Br. J. Cancer (1990), **62**, 257–262

'JEB' – a carboplatin based regimen for malignant germ cell tumours in children

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Summary Between February 1986 and July 1988 a total of 21 children aged 1 to 16 years with malignant germ cell tumours (MGCT), 18 with either metastatic disease or unresectable primary tumour, received the JEB regimen – carboplatin dosage calculated from the EDTA glomerular filtration rate (approximately 600 mg m^{-2}), etoposide 120 mg m^{-2} daily × 3, and bleomycin 15 mg m^{-2} weekly. Primary sites were: testis (6), ovary (8), sacrococcyx (4), pineal gland (2) and vagina (1). AFP levels were elevated in 19, β-HCG in 8. Complete marker response was achieved in 19 out of 19 evaluable patients and complete remission of measurable tumour in 16 out of 19, 12 with chemotherapy alone and 4 with the addition of surgery. A reduction in glomerular filtration rate greater than 10% occurred in 3 of 12 evaluable patients; in none greater than 20%. Sequential audiography was normal in 11 out of 12 evaluated. The regimen was myelosuppressive with WHO grade III or IV myelosuppression occurring in 12 patients.

Three patients have relapsed; one with a pineal germinoma who relapsed in the abdomen six months after diagnosis, and two with sacrococcygeal teratomas and lung metastases. Two of these remain in second complete remission after further treatment. There was one death from probable bleomycin pulmonary toxicity. We conclude that this regimen is simple to administer and, apart from myelosuppression, it is well tolerated. It appears to have comparable efficacy to cisplatin-based regimens but with much less nephrotoxicity and ototoxicity and avoids the use of alkylating agents and anthracyclines.

Dramatic improvement in cure rates of adults with malignant germ cell tumours using cisplatin-based regimens have been mirrored in paediatric practice (Einhorn & Donohue, 1977; Peckham *et al.*, 1983; Williams *et al.*, 1987; Pinkerton *et al.*, 1986; Mann *et al.*, 1987). With short-duration chemotherapy, non-mutilating surgery and avoidance of radiotherapy or alkylating agents, the majority of children, including many with metastatic MGCT, can be cured. With such a favourable outcome emphasis is now placed on avoiding immediate and delayed toxicity. The PVB (cisplatin, vinblastine, bleomycin) or BEP (bleomycin, etoposide, cisplatin) regimens, without alkylating agents, probably avoid sterility and reduce second malignancy risks but are accompanied by significant renal and auditory toxicity. Even with careful hydration, mannitol and monitoring of glomerular filtration rate (GFR) by ^{51}Cr-EDTA clearance, the majority of children will have a significant fall in GFR. Though hearing loss affects only high frequencies in most cases, it is still of clinical significance (Brock *et al.*, 1988). Although long-term studies are few (Brock *et al.*, 1988; Koliouskas *et al.*, 1985), there is little evidence that either renal function or hearing loss shows meaningful improvement with time.

Substitution for cisplatin by a less toxic analogue such as carboplatin has been shown to be effective in ovarian cancer (Calvert *et al.*, 1982; Wiltshaw *et al.*, 1985) and this drug has clear activity in adult Phase II studies with MGCT (Horwich *et al.*, 1988). There is, however, little or no evidence that significant non-cross resistance exists in cisplatin-resistant tumours and its use in the JEB regimen is primarily to avoid toxicity. In this regimen, carboplatin is given at a dose based on renal function calculated from the Calvert formula (Calvert *et al.*, 1989). This is predicted to produce an area under the drug concentration curve (AUC) which may lead to significant but manageable myelosuppression but possibly maximum therapeutic effect. Early studies in adults show clearly that inferior results are achieved with carboplatin unless the dose is pushed to myelosuppressive levels (Horwich *et al.*, 1989).

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Received 29 January 1990; and in revised form 22 March 1990.

