Pediatric and Adolescent Extracranial Germ Cell Tumors: The Road to Collaboration

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A B S T R A C T

During the past 35 years, survival rates for children with extracranial malignant germ cell tumors (GCTs) have increased significantly. Success has been achieved primarily through the application of platinum-based chemotherapy regimens; however, clinical challenges in GCTs remain. Excellent outcomes are not distributed uniformly across the heterogeneous distribution of age, histologic features, and primary tumor site. Despite good outcomes overall, the likelihood of a cure for certain sites and histologic conditions is less than 50%. In addition, there are considerable long-term treatment-related effects for survivors. Even modest cisplatin dosing can cause significant long-term morbidities. A particular challenge in designing new therapies for GCT is that a variety of specialists use different risk stratifications, staging systems, and treatment approaches for three distinct age groups (childhood, adolescence, and young adulthood). Traditionally, pediatric cancer patients younger than 15 years have been treated by pediatric oncologists in collaboration with their surgical specialty colleagues. Adolescents and young adults with GCTs often are treated by medical oncologists, urologists, or gynecologic oncologists. The therapeutic dilemma for all is how to best define disease risk so that therapy and toxicity can be appropriately reduced for some patients and intensified for others. Further clinical and biologic insights can only be achieved through collaborations that do not set limitations by age, sex, and primary tumor site. Therefore, international collaborations, spanning different cooperative groups and disciplines, have been developed to address these challenges.

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INTRODUCTION

Extracranial germ cell tumors (GCTs) are categorized as rare pediatric tumors. In children younger than 15 years, they account for approximately 3% of cancers. However, in adolescents (aged 15 to 19 years), this proportion increases to 14%.^{1,2} The successful introduction of cisplatin-based chemotherapy in adults with GCT from the 1970s informed the design of subsequent pediatric protocols.³⁻⁶

EARLY CLINICAL TRIALS IN PEDIATRIC GCTS

GCTs are a heterogeneous group with respect to patient age, histologic features, and primary tumor location. Pediatric clinical trial design, which has traditionally incorporated all extracranial GCTs, not just a particular extracranial site such as testicular, has been challenged by this heterogeneity, in conjunction with the rarity of the tumor itself. In most

countries, prospective pediatric clinical trials were limited to patients younger than 15 years. Each international pediatric GCT clinical trial organization has developed its own risk stratification and treatment protocols (usually featuring nonrandomized, single-arm studies) for patients they would categorize as low, intermediate, or high risk. In the United States, collaboration was recognized as essential early on in the history of pediatric clinical trials. In 1990, the Pediatric Oncology Group and Children's Cancer Group began one of the first intergroup (INT) collaborations to develop protocols for low-risk (INT-0106) and high-risk (INT-0097) GCTs, on the basis of location and staging. For the purpose of this initial discussion, the postsurgical staging system used in these pediatric trials is described in [Table 1](#). The adult classifications are substantially more complex, and different stages may not be comparable. This is especially true with the staging of testicular GCTs, which will be discussed later.^{7,8} Age

Table 1. Testis, Ovarian, and Extragenadal COG Staging

Stage	Staging Criteria		
	Testis	Extragenadal	Ovary
I	Complete resection: high inguinal or high ligation scrotal orchiectomy and negative nodes	Complete resection at any site with negative margins or coccygectomy for sacrococcygeal teratoma	Limited to ovary (peritoneal evaluation should be negative), no clinical, histological, or radiographic evidence of disease outside ovary*
II	Trans-scrotal biopsy, microscopic disease in scrotum or cord, or failure of serum tumor markers to normalize	Microscopic residual, with lymph nodes negative	Microscopic residual, peritoneal evaluation negative, failure of serum tumor markers to normalize
III	Retroperitoneal lymph node involvement, but no visceral or extra-abdominal involvement	Lymph node involvement, gross residual disease, or biopsy only	Lymph node involvement, metastatic nodule, gross residual disease or biopsy only, contiguous visceral involvement (omentum, intestine, and bladder), peritoneal evaluation positive for malignancy
IV	Distant metastases, including liver	Distant metastases, including liver	Distant metastases, including liver

Abbreviation: COG, Children's Oncology Group.

