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UKCCSG'S Germ Cell Tumour (GCT) Studies: Improving Outcome for Children With Malignant Extracranial Non-Gonadal Tumours—Carboplatin, Etoposide, and Bleomycin are Effective and Less Toxic Than Previous Regimens

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Background. We report the efficacy and late effects of carboplatin, etoposide, and bleomycin (JEB) for extracranial non-gonadal tumours (GCII, 1989-95) compared with the 5 previous regimens (GCI, 1979–1988) consisting of 3 vincristine, actinomycin, and cyclophosphamide (VAC) and 2 platinum-based protocols.

Methods and Results. Median follow-up for 52 patients in the GCI study and 46 in GCII was 105 and 48 months, respectively. For GCI, 5- and 10-year actuarial survival was 63% (95% Confidence Interval 50 to 75%) or 72% (57 to 83%) if 6 cases given low-dose VAC were excluded. For GCII, 5-year survival was significantly greater at 95% (83 to 99%), $P = 0.01$. Event-free survival was 46% at 5 years for GCI (33 to 59%) or 52% excluding the low-dose VAC cases (38 to 66%), while forGCII it was 87% (74 to 94%), $P = 0.002$. Five-year event-free survival of 21 children given cisplatin, etoposide, and bleomycin (BEP) in GCI was 57% (37 to 76%) compared with 87% (74 to 94%) for 46 given JEB in GCII, $P = 0.02$. Late effects in 30 evaluable survivors of GCI and 43 of GCII included renal impairment in 6 in GCI and 0 in GCII and deafness in 11 and 4, respectively. Among 17 survivors of sacrococcygeal tumours treated in GCI, 4 have neuropathic bladder/bowel and another shortening of a leg. In GCII, 4 of 26 have neuropathic bladder/bowel with lower limb weakness in one.

Conclusions. We found JEB to be more effective and less toxic than our previous regimens. Some survivors of sacrococcygeal tumours have neurological late effects. Med. Pediatr. Oncol. 30:217–227, 1998.

Key words: non-gonadal malignant germ cell tumours; efficacy of carboplatin, etoposide, and bleomycin; toxicity and late effects

INTRODUCTION

Advances in therapy have led to greatly improved cure rates in children with malignant germ cell tumours (MGCT) treated in the United Kingdom [1–3], the United States [4,5], France [6–8], Germany [9,10], and India [11]. However, significant treatment-related toxicities have been described in some patients, including bleomycin lung (sometimes fatal), infertility, renal impairment, and deafness. In order to improve the quality of life of survivors without, if possible, reducing cure rates, treatment protocols in the United Kingdom have been planned to limit surgical procedures and, by substituting carboplatin for cisplatin [12] and by reducing bleomycin dosage, it was anticipated that renal and oto-toxicity and lung fibrosis might be avoided.

In adults concern has been expressed that carboplatin-based protocols may not be as effective as cisplatin-based ones especially for advanced stage cases [13,14]. A French protocol for children with non-metastatic non-seminomatous MGCT, which utilised a combination incorporating carboplatin, was also reported to be less efficacious than an earlier cisplatin-containing regimen [15].

We have, therefore, compared the survival rates, toxicity, and late effects of the United Kingdom Children's Cancer Study Group's (UKCCSG) previous Germ Cell Tumour Studies (GCI), which employed VAC and cisplatin-based regimens, with those of the current carboplatin-based protocol (the GCII study). In this initial analysis, we report the results in the children believed to be at greatest risk of relapse, that is those with non-gonadal extracranial tumours.

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TABLE I. Staging

Stage	Site of origin of tumour: Uterine, vaginal, prostatic, or sacrococcygeal	Site of origin of tumour: Abdominal, retroperitoneal, thoracic, or other
I	Tumour confined to organ/site of origin	Tumour confined to the site of origin and resectable
II	Tumour spread limited to the pelvis	Local spread
III	Tumour spread limited to the abdomen (excluding liver)	Extensive spread confined to one side of the diaphragm (excluding liver)
IV	Tumour spread to the liver or beyond the abdominal cavity	Tumour spread to the liver, to both sides of the diaphragm, and/or to bones, bone marrow, or brain

TABLE II. Histopathology Classification of Germ Cell Tumours*

Germinoma	(a) Intratubular germ cell neoplasia
	(b) Invasive (dysgerminoma, seminoma)
Teratoma	(a) Mature/benign
	(b) Immature
	(c) Malignant (teratoma plus one or more malignant elements)
Embryonal carcinoma (adult type)	
Endodermal sinus tumour (yolk sac tumour)	
Choriocarcinoma	
Gonadoblastoma	

*Based on Dehner [16].

METHODS

Patients

Children less than 16 years of age with biopsy-proven localised or metastatic non-gonadal, extracranial MGCT treated by members of the UKCCSG were eligible, provided that no prior chemotherapy had been given.

Investigations

Standard investigations undertaken in GCI [1] included appropriate tumour imaging. AFP and HCG were measured before and 5 days after the initial treatment, weekly until normal values were reached, monthly for 2 years, and every 3 months for a further year. In GCII, investigations were similar although bone marrow examinations were done only when there was evidence of blood borne metastatic disease. If possible GFR, measured by chromium EDTA clearance, and audiometry were performed before chemotherapy was commenced.

