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Original Research

Results from the UK Children's Cancer and Leukaemia Group study of extracranial germ cell tumours in children and adolescents (GCIII)☆

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Abstract ***Background:*** For extracranial malignant germ cell tumours (MGCTs) in the UK, the GCII study used carboplatin-based chemotherapy (JEb) and demonstrated equivalent survival to cisplatin-containing protocols. GCIII, a single-arm observational study, used new risk stratification, replaced consolidation chemotherapy with a standard number of cycles and introduced surveillance for all stage I MGCTs. Pure teratomas were registered to understand their natural history.

Methods: Patients with MGCTs were stratified to three risk groups – low risk (LR), intermediate risk (IR) and high risk (HR), using stage and prognostic factors. Patients with alpha fetoprotein (AFP) >10,000 kU/L, stage IV disease (except testis <5 years and all germinomas) or stage II-IV mediastinal tumour were classified HR. Stage I tumours (LR) received chemotherapy only if disease progressed. IR and HR patients received 4 and 6 JEB cycles, respectively. Carboplatin dose was calculated using glomerular filtration rate to give an area under the curve of 7.9 ml/m^2.min.

Results: Eighty-six patients with MGCTs were enrolled from 2005 to 2009: 59% female, median age, 5.7 years. Twenty-five patients were LR, 21 IR and 38 HR. Seven LR patients had

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disease progression; all were successfully treated with chemotherapy. Overall survival (OS) for the whole group was 97%; 5-year event-free survival for JEb-treated patients was 92%, and OS, 95%. JEb was well tolerated with no observed significant hearing or renal side-effects. There was no discernible difference in carboplatin dose whether calculated by body surface area or creatinine clearance. Forty-seven patients with teratoma were managed with surgery and one had malignant transformation.

Conclusion: Carboplatin-based chemotherapy as part of a risk-stratified approach leads to excellent survival in paediatric MGCTs, minimising potential burden of long-term effects.

1. Introduction

Extracranial germ cell tumours (GCTs) constitute a heterogeneous group in age, site and pathology that represent 3% of paediatric cancers but rise to 14% to become the second most common malignant tumour group in adolescents [1]. Introduction of the cisplatin-based bleomycin x3, etoposide, cisplatin (BEP) regimen transformed outcomes in adult disseminated testicular tumours [2]. Initial use of BEP for paediatric malignant GCTs (MGCTs) was efficacious [3] but associated with significant cisplatin-related ototoxicity and nephrotoxicity, bleomycin lung fibrosis and etoposide-induced leukaemia [4,5]. Modifications included reducing bleomycin dose in combination with cisplatin (PEb) or substituting bleomycin with ifosfamide (PEI), resulting in excellent 6- to 10-year event-free survival (EFS) of 81–87% for patients with locally advanced or metastatic disease [6,7]. To ameliorate toxicity, the UK Children's Cancer and Leukaemia Group (CCLG) approach has been a carboplatin-based strategy and reduction in bleomycin (JEb) which resulted in equivalent survival in the GCII study (5-year overall survival [OS]: 91%; EFS: 88%) [8]. JEb was administered as an n+2 strategy, i.e., the number of cycles required to achieve remission plus two additional (median: 5 cycles; range: 3–8), whilst patients with analogous risk stratification received only 3–4 cycles of PEb/PEI [6,7].

The aim of this single-arm study was to de-escalate treatment whilst maintaining excellent survival with the use of carboplatin. GCIII applied (1) A watch-and-wait policy for all completely resected MGCTs (low risk [LR]), extending the accepted practice of surveillance for testicular tumours [9]; (2) Risk stratification for those requiring chemotherapy according to prognostic factors found to be significant in GCII and other studies [6–8,10,11] (poor: AFP >10,000 kU/L, mediastinal site; good: testicular < 5 yrs, germinomas); (3) a standard number of JEb cycles to intermediate-risk (IR) and high-risk (HR) groups and (4) dosing of carboplatin by glomerular filtration rate (GFR) rather than body surface area (BSA) to improve effective dose exposure. Pure teratomas were registered to better understand their natural history, and a common surgical and surveillance strategy was adopted.