*The presence of gliomatosis peritonei does not result in a stage change.

eligibility varied, but these pediatric trials did include patients from the adolescent young adult (AYA) cohort, although the numbers were small (Table 2). For INT-0106, immature teratomas and stage I testicular malignant GCTs (< 10 years) were managed with observation only after initial surgery. Other tumors deemed low risk (INT-0106) that required chemotherapy, defined as stage II testicular (< 10 years) and stage I/II ovarian (< 21 years) malignant GCTs, were treated with a modification of the successful adult bleomycin, etoposide, and cisplatin (BEP) regimen, with reduced-dose bleomycin because of concerns regarding fatal pulmonary fibrosis.^{14,16} Pediatric BEP (PEb) consisted of four cycles of standard adult doses of cisplatin (20 mg/m² per day administered for 5 days) and etoposide (100 mg/m² per day administered for 5 days), with bleomycin (15 mg/m²) administered only on day 1 of each cycle, rather than once per week as in adult protocols. The overall 6-year survival rate for patients treated with PEb was 95.7%.⁹

High-risk tumors, defined as stage III/IV ovarian, stage III/IV testicular, and stage I-IV extragenadal malignant GCT (all < 21 years) were treated in Intergroup Study INT-0097. High-dose cisplatin (200 mg/m²) had shown promise both in a small randomly assigned trial from the National Cancer Institute in poor-prognosis GCTs¹⁷ and in the treatment of progressive neuroblastoma.¹⁸ Patients were randomly assigned between high-dose (HDPEb) and standard-dose (PEb) regimens.¹⁰ Despite improved event-free survival (EFS), HDPEb did not improve overall survival (OS), most likely because of increased therapy-related toxicity. The study was not powered to detect differences in EFS or OS in separate strata. In addition, significant ototoxicity was noted with high-dose cisplatin, which was deemed unacceptable, especially given the young age of many patients with extragenadal disease.¹⁰

RECENT PEDIATRIC GCT CLINICAL TRIALS

By the late 1990s, it became apparent that a wider Children's Cancer Group and Pediatric Oncology Group collaboration across the disease spectrum would benefit childhood cancer research by increasing sample size and decreasing administrative costs. After the merger of the four pediatric cooperative groups to form the Children's Oncology Group (COG), the COG GCT subcommittee redefined risk groups

and developed the next generation of US GCT studies (Table 2). For COG study AGCT0132, stage I ovarian GCTs were added to a low-risk group, and observation after surgical resection was advised, which had been proven effective for those with a testis primary tumor and on the basis of experience in ovarian primary tumors.^{15,19} Because the requirements for complete staging of an ovarian primary tumor are more complicated than for a testicular primary tumor, a rapid surgical review (within 72 hours of patient enrollment) was instituted to ensure that local physicians had complied with the protocol-mandated surgical guidelines. Among the 25 patients with ovarian stage I GCTs enrolled onto AGCT0132, the 4-year EFS and OS were 52% and 96%, respectively.¹³ All but one patient, who had disease recurrence on observation, received salvage treatment with chemotherapy. The intermediate-risk groups for AGCT0132, defined as COG stage II to IV testicular, COG stage II/III ovarian, and COG stage I/II extragenadal GCT, were treated with three cycles of PEb (reduced from four cycles in a previous trial), and therapy was compressed from 5 to 3 days' duration per cycle, but maintaining overall dosing. The study has been closed, and data are being analyzed.