Staging

The same scheme was used for both studies and is shown in Table I.

Histopathology

A slightly modified version of Dehner's [16] classification was used and is shown in Table II. The original slides were requested from every case and were reviewed by a panel of paediatric histopathologists whose agreed diagnosis was used to classify the tumours. Only the malignant subtypes of germ cell tumour, that is germinoma, malignant and mixed teratomas, yolk sac tumour, and choriocarcinoma, were considered to be eligible. However, two cases of immature teratoma with aggressive behaviour were also included in GCII.

Treatment

All tumours were completely excised if this was possible without major morbidity; otherwise biopsy was performed. Chemotherapy was recommended for all patients although 3 neonates in the GCI study with microscopic yolk sac tumour in otherwise mature sacrococcygeal tumours were treated by surgery alone. In GCI after 6–12 weeks of chemotherapy and in GCII usually after completion of chemotherapy, patients were re-evaluated and surgery to any residual tumour undertaken. Radiotherapy was used only for palliative treatment, if surgery and chemotherapy were ineffective.

Chemotherapy

In GCI, patients were recruited over a 10-year period, 1979–1988. The chemotherapy regimens are shown in Figure 1 and comprised 3 vincristine/actinomycin/cyclophosphamide (VAC)-based regimens: low-dose VAC for 2 years (which was ineffective, all cases treated with this having incomplete response and eventually dying of disease), high-dose VAC or high-dose Adriavac (VAC with doxorubicin) for 1 year, and, subsequently, cisplatin/vinblastine/bleomycin (PVB) or bleomycin/etoposide/cisplatin (BEP) [1]. PVB or BEP were given every 3 weeks if blood counts permitted, otherwise every 4 weeks to produce remission, defined as normal tumour markers and no detectable residual malignant tumour, after which two further courses were administered.

In GCII, patients were recruited from 1989–1995. Carboplatin, etoposide, and bleomycin (JEB) was used, which was based on the previous BEP regimen, but with

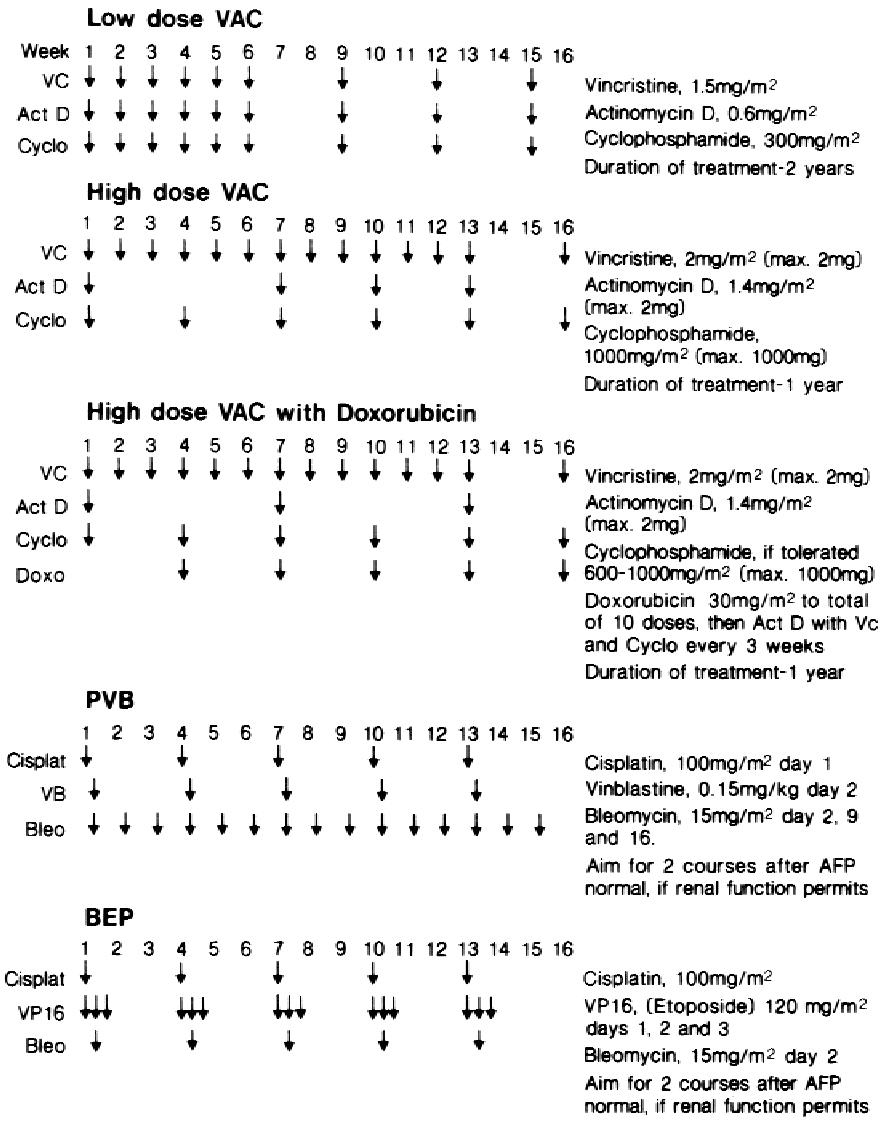


Fig. 1. Chemotherapy regimens used in GCI.