Etoposide and bleomycin are used as in the standard BEP regimen (Peckham *et al.*, 1983). There is some controversy about the necessity of weekly rather than 3-weekly bleomycin. In this study, if it was possible to monitor lung function, children were given this drug weekly. Infants, whose lung function could not be tested, received bleomycin 3-weekly after the first two cycles of chemotherapy.

Patients and methods

Twenty-one children aged 1 to 16 years (median 11 years) received the JEB regimen. Nineteen were previously untreated and two had received single courses of PVB and BEP chemotherapy respectively. Clinical details are shown in Table I. Serum markers (α-fetoprotein and β-HCG) were estimated in all patients by immunoassay. Staging investigations included PA and lateral chest X-ray, CT chest scan, isotope bone scan and abdominal ultrasound or CT scan. Lymphography was not performed.

Indications for chemotherapy were the presence of metastatic disease in lung (6), lymph nodes (6), or peritoneum (1); bulky, unresectable primary tumour (5), peritoneal spill at surgery (3), or an intracranial primary (2). The testis was the primary site in 6 patients, ovary in 8 and sacrococcygeal area in 4. A one-year-old infant with a large vaginal tumour was treated electively with chemotherapy alone to avoid mutilating surgery. One boy with a pineal germinoma received JEB after complete resection and before irradiation. A second patient with a pineal tumour had undergone surgery but developed rapidly progressive disease within a month of this. α-FP was elevated in 19 patients, β-HCG in 8. In no patient was both α-FP and β-HCG normal. The chemotherapy is outlined in Figure 1. Bleomycin (15 mg m^{-2}) was given weekly as a slow intravenous infusion. Etoposide (120 mg m^{-2}) was administered daily × 3 as a 1 to 3 hour infusion and carboplatin infused over one hour. The formula for calculating the dose of carboplatin was based on the uncorrected ^{51}Cr-EDTA clearance. In four children the GFR was not measured before treatment and doses based on surface area were given (400–500 mg m^{-2}). In four the carboplatin dose was given according to surface area despite the

GFR being known, and in three patients an AUC of less than 5 mg ml^{-1} min^{-1} was electively chosen by the physician. Tumour response was reassessed after 2 and 4 courses and CR documented using markers and imaging with X-ray or CT scan. Patients were given a minimum of four courses of JEB with additional cycles dependent on initial bulk of disease and the time to CR. Usually, chemotherapy was continued for 2 courses beyond CR.

Table I Clinical characteristics of patients

Patient	*Age at diagnosis (years)*	*Pathology[a] & serum markers*	*Sites of disease*
1	1	Yolk sac α-FP 4000	Relapse in abdominal nodes 3/12 after testis primary resected
2	11	Mixed yolk sac & mature α-FP 3000	Ovary (resected with rupture)
3	11	Germinoma α-FP 43	Pineal mass; complete macroscopic resection
4	15	Yolk sac α-FP 38	Testis, (resected) Para-aortic nodes
5	2	Yolk sac α-FP 8855	Sacrococcyx Lung
6	13	Dysgerminoma β-HCG 99	Ovary (resected with rupture). Para-aortic nodes.
7	15	Immature & choriocarcinoma α-FP 115 β-HCG 438	Testis, (resected) Lung and para-aortic nodes
8	13	Yolk sac choriocarcinoma α-FP 7000 β-HCG 113000	Ovary Lung
9	16	Yolk sac & mature α-FP 1340	Ovary (resected) Masses R. ovary & peritoneum
10	11	Yolk sac & mature α-FP 45	Testis, para-aortic nodes
11	1	Yolk sac α-FP 545	Vagina
12	16	Yolk sac α-FP 155 β-HCG 592	Testis (resected) Bilateral lung 2°
13	(birth)	No Biopsy α-FP 23820	Lung 2° 13/12 after removal of 'benign' sacrococcygeal teratoma
14	9	Yolk sac α-FP 2015 β-HCG 1455	Ovary resected with rupture
15	2 ½	No Biopsy α-FP 103000	Sacrococcyx Lung 2°
16	14	Immature α-FP 7300	Ovary
17	12 ½	Dysgerminoma β-HCG 490	Ovary
18	16	Immature α-FP 25 β-HCG 13	Testis, (resected) Para-aortic nodes
19	8	No Biopsy α-FP 1500 (CSF 2400)	Pineal
20	17½	Yolk sac α-FP 291000	Ovary
21	2	Yolk sac α-FP 66000 β-HCG 105	Sacrococcyx

[a]Dehner classification (Dehner, 1986).