Patients who were high risk, defined as COG stage III/IV extragenadal disease, were enrolled onto sequential pilot studies of intensified therapy (Table 2). The COG trial P9749 treated patients with HDPEb with the addition of the otoprotectant, amifostine, but unfortunately, rates of ototoxicity were not reduced.¹¹ In a second pilot AGCT01P1, escalating doses of cyclophosphamide did not improve on the response of standard PEb.¹² Patients with stage IV ovarian GCT were excluded from both of these trials.

CARBOPLATIN IN PEDIATRIC GCT TRIALS

The approach by pediatric oncologists in the United Kingdom has historically been different from the United States' approach. The first pediatric germ cell study used various chemotherapy regimens (Table 2). Since 1989, because of toxicity concerns, the United Kingdom replaced cisplatin with carboplatin in its clinical regimens. Although carboplatin had already been shown to be definitively inferior to cisplatin in clinical trials in adults with testicular GCT,^{20,21} the higher doses of carboplatin used in pediatric compared with adult trials produced promising results in children.¹⁵ In the second GCT study,

Table 2. US and UK Pediatric GCT Trials

Study	Age Eligibility/Site/Stage	No. Enrolled/Age*	Treatment	Outcome	Points
INT-0106/POG9048/CCG8891 (Rogers et al ⁹)	< 21 years/ovary/I	41/median: 10.5 years	PEb, CDDP 20 mg/m ² D 1-5, ETOP 100 mg/m ² D 1-5, BLEO 15 mg/m ² D 1 only, four cycles (+ 2 if PR)	6-year EFS and OS, 95%	Is surgery and observation possible for patients with ovarian GCT stage I?
	< 21 years/ovary/II	16/16 months to 16.7 years	PEb, four cycles (+ 2 if PR)	6-year EFS, 87.5%; 6-year OS, 93.8%	Can PEb be reduced in patients with stage II ovarian GCT?
	< 10 years/testis/I	63/median: 16 months (1 month to 6.5 years)	Surgery/observation/salvage PEb	6-year EFS, 78.5%; 6-year OS, 100%	Surgery and observation for < 10 years of age is appropriate strategy
	< 10 years/testis/II	17/< 10 years	PEb, four cycles (+ 2 if PR)	6-year EFS and OS, 100%	Most stage II patients were initially stage I with subsequent AFP elevation
US INT-0097/POG9049/CCG8882 (Cushing et al ¹⁰)	< 21 years/ovary/III	18 /< 10 years	Randomized trial a. PEb, CDDP 20 mg/m ² D 1-5, ETOP 100 mg/m ² D 1-5, BLEO 15 mg/m ² D 1 only, four cycles (+ 2 if PR); b. HDPEb, CDDP 40 mg/m ² D 1-5, ETOP 100 mg/m ² D 1-5, BLEO 15 mg/m ² D 1 only, four cycles (+ 2 if PR)	6-year EFS, 94.4%; 6-year OS, 100% 6-year EFS, 97.5%; 6-year OS, 97.5% 6-year EFS, 66.7%; 6-year OS, 83.3% 6-year EFS, 97.5%; 6-year OS, 97.5%	Can PEb be reduced in patients with stage III ovarian GCT?
	< 21 years/ovary/IV	8/< 10 years			Too few patients to make conclusions; no evidence that PEb can be reduced
	< 21 years/testis/III	11/< 15 years		6-year EFS, 100%; 6-year OS, 100%	Can PEb be reduced in stage III testicular GCT?
	< 21 years/testis/IV	6/> 15 years		6-year EFS, 100%; 6-year OS, 100%	
	< 21 years/EG/II	18/< 15 years		6-year EFS, 94.4%; 6-year OS, 100%	May be able to reduce PEb in young boys
	< 21 years/EG/III	28/> 15 years		6-year EFS, 84%; 6-year OS, 84%	
	< 21 years/EG/IV	30/< 21 years		6-year EFS, 89.4%; 6-year OS, 92.8%	Most patients were stage I; few patients were postpubertal;
	< 21 years/EG/III	61/< 21 years		6-year EFS, 75.1%; 6-year OS, 80.9%	52% of all EG, including stages III/IV, were < 2 years of age
	< 21 years/EG/IV	74/< 21 years		6-year EFS, 78%; 6-year OS, 81.5%	with SCT; new strategies for high risk will be explored
POG 9749 (Marina et al ¹¹)	< 15 years/EG/III/IV	25/0.6-13.9 years	HDPEb CDDP 40 mg/m ² d 1-5, ETOP 100 mg/m ² d 1-5, BLEO 15 mg/m ² d 1 only, plus amifostine 825 mg/m ² days 1-5, 4 cycles (+ 2 if PR)	2-year EFS, 83.5%; 2-year OS, 85.6%	Similar EFS and OS were observed compared to HDPEb in INT-0097, but there was no otoprotection
AGCT 01P1 (Malogolowkin et al ¹²)	< 21 years/EG/III/IV	19/0-18 years	PEb, CDDP 20 mg/m ² D 1-5, ETOP 100 mg/m ² D 1-5, BLEO 15 mg/m ² D 1 only, cyclophosphamide D 1 of each cycle (escalating doses (1.2, 1.8, and 2.4 g/m ²), four cycles (+ 2 if PR)	4-year EFS, 74%; 6-year OS, 89%	OS survival similar to HDPEb in INT-0097, but this was only feasibility study and numbers are too small to make any conclusions
AGCT 0132 (Billmire et al ¹³)	< 16 years/ovary/I	8/< 10 years; 17/> 10 years	Compressed PEb, CDDP 33.3 mg/m ² D 1-3, ETOP 167 mg/m ² D 1-3, BLEO 15 mg/m ² D 1 only, three cycles (3 if PR)	4-year EFS, 52%; 4-year OS, 96%	Observation and salvage may be possible for stage I ovarian tumors, but perhaps a rapid surgical review is necessary to confirm stage I
	< 21 years/ovary/II/III; EG-IV/< 15-years/testis/IV	NA	Surgery/observation/salvage compressed PEb, Compressed PEb, CDDP 33.3 mg/m ² D 1-3, ETOP 167 mg/m ² D 1-3, BLEO 15 mg/m ² D 1 only, three cycles (+ 3 if PR)	NA	Study awaiting analysis