2. Methods

2.1. Eligibility

Patients younger than 18 years with newly diagnosed histology-proven extracranial MGCTs or mature teratomas (MTs)/immature teratomas (ITs) were eligible. In cases with unequivocally raised AFP/human chorionic gonadotropin (HCG) and risk of biopsy, diagnosis could be made clinically/radiologically. Age-appropriate informed consent/assent was obtained. Research ethics committee approval was obtained.

2.2. Risk stratification

Patients were investigated with AFP/HCG levels, cross-sectional imaging of the primary site, chest x-ray, lung and liver computed tomography (CT) and bone scan. A tumour-node-metastasis–based staging system was used (Table 1). Patients with MGCTs were allocated to one of three risk groups as per Table 2.

2.3. Surgical treatment

Testicular tumours were excised by radical inguinal orchidectomy and high ligation of the spermatic cord. Retroperitoneal lymph node dissection was not recommended.

Oophorectomy was performed for ovarian tumours; any enlarged para-aortic nodes, peritoneal, omental or contralateral ovarian nodules were biopsied, and peritoneal fluid sampled. Biopsy was reserved for unresectable/advanced disease.

Non-secreting extragonadal tumours or neonatal sacrococcygeal tumours (SCTs) had upfront complete surgical resection if possible. Secreting tumours were managed with biopsy and delayed resection.

Table 1
Staging classification.

Stage I	Complete resection of the localised tumour with no clinical, radiographic or histologic evidence of local or distant disease spread. In patients with no initial biopsy or surgery, localised primary tumour < 5 cm with no locoregional or distant spread.
Stage II	Complete resection of the localised tumour with involved regional nodes completely removed. Complete resection of a tumour with locoregional extension and no involvement or complete resection of involved regional nodes. Scrotal biopsy in the case of localised testicular tumours Localised ovarian tumours with capsular breach In patients with no initial biopsy or surgery, localised primary tumour > 5 cm with no locoregional or distant spread.
Stage III	Microscopic or macroscopic residual tumour Ovarian tumours with clinically significant ascites even if negative on cytology Mediastinal tumours with clinically significant pleural effusions Involvement of regional lymph nodes incompletely removed In patients with no initial biopsy or surgery, primary tumour with locoregional spread or clinical or imaging node involvement
Stage IV	Presence of metastatic disease Ovarian tumours with clinically significant pleural effusions

Table 2
Risk group classification of MGCTs.

Low risk	Gonadal stage I tumours (regardless of AFP level if secreting). Testicular tumours completely resected by inadvertent trans-scrotal resection but otherwise stage I included in this group with very close follow-up Extragonadal stage I tumours with normal tumour markers after appropriate half-life decline
Intermediate risk	Testis <5 yrs, any AFP, stage II, III + IV Testis > 5 yrs, AFP <10,000 kU/L, stage II + III All other sites, AFP <10,000 kU/L, stage II + III except thoracic tumours Pure germinoma/seminoma, any site, stage II, III + IV Pure HCG-secreting tumours, any HCG, stage II + III
High risk	All stage IV tumours except testis < 5 yrs and germinoma/seminoma AFP >10,000 kU/L except all stage I tumours and testis < 5 yrs stage II, III + IV All thoracic tumours, stage II, III + IV

AFP level cut-offs in infants adjusted by age.

If feasible, residual masses after chemotherapy were resected. Rare cases where viable tumour remained were discussed with the study committee.

2.4. Chemotherapy

MGCTs received adjuvant chemotherapy according to the risk group. LR patients were placed on surveillance. IR patients received 4 and HR patients 6 courses of JEb chemotherapy as per GCII [8] apart from carboplatin dose which was calculated using the modified Calvert formula [12] to give an area under the curve (AUC) of 7.9 mg/ml.min. Dosing tables were provided to calculate dose directly from ^{51}CrEDTA/^{51}CrDTPA half-life and body weight. If GFR was unavailable, carboplatin was dosed at 600 mg/m^2.

For adolescents with predominantly adult-type histology, e.g., choriocarcinoma (CC) or embryonal carcinoma (EC), cisplatin-based chemotherapy was recommended given reduced evidence of carboplatin efficacy in this group.

