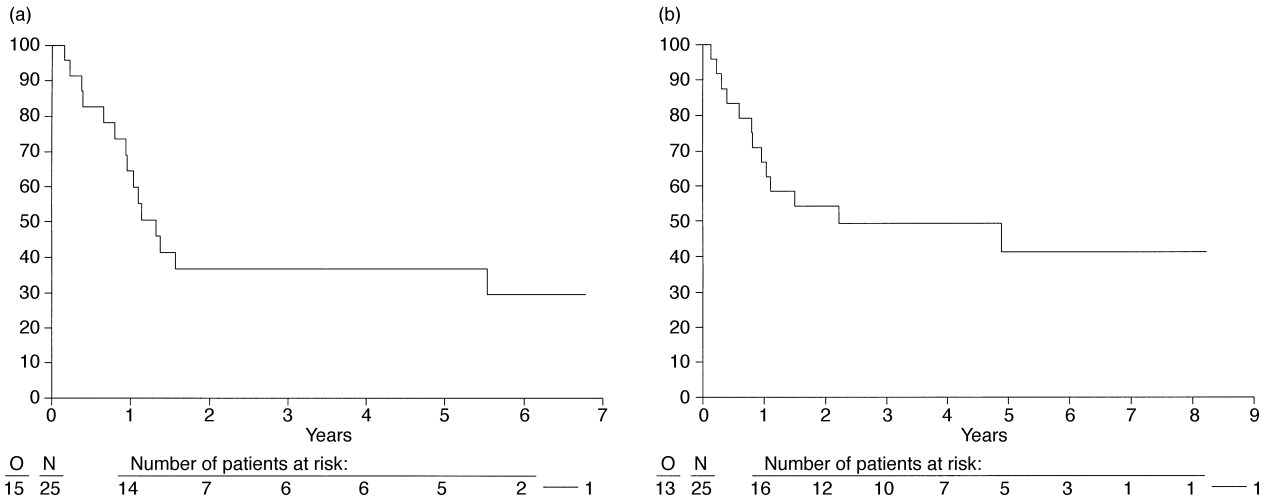

Figure 2. (a) Time to progression, (b) Overall survival for group 1. O, number of observed events; N, number of patients at risk.

leucopenia and/or anaemia were reported in almost all patients and half had additional thrombocytopenia. Grade III or IV myelotoxicity was reported in 10 patients. The median leucocyte count nadir was 1.2×10^9/l (range 1.0–2.2), the platelet count nadir was 108×10^9/l (range 26–190) and the nadir haemoglobin was 5.7 mmol/l (range: 3.5–7.5). No cisplatin-related nephrotoxicity and only mild/moderate signs of bleomycin-related pulmonary toxicity were reported in 2 patients.

All pre- and post-treatment evaluations were clinically assessed using CT. The response rate (CR + PR) was 10/13 (77%, 95% confidence limit: 46.2–95.0%), 5 patients had complete and 5 had partial responses, 1 patient had stable disease during PVB treatment; 1 died early and 1 went off-study after 1 cycle.

The median duration of response was 20 months. When last traced, 6 patients were still alive (median follow-up: 50 months, range: ≥18–74), 1 with no evidence of disease and 5 with disease. Of the 7 patients who died, 6 died due to malignant disease and 1 died due to another cause shortly after starting PVB treatment. The patient, a 74-year-old (pt 33), received 2 PVB cycles with a reduced dose of bleomycin for the second cycle. She suffered from accompanying side-effects: grade III nausea/vomiting and diarrhoea grade II and was administered calcium, magnesium and loperamide. Her condition deteriorated rapidly and she died due to a cerebrovascular event 39 days after starting treatment. Autopsy was refused.

The median time to progression of these 13 patients was 19.3 months. The median duration of survival was 41.1 months.

DISCUSSION

The literature concerning the use of postoperative chemotherapy in advanced or recurrent GCTs consists mainly of some small series of case reports. Initially objective responses were reported with alkylating agents [12–16]. Thereafter reports appeared on the use of doxorubicin [17], doxorubicin/bleomycin [18] and actinomycin/5-fluorouracil/cyclophosphamide [16, 19]. These and other available reports suggested that GCTs were indeed responsive to single-agent and combination chemotherapy but the duration of response was usually only a few months [17].