(continued on following page)

Table 2. US and UK Pediatric GCT Trials (continued)

Study	Age Eligibility/Site/Stage	No. Enrolled/Age*	Treatment	Outcome	Points
UK GC1 (Mann et al ¹⁴)	< 16 years	42 testis/all but 1 < 6 years	Observation and salvage	Testis 5-year OS, 100% (n = 41);	5-year OS I for stage I was 97%; 12 testis stage I and 1 ovary stage I not included here had chemotherapy as markers rose
		2 ovary		Ovary 5-year OS 100% (n = 2)	
		1 EG/< 4 years;		SCT 5-year OS, 100% (n = 1)	
		16 stage II		5-year OS, 75%	
		23 stage III		5-year OS, 62%	
UK GC2 (Mann et al ¹⁵)	< 16 years	20 stage IV	5 different strategies settled on BEP, CDDP 100/m ² D 1, ETOP 120 mg/m ² D 1-3, BLEO 15 mg/m ² 1 only, cycles to marker normalization then n + 2	5-year OS, 55%	Several strategies with significant toxicity; BLEO reduced to once per cycle
		20/< 10 years; 3/> 10 years		Testis 5-year OS, 100%	
		17/< 10 years; 31/> 10 years		Ovary 5-year OS, 92.3%	
		37/< 10 years		SCT 5-year OS, 87.6%	

Abbreviations: AFP, α -fetoprotein; BEP, similar to PEB but cisplatin given on day 1 and etoposide days 1-3; BLEO, bleomycin; CDDP, cisplatin; D, day chemotherapy administered; EFS, event-free survival; EG, ; ETOP, etoposide; GCT, germ cell tumor; HDPEB, PEB with high-dose cisplatin; INT, intergroup study; J, carboplatin; NA, analysis not available or published; OS, overall survival; PEB, pediatric BEP (four cycles of standard adult doses of cisplatin [20 mg/m² per day administered for 5 days] and etoposide [100 mg/m² per day administered for 5 days], but bleomycin [15 mg/m²] was administered only on day 1 of each cycle, rather than once per week); PR, partial response by markers or residual tumor; SCT, malignant sacrococcygeal teratoma.