carboplatin substituted for cisplatin with a view to reduce toxicity, particularly nephro- and oto-toxicity. Thus, etoposide 120 mg/m^2 was given IV over 1 hour on each of Days 1–3, carboplatin IV over 1 hour on Day 2 in a dose calculated as 600 mg/m^2 or using the formula 6 × [uncorrected GFR + (15 × surface area)], and bleomycin 15 mg/m^2 was given IV over 15 minutes on Day 3. The formula for carboplatin dose was one under investigation at the Royal Marsden Hospital in 1988 for use in children (A.H. Calvert, personal communication), the target AUC (area under the plasma carboplatin concentration vs. time curve) being 6 mg/ml.min. This formula has subsequently been refined [17], but the original formula was used in this study. Courses were given until remission was achieved, judged by normal AFP/HCG and imaging, followed if possible by two further courses.

Incomplete response or relapse was usually treated in patients who had received an AdriaVAC-based regimen by a platinum-based one, with surgery as appropriate, and vice versa, the exact protocol used for these cases being determined by the treating physician.

Assessment of Chemotherapy and Surgical Toxicity, Late Effects, and Quality of Life

These were assessed from the information supplied by doctors on annual follow-up forms and also from a questionnaire on late effects completed for each surviving patient in 1995–1996. The questionnaire included requests for details of growth and pubertal development and of blood pressure, and any neurological effects of the tumour or treatment, either at presentation or at follow-up, particularly for children with sacrococcygeal tumours. Renal function was evaluated on the basis of serum creatinine, or preferably ^{51}Cr EDTA clearance, and otoxicity by audiometry, the frequency of these tests being determined by the patient's doctor. Chest X-rays

were performed regularly in the early years of follow-up in all patients but formal tests of pulmonary function were seldom undertaken in the absence of respiratory symptoms or abnormal radiology, because of the young age of many of the patients. The numbers with abnormalities reported must, therefore, be considered a minimum estimate. For renal and pulmonary toxicity, WHO grading criteria [18] were used, or for ototoxicity, Brock grading [19]. A review of survival and toxicities in previously reported series was undertaken for comparison with the UKCCSG's results.

Statistical Methods

Overall and event-free survival distributions were estimated by the method of Kaplan and Meier [20]. The log-rank test [21] was used to assess the statistical significance of possible prognostic factors such as site and stage and to compare the GCI and II regimens.

Survival time was defined as the time from diagnosis to death from any cause, censoring surviving patients at the date of last follow-up. Event-free survival was defined as time to first relapse or time to death, censoring other patients at the date of last clinical follow-up. The 95% Confidence limits for probabilities of survival utilised the method of Rothman [22] and are quoted in brackets after each survival statistic. In patients whose initial diagnosis was mature teratoma but who developed yolk sac recurrence, survival and event-free survival were calculated from the date of yolk sac recurrence, with clinical stage defined as that at the time of yolk sac recurrence.

Ethical Approval

Approval was obtained by each institution from the local District Research Ethics Committee to allow participation in these studies.

RESULTS

Clinical Details and Histology

The numbers of children with non-gonadal, extracranial malignant germ cell tumours registered in GCI (1979–1988) and GCII (1989–June 1995) are shown according to site of origin in Table III. One additional patient with a thoracic primary in GCII, in whom there was major protocol violation consisting of weekly administration of bleomycin, was excluded from the survival analyses, but another, who had three courses of JEB and then Adriavac because of myelotoxicity, was retained.

In GCI, there were 5 patients with congenital, apparently mature, teratomas who developed malignant yolk sac tumour recurrence at 8, 12, and 17 months of age (sacrococcygeal cases), 48 months (lip), and 11 months (neck). There were 3 others with congenital sacrococcygeal tumours, which were reported to be mainly mature but contained microscopic yolk sac elements, all of whom were treated by surgery alone and did not develop recurrence. In GCII, there were also 5 patients with congenital, apparently mature, teratomas who developed malignant yolk sac tumour recurrence at 15, 20, 20, 32, and 37 months of age, respectively (all sacrococcygeal). Three of these were diagnosed as a result of serial serum AFP measurement, whereas 2, not monitored in this way, presented clinically.

TABLE III. Malignant Non-Gonadal Germ Cell Tumours

Sites of origin	GCI	GCII
Sacrococcygeal	31	28
Vagina, uterus, prostate	4	3
Thorax	7	8
Other extracranial	10	7
Abdomen/retroperitoneum	7	4
Liver		2
Orbit		1
Bile duct	1	
Neck	1	
Lip	1	
Total	52	46

There were 2 infants who presented after the neonatal period with apparently mature sacrococcygeal teratomas and who later develped yolk sac tumour recurrence: one in GCI whose original tumour, resected at 5 months of age, recurred at 24 months, and one in GCII whose original tumour resected at 6 months, recurred at 37 months. The other patients all had malignant germ cell tumours at the time of initial diagnosis. The histology of the tumours in both the studies is summarised in Table IV and the distribution of patients by clinical stage in Table V.