In recent years, combination chemotherapy including cisplatin has proven to be more effective [7–9, 15, 20–27] In a medline search of published trials between 1966 and 1998, 6

Table 3. Cisplatin (P) containing combination chemotherapy in advanced/recurrent GCT

Author [ref.]	Chemotherapy	Number of patients	Complete response	Partial response	Response rate (%)
Jacobs [20]	PA	2	—	2	
Schulman [21]	PAC	1	—	1	
Camlibel [22]	PAC	1	1	—	
Kaye [23]	PAC	2	—	2	
Gershenson [24]	PAC	8	3	2	63
Muntz [25]	PAC	1	1	—	
Pectasides [26]	PAC	10	5	1	60
Neville [15]	PAVcC	1	—	—	
Chiara [27]	PA, PAC, BEP	9	5	1	66
Gershenson [7]	BEP	5	1	3	80
Columbo [8]	PVB	11	6	3	82
Zambetti [9]	PVB	7	3	1	57
Current trial	PVB	25	7	6	52

A, doxorubicin; B, bleomycin; C, cyclophosphamide; E, etoposide; P, cisplatin; V, vinblastine; Vc, vincristine.

phase II trials and 6 case reports [7–9, 15, 20–27] testing the activity of various cisplatin-based chemotherapeutic regimens in patients with advanced/recurrent GCTs were identified (Table 3). The combinations included cisplatin/doxorubicin (PA) [20], cisplatin/doxorubicin/cyclophosphamide (PAC) [21–26], cisplatin/doxorubicin/vincristine/cyclophosphamide (PAVcC) [13], cisplatin/etoposide/bleomycin (PEB) [7, 27] and cisplatin/vinblastine/bleomycin (PVB) [8, 9]. The number of patients entered into the phase II trials varied from 5 to 11 and the response rates ranged from 57 to 82%. However, the small number of cases did not permit an adequate evaluation and further investigation on a larger number of cases was necessary. In patients with poor prognosis GCT, combination chemotherapy consisting of PVB has the highest identified response rates [5].

Colombo and colleagues [8] first reported the use of the PVB regimen. 11 predominantly untreated women with recurrent and/or metastatic GCT were administered 2–6 PVB cycles with a median of 4 cycles. Six pathologically documented complete responses and an additional 3 partial responses were obtained for a response rate of 82%. Of the 9 therapeutic responders, 6 remained disease-free at a median follow-up of 20 months (range: 6–36 months). However, it should be noted that all complete responses were obtained in patients with small residual disease. One patient developed progressive disease and subsequently died. 2 others died due to leucopenia-related sepsis after the second cycle of PVB and due to intercurrent respiratory distress after 5 cycles.

Later another group from Milan [9] treated 7 patients with advanced/recurrent GCTs with the PVB combination chemotherapy. The median number of PVB cycles was 5 (range: 1–8). Their results showed 3 complete responses and a single partial response with a response rate of 57%. Of the 4 therapeutic responders 3 remain without evidence of disease at a median follow-up of 19.7 months (range: 7–26 months). The remaining patient relapsed at 15 months and consequently died 9 months later. Signs of peripheral neurotoxicity were documented in 3 patients and 1 patient died of leucopenia-related sepsis after the first course of treatment.

Although the previous two studies reported high response rates to the use of PVB in GCTs, iatrogenic toxicity was severe even inducing 3 toxic deaths. Therefore, it was decided to adjust the regimen by reducing the cumulative doses of vinblastine and bleomycin and by using a 28-day regimen. The latter could have influenced the response rate since the literature concerning the use of PVB in GCTs recommends a 21-day regimen [28–30].

This study of 25 women with advanced or recurrent GCTs of the ovary with no prior therapy except surgery showed a response rate of 52% (95% confidence limits: 31.3–72.2%). Though the population size was too small to define response rates precisely, this finding corroborates the two previous reports. Durable remissions after PVB occurred in only 5 patients at a median of 70 months (range $\geq$ 24-81 months). Accompanying toxicity from our modified schedule was significant, particularly bone marrow and neurotoxicity, but there was no toxic death documented.

An additional 13 patients in our study had received prior radio- and/or chemotherapy. In this subgroup we observed a higher response rate which is in contrast with the literature stating that prior irradiation is associated with decreased response to chemotherapy. However, it should be noted that all patients had recurrences and not all indicator lesions were previously irradiated. Therefore it is impossible to draw any conclusion concerning response rate in this heterogeneous group. Due to the small number of patients, the confidence intervals are very wide for response rate in both groups and overlap. Severe toxicity from the PVB regimen was equally divided over the subcategories in both groups but seemed slightly worse in the previously irradiated or chemotherapy-treated patients.

In conclusion, the present data confirm the therapeutic activity of our modified PVB regimen in GCTs. Although the reported median survival of postoperative PVB-treated patients appears to be superior to that of patients treated with surgery alone, this has not been confirmed in a randomised setting. The optimal postoperative therapy for patients with advanced or recurrent GCTs is still unknown. Cisplatin-based chemotherapy is effective for patients with GCTs and superior to previous regimens. To date we would recommend the use of BEP or EP instead of PVB because of its lower toxicity [29, 30].

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