2.5. Disease monitoring

AFP/HCG were monitored at diagnosis, weekly until normal and then monthly for year 1, two-monthly for year 2 and three-monthly for year 3. Imaging during chemotherapy was only indicated for non-secreting tumours or for secreting tumours with slow marker decline. All patients were imaged at the end of treatment.

Post-treatment surveillance ultrasound (USS) of the primary site and CXR were performed 3 monthly for 2 years for non-secreting MGCTs.

2.6. Toxicity monitoring

Regular monitoring of renal function (including GFR), routine chemistry, blood counts and hearing were undertaken before, during and at the end of treatment. Bleomycin toxicity was monitored with respiratory history/examination before each cycle. Older children had lung function tests at the start and end of treatment. Follow-up included annual blood pressure measurement. Hearing and renal function monitoring was required if abnormal during or at the end of treatment.

2.7. Teratoma

Surgery was the mainstay of treatment. After resection, AFP was monitored for MGCTs. ITs and incompletely resected MTs were followed up with imaging 3 monthly for 3 years.

2.8. Statistical analysis

Five years of enrolment was planned for each risk group and MT/IT. Each subgroup had a specific design as described in the supplementary materials. EFS and OS as functions of time since study enrolment were estimated by the method of Kaplan and Meier [13]. LR patients with postsurgical recurrence treated with JEb were included in IR survival analysis.

The target total mg dose of carboplatin based on BSA was compared with the total dose based on GFR. The analytic approach is described in the supplementary materials.

Table 3
Clinical, pathological and treatment characteristics of patients with MGCTs and teratomas.

Characteristics	LR (N = 25)			IR (N = 23)			HR (N = 38)			Total MGCTs (N = 86)			Teratomas (N = 47)		
Gender															
Male	21			6			8			35			12		
Female	4			17			30			51			35		
Stage															
1	25			0			0			25			30		
2	0			3			1			4			7		
3	0			17			15			32			10		
4	0			3			22			25			0		
Subtype															
MT	0			0			0			0			25		
IT	0			0			0			0			22		
Germinoma (G)	4			7			1			12			0		
Embryonal Ca (EC)	0			0			1			1			0		
Yolk sac (YS)	14			8			20			42			0		
Mixed MGCT[a]	7			7			16			30			0		
Other MGCT[b]	0			1			0			1			0		
Tumour site															
Testis	21			5			1			27			6		
Ovary	3			14			14			31			20		
Vagina/Uterus	0			2			1			3			0		
Sacrococcygeal	1			0			14			15			11		
Retroperitoneal	0			0			0			0			2		
Mediastinum	0			0			5			5			5		
Other	0			2			3			5			3		
Age (years)															
0–4	15			6			21			42			26		
5–10	1			5			8			14			5		
11–14	2			10			8			20			13		
15+	7			2			1			10			3		
Total courses of JEb															
4	4[c]			21			0			25			3[d]		
5	0			1			1			2			0		
6	0			1			37			38			0		
	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
Age (years)	6.6	2	0–17	8.7	11	0–16	5.8	3.5	0–15	6.8	5	0–17	5.7	3	0–15
Age (months)	83.1	28	1–210	110.9	135	5–198	76	49	11–183	87.4	69	1–210	72.9	40	0–190

GCT, germ cell tumour; LR, low-risk.
[a] Malignant component of mixed MGCTs: YS = 15; YS + G = 1; YS + G + CC = 1; YS + EC = 3; YS + EC + CC = 1; YS + EC + CC + G = 1; EC + G = 1.
[b] Difficult to classify primitive embryonal GCT secreting HCG.
[c] 4 LR patients were treated with JEb after postsurgical disease progression (Table 4).
[d] 3 patients with teratoma were treated with JEb – one for malignant transformation and two to try and stabilise immature teratoma disease.

3. Results

Between September 2005 and August 2009, 136 patients were enrolled into the GCIII study (133 UK, 2 New Zealand and 1 Ireland). Three patients were excluded (incorrect histology [hepatoblastoma], inadequate consent and incomplete site approvals). Of 133 patients, 47 had teratomas and 86 MGCTs. Table 3 lists the clinical and pathological characteristics.