Survival

Survival analyses were made in November 1996 when the median duration of follow-up for the 52 GCI cases was 105 months (range 50–168) and for the 46 GCII cases was 48 months (range 10 to 82). Five- and ten-year actuarial survival for all cases in GCI was 63% (95% Confidence Interval 50 to 75%) or 72% (57 to 83%) when the 6 cases given the ineffective low-dose VAC regimen were excluded. For cases in GCII, 5-year actuarial survival was 95% (83 to 99%). The greater 5-year survival in the GCII compared with the GCI cases (all sites excluding the 6 low-dose VAC cases) was significant, $P = 0.01$ (Fig. 2A). The 5-year actuarial survival for GCI and GCII cases, respectively, by site was: sacrococcygeal 77% (58 to 89%) and 96% (80 to 99%), $P = 0.12$; vagina/uterus/prostate 100% (40 to 100%) and 100% (29 to 100%), $P = 1.0$; mediastinum/thorax 29% (8 to 64%) and 100% (63 to 100%), $P = 0.03$; and all other sites 78% (45 to 94%) and 83% (44 to 97%), $P = 0.88$.

TABLE IV. Malignant Non-Gonadal Germ Cell Tumours

Histological types	GCI	GCII
Germinoma, invasive	2	0
Teratoma, immature	0	2
Teratoma, malignant (mature/immature teratoma + one or more malignant elements)	14	20
Embryonal carcinoma	0	0
Endodermal (yolk sac)	32	24
Choriocarcinoma	0	0
Not available for review	4	0
Total	52	46

TABLE V. Malignant Non-Gonadal Germ Cell Tumours

Clinical stage	GCI	GCII
I	5	5
II	13	7
III	10	8
IV	24	22
Not recorded	0	4
Total	52	46

Event-free survival for all 52 cases in GCI was 46% at 5 and 10 years (33 to 59%) or, when the 6 low-dose VAC cases were excluded, it was 52% (38 to 66%) while for cases in GCII it was 87% (74 to 94%) at 5 years (Fig. 2B). The difference in EFS between GCI and GCII was significant ($P = 0.002$). The 5-year EFS for GCI and GCII cases, respectively, by site was: sacrococcygeal 54% (35 to 71%) and 93% (77 to 98%), $P = 0.004$; vagina/uterus/prostate 75% (30 to 95%) and 50% (1 to 99%), $P = 0.96$; mediastinum/thorax 29% (8 to 64%) and 88% (53 to 98%), $P = 0.08$; and all other sites 56% (27 to 81%) and 71% (36 to 92%), $P = 0.94$. In neither GCI nor GCII did EFS differ statistically significantly between the largest group with sacrococcygeal primaries and the cases arising in other sites. However, the numbers of cases with tumours in other sites were rather small for such analyses.

The 5-year EFS for GCI and GCII cases, respectively, by stage was: Stage I 80% (38 to 96%) and 100% (16 to 100%), $P = 1.0$; Stage II 41% (19 to 68%) and 86% (49 to 97%), $P = 0.22$; Stage III 50% (22 to 78%) and 100% (3 to 100%), $P = 0.13$; Stage IV 52% (32 to 72%) and 77% (56 to 90%), $P = 0.20$. The differences in EFS between stages were not significant for either GCI or GCII. Stage IV cases in GCII appeared to do worse than cases of Stage I to III, EFS being 77 and 95%, respectively, but this was not statistically significant, $P = 0.99$.

Our attempts to identify a high-risk group of patients using site and stage were hampered by the small numbers in some groups. However, for GCII patients there was a suggestion that patients with non-sacrococcygeal primaries and Stage IV disease might constitute such a group since 4 of these 9 patients relapsed compared with 2 of 33 other patients in whom stage was known, $P = 0.002$.

Event-free survival according to the chemotherapy regimens given is shown for GCI (low-dose VAC 6 cases, high-dose VAC/Adriavac 8 cases, PVB 3 cases, or BEP 21 cases) and for GCII (JEB 46 cases) in Figure 2C. (The 3 cases in GCI treated by surgery alone are not included in the comparisons between the chemotherapy regimens.) The 5-year event-free survival of the 21 children given BEP in GCI (57%, 37 to 76%) is significantly different from that in the 46 children given JEB in GCII (87%, 74 to 94%), $P = 0.02$. The median number of courses given of both BEP and JEB was 6 (range 2 to 7 for BEP and 3 to 8 for JEB). In the JEB-treated patients, the carboplatin dose was calculated on the basis of surface area in approximately two-thirds of the children and by using the formula in the remainder. A more detailed analysis of dose intensity and acute toxicities and outcome in all patients treated in GCII is being prepared (Oakhill et al.).