*Median age and range were not always available.

137 patients (< 15 years) were treated with JEB (carboplatin [600 mg/m², equivalent to area under the [concentration-time] curve of 7.9 mg/mL per minute], etoposide [120 mg/m² administered for 3 days], and bleomycin [15 mg/m² on day 1 of each cycle]). Patients were treated with an n + 2' strategy, where patients were administered two further JEB cycles after documentation of radiologic and marker remission. The 5-year EFS and OS were 87.6% and 90.9%, respectively.¹⁵ The UK Children's Cancer and Leukemia Group (CCLG) third study is now closed and awaiting analysis. In this trial, all standard-risk patients received four cycles, and high-risk patients received six cycles, of JEB. In the third study, therapy was not extended for two more cycles after remission was documented, to avoid potential overtreatment.

INTERNATIONAL PEDIATRIC GCT COLLABORATION

Every national pediatric GCT group has struggled with few patients and the stratifications.^{15,19,22,23} The lack of consensus between different national groups on the relative importance of age, site, stage, and elevation in tumor marker levels resulted in variable treatment approaches. National nonrandomized trials for pediatric GCTs from the French, German, and Brazilian germ cell groups are shown in Table 3. The major aspects of these trials were an attempt to modify therapy on the basis of response and, in German Maligne Keimaelumoren studies, to use neoadjuvant chemotherapy before definitive surgery.²⁴⁻²⁷ Investigations also include the addition of ifosfamide and the deletion of bleomycin. Results were good, but there were no comparison groups and the number of patients was small.

There was consensus, however, for the need for further clinical innovation, with three key questions to be addressed: Could late effects be reduced through either the elimination of chemotherapy in patients likely to be cured by surgery or the substitution of cisplatin with similarly effective, but less toxic, drugs? Could clinical outcomes be improved in those patients who were unlikely to be cured with standard therapy? And could biologic markers of prognostic significance be identified? A major limitation to this task was that without a common language, such as the International Germ Cell Consensus Classification (IGCCC),²⁸ developed for metastatic adult testicular GCT, designing trials across cooperative group boundaries would be impossible.

Consequently, investigators from the COG and CCLG established the Malignant Germ Cell International Collaborative (MaGIC) initiative and, in 2009, a memorandum of agreement was signed. Data from seven COG and CCLG pediatric GCT trials, which ran from 1985 to 2009 (Table 2), were combined to form a data set of more than 1,000 patients. The primary goals of the collaboration were to establish risk factors for disease recurrence, incorporate these into a common risk stratification, and use this stratification as the basis for subsequent clinical trials.

By using the parametric cure model²⁹ to predict estimated long-term disease-free (LTDF) survival, multivariable analysis of the MaGIC data resulted in a revised risk stratification that was internally validated using the bootstrapping method (Table 4).³⁰ Poor outcome was associated with patients age 11 years or older, tumor site (ovarian or extragonadal v testicular), and stage IV disease. Poor risk was defined as less than 70% LTDF survival. In this data set, neither elevation of tumor marker serum α -fetoprotein (AFP) nor type of

therapy (PEB v JEB) was predictive of outcome. The fundamental change in this risk-stratification system was the recognition that only children age 11 years or older were poor risk (expected LTDF survival, < 70%); younger children, even with advanced disease or extragonadal primary site, still had an excellent prognosis. The MaGIC database was an important first step toward development of treatment strategies on the basis of specified outcomes combining the importance of age, site, stage, and sex. However, although derived from the largest data set described in pediatric GCT, the parametric cure model warrants external validation in an independent cohort, which is currently being conducted using data from the Brazilian GCT-99 cohort.²⁷