3.1. Malignant GCTs

The outcomes for all MGCTs were excellent with a 5-year OS of 97% and for patients treated with JEb with 5-year EFS of 92% and OS of 95% (Fig. 1). There were no events in patients with germinoma; for non-germinoma MGCTs, 5-year OS was 96% (88–99%) and EFS and OS for JEb-treated patients were 91% (79–96%) and 94% (83–98%), respectively.

Eighty-six patients with MGCTs were enrolled, 59% female and 41% male, median age, 5 years (0–17 years). Sixty-five percent were <11 years. Twenty-nine percent were LR, 27% IR and 44% HR patients. Two-thirds had advanced disease: 37% Stage III and 29% stage IV. Forty-eight percent had AFP >10,000 kU/L; 21% had raised HCG >5 IU/L (median: 69; range: 7–24,107), with a median age of 14 years (range: 9 months–16 yrs).

Five unwell patients with raised tumour markers did not have a biopsy. Two patients with biopsy revealing MTs were treated as MGCTs in view of AFP >10,000 kU/L.

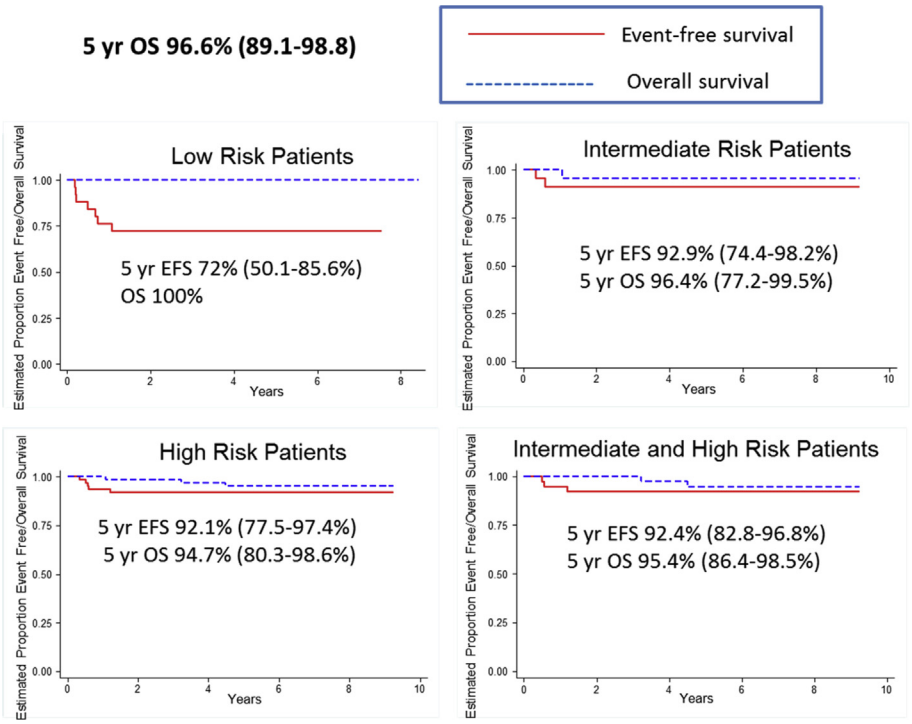

Fig. 1. MGCT 5-year OS and EFS curves by risk group. IR/HR patients treated with JEb.

The most common malignant histology was pure yolk sac (49%). Twelve patients (14%) had pure germinoma − 4 were LR, 7 IR received 4 cycles of JEb and 1 with metastatic disease wrongly classified as HR received 6 JEb cycles. There were no germinoma relapses. Nine (10%) patients had EC or CC elements: 8 on histology and 1 presumed as HCG 24,107U/L. Six were adolescents with testicular tumours: 4 LR, 3 of whom relapsed post-resection and were treated with BEP/PEb. The two patients with IR/HR disease were treated with JEb chemotherapy despite the recommendation for cisplatin-based regimens.