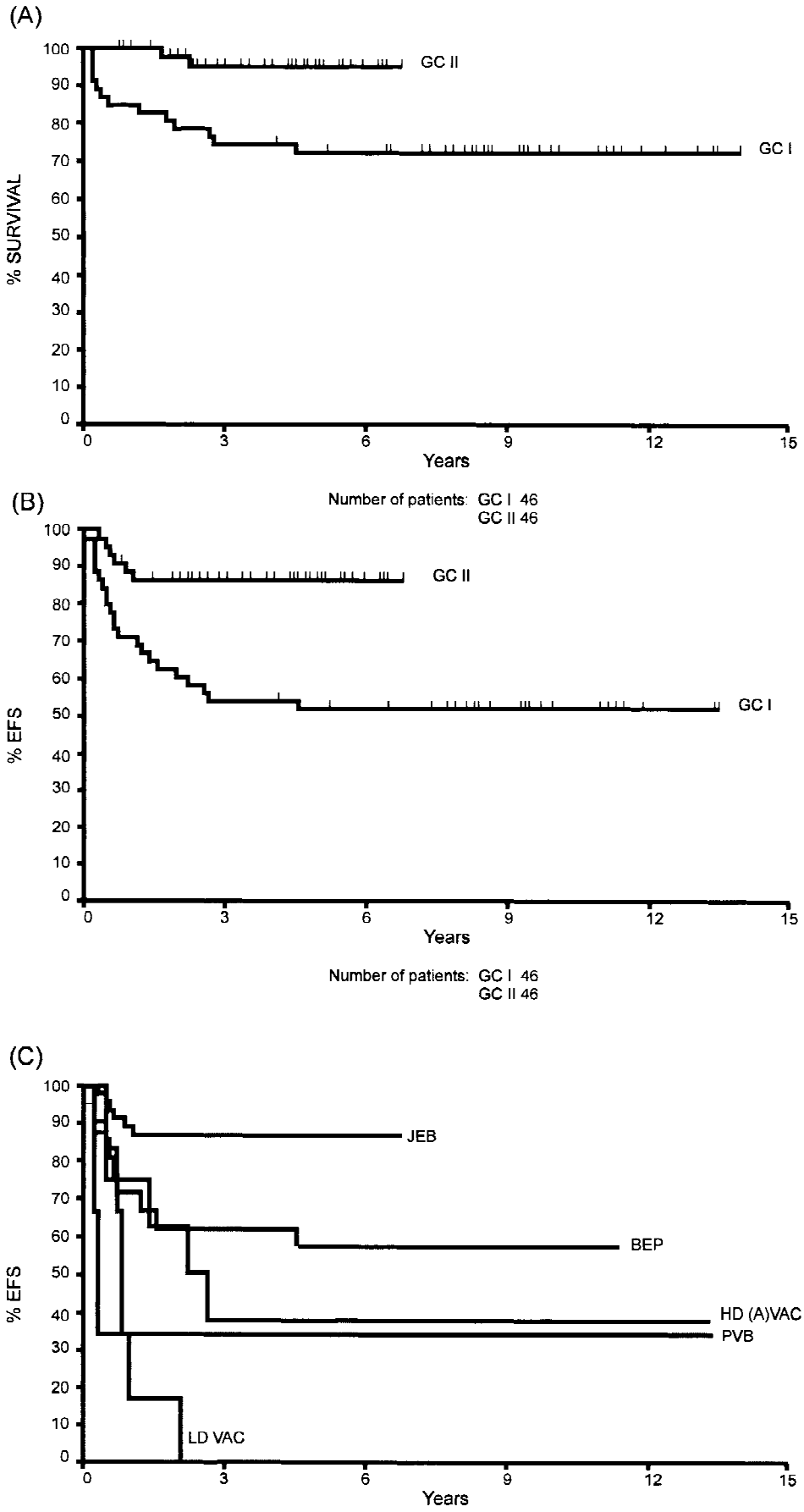
Recurrences and Deaths

In GCI, in which the chemotherapy regimens were generally less effective than in GCII, recurrences were seen in a proportion of cases with tumours in each of the various sites, stages, and histological subgroups. In GCII only 6 ''events'' (recurrence or incomplete response) have been observed and it may be relevant that in one the primary site was unusual (the liver) and in a child with a Stage II sacrococcygeal primary the residual tumour consisted mainly of PNET elements. Five of the 6 patients in GCII with recurrence or incomplete response had Stage IV tumours.

There were two deaths from pulmonary toxicity due to bleomycin in GCI, in a girl given bleomycin weekly in the PVB regimen as per protocol (cumulative bleomycin dose 105 mg/m^2) and in a boy given a modified PVB protocol (cumulative dose 186 mg/m^2). One other child in GCI died of infection following high-dose VAC. All other deaths in both the GCI and GCII cases were due to tumour.