Day:	1	2	3	9	12
JM8[a] (Carboplatin)	↓				
Bleomycin 15 mg m^{-2} I.V.		↓		↓	↓
Etoposide 120 mg m^{-2} I.V.	↓	↓	↓		

[a]Dose mg = ([EDTA uncorrected × 1.2] + 20) × AUC (6).

Figure 1 Outline of JEB chemotherapy. Each course was repeated at 21-day intervals provided the neutrophil count $>1.0 \times 10^9 l^{-1}$ and platelets $>100 \times 10^9 l^{-1}$.

Monitoring Toxicity

Estimates of plasma urea and creatinine have been shown to be inaccurate indicators of renal impairment in children receiving cisplatin (Womer *et al.*, 1985). ^{51}Cr-EDTA GFR was therefore estimated before treatment and repeated during treatment in most patients. Formal audiometry was done during and following treatment in patients old enough to co-operate. The hearing was graded according to a scale devised specifically to quantify cisplatin-related ototoxicity in children (Brock *et al.*, 1988). In patients who could co-operate, spirometric respiratory function tests and CO diffusion tests were performed at intervals during and following treatment.

Results

Tumour response and outcome

The total number of courses given ranged from 4 to 6 (median 4). Marker CR was achieved in all patients after between two and four courses of chemotherapy. The estimated serum α-FP t½ ranged from 3 to 12 days (median 7 days) and of β-HCG from 3 to 15 days (median 4) (Table III). One boy with a pineal germinoma (case No 3), who had no measurable disease following initial surgery, developed progressive abdominal disease with multiple peritoneal seedlings, probably related to a ventriculo-peritoneal shunt. Despite cranio-spinal irradiation and introduction of an intensive cisplatin-containing regimen he failed to respond. Patient 5 with a sacrococcygeal primary and lung metastases, achieved rapid CR but tumour recurred at the primary site 4 months after completion of treatment. Coccyxectomy had not initially been performed electively because of radiological CR at primary and metastatic sites. Patient 16 developed recurrent lung metastases 6 months after having achieved CR.

With chemotherapy alone complete remission of disease on X-ray or CT scan occurred in 12 of 18 evaluable patients; residual primary disease was completely resected in 4 cases; 2 showed active tumour and 2 mature teratoma (Table IV). 'Second look' surgery was performed in 6 patients with no imageable disease and confirmed clinical CR in each.

Minor residual abnormalities were seen on CT scan in three patients but secondary surgery was not performed. These abnormalities were in the abdomen in two cases and in the lung in a third child. All abnormal CT images subsequently resolved and the patients remain free from disease. One patient (number 10), developed progressive peritoneal disease on CT scan during chemotherapy despite normalization of α-FP levels. At laparotomy, the tumour was resected and shown to consist entirely of differentiated teratoma. No further treatment was given and she remains free from disease 15 months from diagnosis.

Hearing was not evaluated in 7 patients because of their young age. In one of 12 patients, adequately evaluated, there was evidence of high tone hearing loss during treatment (20 dB loss at 4 KHz), but this returned to normal 3 months later. ^{51}Cr-EDTA clearance declined >10% from the original value in 3 of 12 patients adequately studied; 12, 15 and 20% respectively. (See Table II).