Of 25 LR patients, 1 patient with SCT, 14 with testicular tumour and 3 with ovarian tumour were successfully treated with surgery alone. Seven (28%) testicular tumours, all resected via the inguinal route, relapsed. All were detected by rising tumour markers at a median of 6 months (range: 2–13 months) after enrolment (Table 4)). The 3 adolescents with elevated HCG and EC component were treated with BEP/PEb. The other 4 patients were <5 years old and received 4 courses of JEb on study. All patients were successfully treated with chemotherapy (Table 4) .

Of 23 IR patients, 21 were treated with 4 courses of JEb. One patient with a slow fall in AFP received 5 courses of JEb and an infant with a perineal tumour, unusual histology, high HCG and viable malignant tumour after 4 JEb received 2 further courses. There were 2 relapses including one death (Table 4).

Of 38 HR patients, 37 received six cycles of JEb. A patient with a mediastinal tumour had complete resection (CR) of a non-malignant residual mass after 5 courses of JEb and did not receive the sixth course. Within the HR group, there were 3 relapses, 2 died (Table 4). One stage II and 15 stage III patients were considered HR because of mediastinal primary (n = 1), AFP >10,000 kU/L (n = 13) or both (n = 2).

A total of 65 patients with MGCT were treated with JEb.

Thirty patients (35%) were adolescents (≥11 years). Ten had germinoma. Of the remaining 20, 6 had LR testicular disease, 3 progressed (see above). Fourteen IR/HR patients with non-germinoma MGCTs were treated with JEb chemotherapy with only one relapse.

The median time of follow-up for MGCTs was 6.1 years.

3.2. Teratoma

Forty-seven patients were diagnosed with teratoma: 25 MTs and 22 ITs. The median age was 3 years (0–15 years). The most common MT site was sacrococcygeal (9, 36%), 7 were in neonates. Most ITs were ovarian (14, 64%). All patients had upfront surgery. Eight had incomplete resection − 3 had no further surgery, 3 had second-look CR and 2 progressed after further surgery. Median length of follow-up was 5.2 years.

There was one malignant transformation (Table 4) detected by raised AFP. Two patients with stage III ovarian IT and gliomatosis peritonei received JEb chemotherapy after progression. This possibly stabilised

Table 4
Disease recurrence/relapse per group.

Age at diagnosis, sex	Stage/site	Risk group at recurrence	Histology[a]	Time from enrolment to recurrence/relapse	Recurrence/relapse treatment[b]	Outcome (time from the first relapse to the last review)
LR chemo-naïve recurrence						
22 months, M	Stage I/ testicular	IR	YS	9 mths	JEb x4	Alive, NED[c] @ 86 mths
2 yrs, M	Stage I/ testicular	IR	YS	8 mths	JEb x4	Alive, NED @ 72 mths
3 yrs, M	Stage I/ testicular	IR	YS	2 mths	JEb x4	Alive, NED @ 84 mths
17 mths, M	Stage I/ testicular	IR	YS	13 mths	Surgery, JEb x4	Alive, NED @ 72 mths
15 yrs, M	Stage I/ testicular	n/a	EC, YS, IT, MT	3 mths	PEb x4	Alive, NED @ 55 mths
14 yrs, M	Stage I/ testicular	n/a	EC, YS, MT, C	3 mths	surgery, PEb x4	Alive, NED @ 96 mths
16 yrs, M	Stage I/ testicular	n/a	EC, YS	6 mths	BEP x3	Alive, NED @ 62 mths
IR relapse						
1 year, M	Stage 4/ testicular	n/a	Yolk sac	7 mths	VeIP x6	Alive, NED @ 74 mths
14 year, F Turner-like karyotype	Stage III/ ovarian	n/a	Yolk sac	3 mths	Surgery, VeIPx3, GOP	Died from disease progression
HR relapse						
3 yr, F	Stage III/ SCT AFP 39,760	n/a	Yolk sac	7 mths	VeIP x6, surgery, RT	Alive, NED @ 70 mths
5 yr, F	Stage IV/ SCT	n/a	Yolk sac	14 mths	VeIP x6, surgery	Died from disease progression
7 yr, F	Stage II/ ovarian AFP 20,710	n/a	YS, IT	5 mths	VeIP x6, surgery, CAV, etoposide	Died from disease progression
Teratoma malignant transformation						
1 mth, F	Stage I/SCT	IR	MT transformed to YS	6 mths	JEb x4	Alive, NED @ 76 mths