Late Effects

These were evaluable in 30 of the 33 survivors from GCI, 3 having been lost to follow-up 8, 10, and 11 years from diagnosis after moving abroad. Renal impairment attributed to cisplatin therapy was present in 6 children (WHO grades 1 to 3, tubular only in 2 cases) and deafness in 11 (Grades 1–3). Asymptomatic pulmonary changes attributed to bleomycin were present in one survivor. Among the 17 evaluable survivors of sacrococcygeal tumours, 4 have neuropathic bladder and/or bowel and one other child has shortening of a leg. Among these 5 children with neurological late effects, 4 were recorded



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to have neurological problems affecting bladder, bowel, and/or lower limb function at the time of diagnosis of the tumour; one further child with suspected neurological damage at diagnosis has fully recovered from this. Other late effects include a small telangiectatic bladder in a child given AdriaVAC chemotherapy for a thoracic primary, a cosmetic defect following surgery to a teratoma of the neck in another case, and pigmentation due to bleomycin in a third child. Nine children are completely well.

Among the 44 survivors of GCII, 43 are evaluable. Renal impairment has not occurred but four children had Grade 1 to 3 deafness.

All 4 of the children with deafness had normal renal function both before and after chemotherapy. One child whose Grade 1 deafness was recorded after 5 courses of JEB, the carboplatin dose having been calculated using the formula, was found at later follow-up to have normal hearing. Another girl given 7 courses of JEB, the carboplatin dose having been calculated using surface area, has Grade 1 deafness. A third had bilateral middle ear haemorrhages when thrombocytopenic following her third course of JEB, the carboplatin dose having been calculated using surface area, and remains deaf, Grade 3. The fourth had 6 courses of JEB, the carboplatin dose having been calculated by the formula (which gave the same dose as that using surface area), had a questionably slow response to therapy, and was given 2 additional courses of etoposide and cisplatin and could, therefore, be considered to be a protocol deviant. She has Grade 2 deafness. The role of carboplatin in the deafness in these cases is difficult to evaluate, but one has recovered and in two others, other factors might have played a part, i.e., middle ear haemorrhages and 2 doses of cisplatin. In only one case could no other factor be identified.

Among the 26 evaluable survivors of sacrococcygeal tumours, 4 have neuropathic bladder and/or bowel, one of whom also has lower limb weakness. Among these, 3 were recorded to have neurological problems affecting bladder, bowel, and/or lower limb function at the time of diagnosis of the tumour, as did 4 further children who have recovered. The neurological problems were thought to have been caused by the tumour in 7 cases and were diagnosed after surgery in one case. Other problems detected so far in the survivors include pigmentation from bleomycin in one patient, reduced volume of the left hemithorax following treatment of a thoracic tumour in one case, and presumed phrenic and recurrent laryngeal nerve damage following surgery to another patient's thoracic tumour. One child had seizures following treatment of recurrence in the brain.

A comparison of survival and toxicity data in a reported series of children treated for extracranial MGCT is shown in Table VI.

DISCUSSION

Since the mid-1970s there has been major progress in the treatment of adults and children with malignant germ cell tumours, mainly due to better chemotherapy. Previously malignant sacrococcygeal tumours in children were almost always fatal, while metastatic gonadal tumours were treated with limited success with VAC-based regimens. Knowledge gained in adult teratoma patients was applied in paediatric practice but, because of the small numbers of patients available even for nationally organised studies, no randomised comparisons of chemotherapy protocols have been reported. Nevertheless, substantial improvements in cure rates of children with extra-cranial MGCT have been achieved, although with significant toxicity (Table VI). Evaluation of regimens is possible only by comparing published results but in future internationally organised randomised trials should assess protocols, aiming to maintain high cure rates while limiting toxicity.

The UKCCSG's first study, GCI, spanned the period when effective chemotherapy was developed for teratomas in adults and our regimens were changed accordingly, also taking into account the efficacy and toxicity of the new protocols in children [1]. Thus, the initial low-dose VAC regimen was abandoned after 2 years because of poor efficacy, and was replaced by high-dose VAC with or without adriamycin and subsequently by PVB. After 3 deaths from bleomycin-induced pulmonary toxicity, PVB was replaced by BEP and thereafter no treatment-related deaths occurred once bleomycin had been reduced to once per course. Renal impairment and deafness attributed to cisplatin were seen after both PVB and BEP [1] (Table VI). Nevertheless, except in the initial low-dose VAC cases, high cure rates were achieved [1–3] (Table VI). Other late effects included infertility in 5 of 35 survivors of ovarian tumours due to surgery, although one would have been infertile anyway due to XY gonadal dysgenesis [3]. Ejaculatory failure was not anticipated after treatment of testicular primaries, as radiology and AFP monitoring were used for staging, without retroperitoneal node dissection, but boys given VAC-based chemotherapy would be likely to have azoospermia [2,3].

The American Children's Cancer Study Group reported 4-year survival and event-free survival for ovarian non-germinoma MGCT of 67 and 63%, respectively,

Fig. 2. **A:** Survival for 46 cases treated in GCI (the 6 LD VAC cases were excluded) and all 46 cases treated in GCII. **B:** Event-free survival for 46 cases treated in GCII (the 6 LD VAC cases were excluded) and all 46 cases treated in GCII. **C:** Event-free survival according to the chemotherapy regimens given in GCI (low-dose VAC, high-dose VAC/Adriavac, PVB, or BEP) and in GCII (JEB).