Table II Number of JEB courses, toxicity and estimated AUC of carboplatin

No.	Number of courses given	Carboplatin AUC (mg ml^{-1} min)	^{51}Cr EDTA clearance (ml min^{-1} 1.73 m^{-2}) (JEB course) 1	2	3	4	5	6	Haematological toxicity (WHO grade)
1	4	5	112	.	90	117	109	.	Gd 4 neut & tcp
2	5	5	103	114	.	113	.	116	Gd 3 neut; Gd 2 tcp
3	4	5	99	.	106	147	.	.	None
4	4 (+ BEP × 1)	3 (400 mg m^2)*	132	.	.	.	169	.	Not documented
5	5	4.5	135	.	.	107	.	163	Gd 4 tcp
6	6	6	107	.	.	124	.	129	Gd 1 tcp Gd 4 neut
7	4	5	140	140	140	.	.	.	Gd 1 tcp Gd 3 neut
8	4	4 (600 mg m^2)*	194	.	219	.	.	.	Not documented
9	5	6	115	.	140	118	.	.	Gd 3 neut Gd 2 tcp
10	4	5	148	130	.	125	.	.	Gd 2 neut Gd 1 tcp
11	4	6	121	124	97	.	97	.	Gd 4 neut & tcp (Gd 4 sepsis)
12	6	4.5	142	.	129	.	125	.	Gd 1 tcp
13	6	(400 mg m^2)	.	.	.	.	.	.	Gd 1 tcp Gd 2 neut
14	6	4 (500 mg m^2)	112	.	.	.	.	.	Gd 4 tcp Gd 3 neut
15	5	(400 mg m^2)	.	.	.	.	.	.	Gd 4 neut (Gd 3 sepsis)
16	4	(500 mg m^2)	.	.	.	.	.	.	Not documented
17	5	6.5 (500 mg m^2)	63	.	.	.	.	.	Gd neut Gd 4 tcp (Gd 4 sepsis)
18	4	4	138	.	.	.	.	.	Gd 3 tcp Gd 4 neut
19	4	(500 mg m^2)	.	.	170	.	.	.	Not documented
20	2	6	112	.	.	.	.	.	Not documented
21	4 (+ BEP × 1)	6	129	.	.	.	.	.	Gd 4 tcp

neut = neutropenia: tcp = thrombocytopenia *( ) = dose given

As expected, haematological toxicity was comparatively severe with over half the patients developing WHO grade III or IV myelosuppression on one or more occasions. Platelet transfusions were required in only two patients but three required parenteral antibiotics for fever during neutropenic periods. Chemotherapy was given on time in most patients with a median interval between courses of 24 days (range 21–45).

Lung function tests were abnormal in two patients. One girl (case No 2) had a pre-existing restrictive defect which persisted but did not worsen. One boy (case No 4) developed radiological evidence of early bleomycin toxicity with co-existing alterations in lung function tests. This was treated with steroids and has resolved. Case No 14, a 16-month-old girl, died with an acute pneumonitis 3 months after receiving 6 courses of JEB. No pathogen was identified and although no autopsy was performed bleomycin appeared to be implicated. She had received weekly bleomycin with each course of JEB.

Discussion

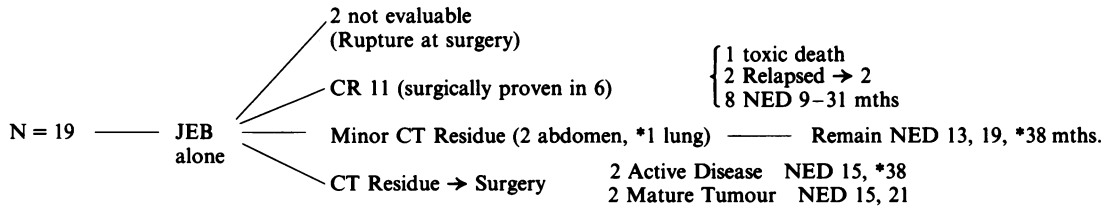
This pilot study demonstrates both the efficacy and the tolerability of substituting carboplatin for cisplatin, combined with etoposide and bleomycin, in paediatric MGCT. In this regimen, a carboplatin AUC of 5–6 mg ml^{-1} min, which in children with normal renal function is equivalent to approximately 600 mg m^{-2}, was recommended. This is somewhat higher than the AUC recommended in adults (4–5) which is predicted to result in moderately severe thrombocytopenia (Calvert *et al.*, 1989). As a single agent, at a dose of 400 mg m^{-2}, carboplatin has produced high response rates in untreated patients with localized seminomatous and non-seminomatous germ cell tumours (NSGCT) (Horwich *et al.*, 1988). In one study using JEB in poor risk NSGCT in adults only 40% achieved CR with chemotherapy and surgery (Motzer *et al.*, 1987). In that study, however, the dose of carboplatin was only 350 mg m^{-2} which would yield an AUC in the range of 2–3 mg ml^{-1} min. With a higher dose of