[a] YS: yolk sac; EC: embryonal carcinoma; IT: immature teratoma; MT: mature teratoma.
[b] PEb: cisplatin, etoposide, bleomycin x1; BEP: bleomycin x3, etoposide, cisplatin; VeIP: vinblastine; ifosfamide, cisplatin; GOP: gemcitabine, oxaliplatin, paclitaxel; CAV: cyclophosphamide, doxorubicin, vincristine.
[c] NED: no evidence of disease.

growth but did not reduce disease burden, and both patients required further surgery.

3.3. Toxicity of JEb chemotherapy

A total of 68 patients were treated with JEb chemotherapy (65 MGCTs and 3 teratomas). Reported toxicities are summarised in Table 5.

The most common Grade 3/4 toxicity was haematological (63%). Myelosuppression led to a chemotherapy delay of ≥7 days in 14 patients (13%) and dose modification in 7 (10%). There were no observed Grade 3/4 renal, hearing or pulmonary toxicities.

3.4. Dosing of carboplatin

Owing to reasons of GFR unavailability or unreliability, 26% of carboplatin doses were calculated on BSA and not GFR. The point estimate of the relationship between the dosing methods from the mathematical model, $\widehat{\beta}$ (supplementary materials), is 0.92 [95% CI: 0.65−1.2]. The p-value of $H_0: \beta = 1$ is 0.56. The data are supportive of the hypothesis that GRF dosing and BSA dosing provide the same average dose. (see supplementary materials)

4. Discussion

The results of GCIII demonstrate that carboplatin-based therapy is highly effective and deliverable in children and adolescents with MGCTs. The strategy of n+2 JEb cycles used in GCII was successfully replaced with 4 or 6 cycles according to risk stratification. This resulted in OS of 97% for all MGCTs and 92% EFS and 95% OS for IR/HR patients treated with JEb which is comparable to survival reported for JEb-treated patients in GCII [8]. This is excellent in a group where 44% were

Table 5
Grade 3/4 toxicity in patients treated with JEb chemotherapy.

Grade 3/4 toxicity (CTCAE)	No of patients (total 68 treated with JEb)	% of patients with toxicity/cycle					
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Haematological	43 (63%)	38%	34%	16%	43%	55%	45%
Febrile neutropenia	33 (48%)	32%	22%	34%	13%	17%	16%
Vomiting	3 (4%)						
Hypokalaemia	2 (3%)						
Hepatotoxicity	2 (3%)						
Haemorrhage	2 (3%)						
Hypophosphataemia	1 (1%)						
Anorexia	1 (1%)						
Diarrhoea	1 (1%)						
AEs of interest							
Pulmonary toxicity							
Grade 1	1 (1%)						
Grade 2	3 (4%)[a]						
Renal toxicity							
Grade 1	15 (22.0%)						
Grade 2	0 (0%)						
Ototoxicity (Brock)							
Grade 1	8 (12%)						
Grade 2	2 (3%)[b]						
Hypomagnesaemia							
Grade 1	9 (13%)						

[a] Secondary to disease/infection; no suspected bleomycin toxicity reported.
[b] One in patient with Rubinstein-Taybi syndrome; other recorded for the first time 7 yrs after chemotherapy.

classified HR, 29% had distant metastatic disease and 35% were adolescents. Our findings support adult and paediatric data that suggest 'consolidation chemotherapy' does not confer a survival advantage [14,15].

GCIII extended initial surveillance from testicular tumours to all stage I MGCTs, although only 16% were non-testicular. Our observed 33% recurrence rate in testicular tumours and 100% chemotherapy salvage rate are consistent with the literature [8,9,16,17]. Reported recurrence rates in ovarian MGCTs are around 50%, the majority being fully salvageable supporting a first-line surveillance strategy [18].