COLLABORATION EXTENDED

The MaGIC pediatric data set is limited by relatively few adolescents (11 to 15 years) and even fewer adolescents older than 15 years and young adults. However, in a single-institution case series, adolescents with testicular GCT, controlling for IGCCC risk group, stage, and histologic features, had a lower 3-year EFS (59.9%) compared with children (87.2%) or adults (80.0%). This GCT study replicates the inferior outcomes for AYA in other malignancies. The cause of this survival gap is likely multifactorial: adolescent patients may experience fragmented care, under-representation in clinical trials, and, perhaps, a contribution from inherently more aggressive biologic factors.³¹⁻³³

Consequently, to further examine how the outcomes in adolescents compare with outcomes in adults, the MaGIC consortium has been expanded to include cohorts of AYA with GCT treated by other cooperative groups. Ovarian and testicular AYA data sets have been provided by the Gynecologic Oncology Group (GOG) and the UK Medical Research Council. The outcomes of adolescent versus young or older patients were analyzed with the goal of validating (and if necessary, amending) the MaGIC revised risk classification,³⁰ thus generating a final common language for future clinical trials.

One large obstacle to comparing outcomes of treatment for adolescents with GCT is the fact that each cooperative group has evolved its own staging system, which may or may not be comparable. Substantial differences exist between the COG pediatric staging system, the American Joint Committee on Cancer (AJCC) testicular staging system (Appendix Table A1, online only), the IGCCC metastatic testicular system (Table 5), and the International Federation of Gynecology and Obstetrics (FIGO) staging system used for ovarian GCT (Appendix Table A2, online only).^{7,8}

Staging of adult testicular GCT may be rationally divided into stage I and advanced/metastatic (outside the testis) disease. Stage I is consistent across age groups. Pediatric stages II to IV testicular GCT would be considered advanced/metastatic disease and be classified in various subcategories (stages II and III) in the AJCC system. The discussion of these differences between the pediatric and adult testicular classifications becomes important when comparing studies in adolescents. Data on adolescents with either staging system are limited. Unfortunately, pediatric data sets lack the important information necessary for AJCC staging. In clinical practice, IGCCC risk-based staging may be more important for determining actual treatment. The FIGO system has been developed for all ovarian cancers, most of which are epithelial (Appendix Table A2). The FIGO management of such tumors dictates substantially more abdominal and pelvic lymph