Table III Clinical and tumour marker response and outcome

No.	*Time to marker remission Half-life*	*Time to clinical response Evaluation of response*	*Outcome*	*Months after diagnosis*
1	CR 2 courses α-FP 6d	CR 4 courses No tumour at surgery	NED	31
2	CR 2 courses α-FP 5d	Non evaluable	NED	33
3	CR 2 courses α-FP 12d	Non evaluable	Died Relapsed in peritoneum (6/12)	9
4	CR 4 courses	Residual lung CT 'abnormalities' PR → CR with surgery 'active tumour'	NED	38
5	CR 3 courses α-FP 6d	CR 5 courses CT scan	Relapsed at primary (4/12) Resected → CR2	17
6	CR 2 courses α-FP 3d	CR 6 courses CT scan	NED	23
7	NE*	Lung CR 3 courses Minimal CT abnormality in abdomen. → CR with surgery 'mature teratoma'	NED	21
8	NE*	PR → CR with surgery 'active tumour'	NED	15
9	CR 3 courses α-FP 8d	NR → CR with surgery 'mature teratoma'	NED	15
10	CR 1 course α-FP 8d	'CR' 4 courses Minimal CT abnormality	NED	13
11	CR 2 courses α-FP 8d	CR 4 courses No tumour at surgery	NED	10
12	CR 2 courses α-FP 8d	'CR' 6 courses Minimal CT abnormality	NED	19
13	CR 2 courses α-FP 8d	CR 1 course CT scan	Died. Bleomcyin lung	5
14	CR 2 courses HCG 4d α-FP 7d	Non evaluable	NED	15
15	CR 5 courses α-FP 10d	CR 3 courses CT scan No tumour at surgery	Lung relapse (6/12) CR 2 after surg. IF, Epi, VCR	17
16	CR 2 courses α-FP 5d	CR 2 courses CT scan	NED	41
17	CR 3 courses HCG 15d	CR 3 courses No tumour at surgery	NED	11
18	CR 1 course α-FP 6d HCG 3d	CR 4 cycles CT scan	NED	9
19	CR 2 courses α-FP 7d	CR 2 courses CT scan	NED	12
20	CR 3 courses α-FP NE	CR 2 courses No tumour at surgery	NED	20
21	CR 4 courses α-FE NE	CR 4 courses No tumour at surgery	NED	11

NED = no evidence of disease. *inadequate data

Table IV Response to chemotherapy in extra-cranial tumours



NED = no evidence of disease

carboplatin and an estimated AUC of over 4 mg ml^{-1} min^{-1}, 39 out of 39 previously untreated metastatic NSGCT patients achieved complete remission (Horwich *et al.*, 1989). Because of concern about compromising antitumour activity an AUC of 5–6 was recommended in this study. Comparatively severe myelosuppression was expected and accepted as a trade-off against reduced renal and auditory toxicity. Formal randomised studies comparing the regimen against PVB or BEP are in progress in adults.

This study confirms that carboplatin is not associated with the ototoxicity seen with the BEP regimen. There was a small decline in GFR in a minority of children but in adults this has been clearly shown to be transient (Hardy *et al.*, 1990).