TABLE VI. Summary of Reported Series of Extracranial MGCT

Country and reference	Number of patients and dates of studies	Regimens	Survival (%) by site[a]	Principal effects from chemotherapy and number affected
UK [1]	122 1979–1987	Low-dose VAC High-dose VAC Adria VAC, PVB, or BEP Surgery alone in 44 cases 78 given GCI chemotherapy protocols	Excluding 12 low-dose VAC cases: Testis 100% Vagina, uterus, prostate 100% Ovary 88% Thorax 40% Other 67%	Deaths from bleomycin lung 4 Renal impairment from cisplatin 16 Deaf > 6
USA, CCSG [4]	93 (non-germinoma) 1978–1984	CCG-861 Vinblastine, bleomycin, cisplatin, cyclophosphamide, actinomycin, doxorubicin	Ovary (non-germinoma) 67% Non-gonadal 48%	Not described
USA, St. Jude [5]	60 1979–1988	VAC Modified PVB or VAC/PVB, alternating Surgery alone in Stage I testicular and ovarian tumours if markers fell appropriately	Testis 100% Ovary Stage I and II 100% Non-gonadal with VAC/PVB 63%	VAC caused severe cystitis in 6 of 41 patients (5 also had pelvic radiotherapy) Acute reactions to bleomycin in 18/22 patients Metabolic problems from cisplatin 3 Deafness 8/22 given PVB
France [6]	82 (non-seminoma) 1978–1984	Actinomycin, cyclophosphamide, vincristine, bleomycin, doxorubicin, cisplatin Surgery alone in Stage I cases if makers fell appropriately	Gonadal 75% Non-gonadal 75%	Died from bleomycin lung 1 Died from septicaemia 1 Died from cisplatin toxicity 1
France [7]	93 (non-germinoma) 1985–1989	TGM 85 Cyclophosphamide, actinomycin, vinblastine, bleomycin, cisplatin Surgery alone for Stage I if markers fell	Disease-free 74% Gonadal 85% Non-gonadal 54%	Not described
France [8]	67 (non-metastatic non-germinoma) 1985–1989	TGM 85 (see above) Surgery alone for Stage I if markers fell	Disease-free 77% Stage I and II 87% Stage III 39%	Toxic death 1 Transient acute toxicities (septicaemia 3, tubulopathy 1, etc.)
France [15]	42 (non-metastatic non-germinoma) 1990–1994	TGM 90 Cyclophosphamide, actinomycin, vinblastine, bleomycin, carboplatin Surgery alone for Stage I if markers fell	Gonadal and non-gonadal CCR 48%	Not described
Germany [9]	66 (non-testicular) 1983–1988	MAKEI 83/86 PVB, VAC, or PVB and etoposide, ifosfamide, cisplatin	Disease-free 83%	Treatment-related deaths 2 Bleomycin-induced pulmonary fibrosis 3
Germany [10]	186 (non-germinoma) 1989–1993	MAKEI 89 BEP/VIP	Event-free 91%	Bleomycin lung 1 Renal toxicity about 25% of cases (?reversible)
India [11]	56 1988–1993	BEP	Gonadal and non-gonadal 83%	Bleomycin lung 3 (fatal 1) Death from sepsis 1 Death from etoposide-related leukaemia 1
UK	46 non-gonadal extracranial (this series) 1989–1995	GCII Carboplatin, etoposide, bleomycin	Event-free 87%	Deafness 4 (recovered in 1)

[a]Overall survival unless stated otherwise.

while for non-gonadal tumours these were 48 and 42% [4]. Late effects were not discussed. St. Jude's patients with extragonadal tumours responded poorly to VAC, but alternating VAC/PVB yielded 63% survival. A range of complications was seen (Table VI) [5].

French workers reported 75% survival in 82 patients with non-seminomatous GCT of gonadal and extracranial non-gonadal origin [6] but there were three chemotherapy-related deaths. The subsequent SFOP protocol (MGCT 1985–1988) was modified to reduce toxicity and only one therapy-associated death occurred [7,8]. Lower complete and continuous complete remission rates were obtained in their next protocol (TGM90) in which carboplatin 400 mg/m^2 was used instead of cisplatin [15].

In Germany, treatment for non-testicular MGCT was stratified according to histology, site, and stage; children with favourable histology, early stage disease receiving surgery alone, and those with more advanced disease also receiving four courses of PVB or VAC [9]. Most cases of malignant histology (yolk-sac, choriocarcinoma, mixed tumours) had four PVB courses, second look surgery, and then four courses of etoposide, ifosfamide, and cisplatin. Good results were achieved but also significant toxicity. In the subsequent (MAKEI 89) study, vinblastine was replaced by etoposide, total chemotherapy was reduced, and the bleomycin was reduced or omitted (i.e., BEP/VIP therapy) [10] but some toxicity still occurred (Table VI).

Five-year actuarial survival was 83% in 56 Indian children given BEP for extracranial MGCT's but 3 developed bleomycin lung (bleomycin given weekly) and other toxicities were seen (Table VI) [11].