Outside of the UK, chemotherapy for paediatric MGCTs has been predominantly cisplatin-based. Reluctance to adopt carboplatin arose after previous adult and paediatric studies appeared to demonstrate inferiority to cisplatin; however, all reported trials used a significantly lower dose, intensity or frequency of carboplatin compared to GCII/III [10,19–21]. Cisplatin is a heavy metal which remains in the body for many years [22], causing persistent and deteriorating sensorineural hearing loss and nephrotoxicity [23]. Long-term follow-up of men with testicular cancer treated with cisplatin demonstrates a significant accumulation of cardiotoxicity and second malignant neoplasm risk over time [24], something of particular worry when extrapolated to paediatric patients with GCT. Although the late-effect risks of carboplatin are less well studied, it is known that carboplatin-related nephrotoxicity and ototoxicity in children are considerably less severe and frequent than those of cisplatin [25,26] Thirty-year follow-up of patients with carboplatin-treated retinoblastoma and MGCT by the largest UK late-effects service has not observed associated significant nephrotoxicity or cardiotoxicity (personal communication). GCIII adds to evidence suggesting that reduction of late effects can be achieved with carboplatin replacing cisplatin in children with MGCTs and possibly also adolescents/young adults if given at adequate dosage [27]. The current international Children's Oncology Group (COG)–led study AGCT1531 for LR and standard-risk GCTs will investigate this question by randomising patients aged 0–25 years between carboplatin- and cisplatin-based regimens [28].

GCII found AFP to be the most significant predictor of poor outcomes, but as with most paediatric GCT studies, conclusions were limited by small patient numbers. Multivariate analysis of 517 patients pooled from 7 COG and CCLG GCT trials found stage IV disease, age >11 years and tumour site to be statistically significant predictors of worse long-term survival. Although elevated AFP was associated with poorer outcome, it did not meet criteria for statistical significance [29]. On this basis, AGCT1531 will exclude HR patients defined as ≥11 years and stage IV ovarian or stage III/IV extragonadal. Within GCIII, only 3 patients (3%) and none of the six relapses met these new HR disease criteria. This together with the low rate of events in our HR group suggests that the majority of patients do not require as many as 6 cycles of JEb and that predictive molecular and biological markers are required to pick out truly poor-risk disease. In AGCT1531, paediatric patients will receive only 4 cycles

of either cisplatin- or carboplatin-based chemotherapy. There was a 100% 5-year EFS for patients with germinoma; investigation of therapy de-escalation for germinomas is warranted.

GCIII used the modified Calvert formula [12] to improve dose accuracy of carboplatin as this approach in adults reduced toxicity and improved efficacy [30]. The evidence in children is less clear. Some have shown it leads to more precise carboplatin dosing [31], whereas others demonstrate only marginal improvement [32] or that children with normal renal function actually have little inter-patient AUC variability when dosed by BSA [33]. There is also wide variation in nuclear medicine GFR measurement between institutions [34]. Our data suggest the use of 600 mg/m^2 carboplatin dose is reasonable for most patients with MGCTs provided they have normal renal function. For neonates, patients with severe renal impairment or with high-dose carboplatin where accurate dosing is essential, individual therapeutic drug monitoring is advisable [35,36].

Of the teratomas registered in GCIII, one patient (2%; 10% of SCTs) had malignant GCT transformation. This is consistent with the reported malignant relapse rate of 3% in all teratomas [37] and 6–8% in SCTs [38]. JEb chemotherapy was used in 2 patients with IT relapse which did not cure disease. Our findings add to the growing body of evidence supporting surgical management of teratomas and the convention in paediatric practice that ITs are not considered malignant [37,39,40].

Limitations include being a single-arm study with relatively few patients although comparable with other national GCT paediatric series, use of a superseded classification system and inclusion of germinomas and non-germinomas within the same protocol although this has been standard paediatric practice. Audiology/renal follow-up was only mandated for those with abnormal results by the end of treatment, potentially missing some late toxicity, although most patients received monitoring as part of standard practice.

Nevertheless, GCIII demonstrates that carboplatin-based chemotherapy used as part of a risk-stratified approach leads to excellent survival in paediatric MGCTs and minimises potential burden of long-term effects. COG AGCT1531 aims to further investigate efficacy and toxicity of carboplatin versus cisplatin for standard-risk MGCTs.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.05.001.

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