The role of bleomycin has not been addressed in this study but major reservations have been expressed in the past about weekly administration of this drug. Deaths from respiratory failure have been reported in children receiving PVB (Mann *et al.*, 1987) and although other contributory factors may have been involved, there is some reason for concern. A link between cisplatin nephrotoxicity and bleomycin toxicity has been suggested (Dalgleish *et al.*, 1984). It is of note that one patient in this series developed clear evidence of lung toxicity although renal function remained normal after carboplatin. A small non-randomised study in adults has suggested that a reduced dose of bleomycin adversely affects the efficacy of BEP, but this was only in patients where the etoposide dose was also suboptimal (Brada *et al.*, 1987). By contrast, with full dose etoposide and cisplatin, the results were impressive despite the reduction to 3-weekly bleomycin. Current studies of BEP against EP in small bulk disease show little difference (Levi *et al.*, 1986; Stoter *et al.*, 1987) but the question has not been settled in high-risk patients. Limiting weekly bleomycin to the first two cycles in patients who cannot have lung function tests done is an option, or alternatively, only monthly treatment could be given in all patients. At present, there is a reluctance to omit the drug altogether in children, but once the results of randomised studies in adults are available this may be indicated. With the JEB regimen the response rate is comparable to that in children receiving cisplatin based regimens, with or without the addition of alkylating agents (Pinkerton *et al.*, 1986, Flamant *et al.*, 1984). With extra-cranial primaries a CR rate of 65% with chemotherapy alone, and 84% with chemotherapy plus surgery was achieved. All three patients not achieving CR have had minimal CT abnormalities which have remained unchanged, or resolved.

The role of surgery in gonadal disease is comparatively clear and is a useful way to confirm CR after chemotherapy or to resect any residual active disease. In the case of sacrococcygeal disease the necessity of coccyxectomy after radiological CR has been questioned. This procedure is however justified as an elective measure because of the difficulty in being sure that there is no residual tumour in this complex bony structure. The operation should be safe and without sequelae. In one child in the present series (No 5) disease recurred locally in the coccyx despite apparent CR.

Radiotherapy has little role in paediatric MGCT except in the event of refractory or relapsed disease. It continues to be used in pineal tumours because of reservations about the reliability of drug access to the CNS. It is becoming clear that this concern may be unfounded in some cases (Rustin *et al.*, 1989). There are, however, no reports yet of large series where radiotherapy was not given electively. It is likely that information will be gained from small infants in whom irradiation is omitted owing to concern about late sequelae.

Although there were no patients with very bulky mediastinal primaries or bone marrow or bone metastases, this was a comparatively high risk group and included six children with lung metastases and six with nodal disease. The risk categories devised for adult MGCT cannot readily be applied to paediatric patients. The absolute peak serum α-FP or β-HCG are not of the same significance as in adults provided levels decline within a relatively short half-life. 'Bulk disease' is difficult to define in the small child because the absolute tumour volume may be of more importance than volume in relation to the child's size. In adults, extragonadal tumours, mediastinal tumours in particular, continue to pose a therapeutic problem (Logothetis *et al.*, 1985). This may be a consequence of bulk disease or difficulty achieving complete resection of residual disease. It is of note that prognosis appears better with pure yolk sac histology in this subgroup. It is likely that JEB will not be sufficient for some patients and alternative strategies such as high-dose platinum and etoposide or high-dose intensity regimens such as the BEP/BOP or POMB/ACE may be necessary (Horwich *et al.*, 1989; Newlands *et al.*, 1983). Evaluation of the JEB regimen in unselected MGCT patients on a multicentre basis is currently underway by the United Kingdom Children Cancer Study Group. This study may help to define if there is a high risk group of patients in whom more toxic chemotherapy is justifiable.

J. Pritchard acknowledges financial support from the Imperial Cancer Research Fund and C.R. Pinkerton from the Leukaemia Research Fund and Sterling Oncology. T.J. McElwain is supported by the Cancer Research Campaign and the Medical Research Council. We are grateful to Tereza Gladwell for help with preparation of the manuscript.

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