In summary, most recent paediatric series report high cure rates for gonadal MGCT, but, as in adults [23], results have been less satisfactory for non-gonadal tumours, only 42% of adults treated during the cisplatin era for non-gonadal MGCT achieving long-term survival [24]. Significant toxicity has been reported where this has been assessed, attributable mainly to bleomycin and cisplatin. In older series, radiotherapy also led to serious late effects, but this is seldom used in paediatrics now except for intracranial cases. Surgical morbidity has been significant, but can be reduced if limited to biopsy or non-mutilating resection, as recommended in current UKCCSG protocols.

Reduction in bleomycin dosage, as used in the UKCCSG modification of BEP and in our JEB protocol, has been successful in eliminating deaths from pulmonary toxicity. The substitution of carboplatin for cisplatin in the combination has led to no worsening of the results either for non-gonadal cases (this report) or for children we have treated with gonadal primaries (to be reported). Indeed, our preliminary results with JEB are producing significantly higher 5-year event-free survival rates in children with non-gonadal tumours (87%) than we achieved with BEP (57%). The better results in GCII were not due to patients having more favourable clinical features, as the proportions in each clinical site, stage, and histology group were remarkably similarly to those in GCI (Tables II–IV). Nor can the better results of JEB compared with BEP be explained by greater familiarity with platinum compounds, since neither protocol caused treatment-related deaths albeit the numbers treated were small (46 and 21, respectively). The poorer results using carboplatin in the French study were probably related to lower dose (400 mg/m^2, compared with 600 mg/m^2 in the UKCCSG protocol) [15]. In adults with metastatic testicular non-seminomatous GCT, significantly higher failure rates were found in patients given less than, compared with more than, 400 mg/m^2 carboplatin dose per treatment in the CEB (JEB) combination [25]. Moreover, the use of carboplatin in the UKCCSG studies has eliminated the nephrotoxicity and reduced the ototoxicity caused by cisplatin in previous protocols. Absence of significant renal toxicity from conventional doses of carboplatin has been demonstrated in adults [26] and children [27].

Further improvement in chemotherapy is still required for non-gonadal MGCT to enable all patients to be cured. Sadly, dose escalation of cisplatin (from 20 to 40 mg/m^2 per day for 5 days) in a randomised study of adults with poor risk MGCT resulted in excess toxicity and no accompanying therapeutic benefit [28]. Strategies to improve results in children might include dose escalation of carboplatin and/or the use of other agents such as ifosfamide and vinblastine, or ''megatherapy'' with autologous bone marrow or PBSC rescue. However, such treatments would be associated with significant toxicity and perhaps should be considered only for high-risk or unresponsive/chemotherapy-resistant or relapsed cases. Definition of a high-risk group in our JEB-treated cases was difficult because of the small numbers and the high cure rate. The event-free survival of 93% in the largest subgroup, with sacrococcygeal primaries, was not significantly different from that in the other smaller sub-group, and, while 5 of the 6 events in the JEB-treated cases occurred in patients with Stage IV disease, overall 77% of Stage IV cases remained event-free. The non-sacrococcygeal Stage IV cases might be a higher-risk group, but the numbers were small. A strategy utilising JEB for initial therapy, with more toxic regimens reserved for the few patients who fail or relapse, might be preferable to intensification of therapy for all cases.

Previous reports have not detailed the neurological handicaps present in some survivors of sacrococcygeal primaries. The majority appear to be caused by the tumour rather than by surgical procedures and recovery may occur after successful chemotherapy. Earlier diagnosis might reduce the number with neurological damage, and surveillance by clinical examination and serum

AFP monitoring of infants with congenital, apparently mature teratomas is being studied as part of the UKCCSG's current germ cell tumour protocol.

CONCLUSIONS

In infants and children with malignant extracranial non-gonadal germ cell tumours, cure rates have improved progressively in the last 15 years. In this small series, the JEB chemotherapy combination, with carboplatin instead of cisplatin, is producing high cure rates without the long-term renal and pulmonary toxicity and with less ototoxicity than resulted from the previous cisplatin-based regimens. While physicians' skills in using platinum-containing agents will have improved with experience over the period covered by these studies, it is well recognised that carboplatin is less nephro- and ototoxic than cisplatin. The quality of life in some survivors of malignant sacrococcygeal teratomas is impaired by neurological damage to the bladder, bowel, and lower limbs. Future studies should aim to find treatments that will cure the approximately 15% of patients failing to respond adequately to JEB and achieve earlier diagnosis of sacrococcygeal cases in order to prevent neurological handicap.

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Centres that entered patients	
Aberdeen	1
St Bartholomew's, London	2
Belfast	2
Birmingham	9
Bristol	9
Cambridge	1
Cardiff	4
Edinburgh	3
Glasgow	1
Great Ormond Street, London	15
Leeds	7
Leicester	3
Liverpool	8
Manchester	13
Newcastle	4
Nottingham	1
Royal Marsden, London	5
Sheffield	6
Southampton	4
Total	98

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