Table 3. International Pediatric GCT Reports

Publication	Eligibility/Age	Protocol	Treatment	Outcome	Comment
Baranzelli et al ²⁴	Ovarian secreting GCT/median, 12 years (range, 3 months to 18 years)	TGM 85	A: 10 $\mu\text{g}/\text{m}^2 \times 5$ D; C, 300 $\text{mg}/\text{m}^2 \times 5$ D; V: 2 mg/m^2 D 22 and D 23; B: 15 mg/m^2 D 22 and D 23; P: –100 mg/m^2 D 24 (three cycles) TGM 90 V: 3 mg/m^2 D 1 and 2; B: 15 mg/m^2 D 1 and 2; J: 400 mg/m^2 D 3; A: 15 $\mu\text{g}/\text{m}^2$ D 22, 23, 24; C: 300 mg/m^2 D 22, 23, 24, CR + two cycles, if markers not normal after two cycles than second line below; P: 20 $\text{mg}/\text{m}^2 \times 5$ D; E: 100 $\text{mg}/\text{m}^2 \times 5$ D; I: 1.8 $\text{g}/\text{m}^2 \times$ days	49 Patients from both studies; 5-year EFS, 74%; OS, 85%	Several regimens were explored, but there were too few patients per regimen to make significant conclusions
Schneider et al ²⁵	Medistinal secreting GCT	MAKEI 83/86	For all MAKEI: E: 100 mg/m^2 for 3 D; P: 20 mg/m^2 for 5 D; I: 1.5 g/m^2 for 5 D; V: 3 mg/m^2 for 2 D; B: –15 mg/m^2 for 3 D as CI; 4 $\times$ PVB, surgery, 4 $\times$ PEI MAKEI 89 3-4 $\times$ BEP, surgery, 3-4 $\times$ VIP MAKEI 96 3-4 $\times$ PEI, surgery, 1-2 $\times$ PEI	26 Patients secreting tumors (16 were < 10 years and 10 were > 10 years); 5-year EFS, 87%; OS, 87%	The most important factor was resection; this group stresses that neoadjuvant therapy can improve resection
Göbel et al ²⁶	Sacroccygeal teratoma (malignant)/median, 17.4 months (range, 7 to 119 months)	MAKEI 83/86 MAKEI 89	Doses as detailed above for MAKEI, 4 $\times$ PVB, surgery, 4 $\times$ PEI 3 $\times$ BEP, surgery, 3 $\times$ VIP	66 Patients were evaluable; 5-year EFS, 76%; OS, 81%	Neoadjuvant therapy aided in resection
Lopes et al ²⁷	IR/EG stage I/II, testis stage II, ovary I/II, and FIGO IC (latter would be stage III in COG) HR/stage III/IV all sites	GCT-91 GCT-91	P: 20 $\text{mg}/\text{m}^2 \times 5$ D; E: 100 $\text{mg}/\text{m}^2 \times 5$ D, two cycles, if CR + two cycles of PE, < CR two cycles of: I, –1.5 $\text{g}/\text{m}^2 \times 3$ D; V: 3 $\text{mg}/\text{m}^2 \times 1$ D; B: 15 $\text{mg}/\text{m}^2 \times 1$ D HPE: P: 30 $\text{mg}/\text{m}^2 \times 5$ D; E: 120 $\text{mg}/\text{m}^2 \times 5$ D, follow with three cycles of IVB	5-year OS, 88.9%; 54 CR after two cycles; 5-year OS, –85.2%; 17 < CR after two cycles, 5-year OS, 56.8% 5-year OS, 73.5%; 36 CR after two cycles, –5-year OS, 83.3%; 17 < CR 5-year OS, 58.8%	This study included many dysgerminomas (low stage); it is known that these patients respond well to less therapy PE is probably inadequate induction therapy; some patients will avoid bleomycin, but increased numbers may be exposed to ifosfamide and cisplatin

NOTE. Secreting GCT refers to elevated tumor markers, usually α -fetoprotein.

Abbreviations: A, actinomycin; B, bleomycin; BEP, bleomycin, etoposide, and cisplatin; CI, continuous infusion; COG, Children's Oncology Group; CR, complete remission; D, day chemotherapy administered; E, etoposide; EFS, event-free survival; EG, extragonadal; FIGO, International Federation of Gynecology and Obstetrics; GCT, germ cell tumor; GCT-91, Brazilian pediatric GCT trial; HPE, higher than standard cisplatin and etoposide; HR, high risk; I, ifosfamide; IR, intermediate risk; J, carboplatin; MAKEI, German pediatric GCT trials; OS, overall survival; P, cisplatin; PE, cisplatin and etoposide; PEI, cisplatin, etoposide, and ifosfamide; PVB, cisplatin, vinblastine and bleomycin; TGM, French pediatric GCT trials; V, vinblastine; VIP, vinblastine, ifosfamide, and cisplatin.

Table 4. Proposed Risk Assignment: Pediatric Fraction Cured

Risk	Age, Years	Location	COG Stage	Overall Survival, %
Low	< 11	Testis	I	100
	< 11	Ovary	I	96
	< 11	Extragenadal	I	93
Intermediate	< 11	Testis	II/III	99
	< 11	Testis	IV	96
	≥ 11	Testis	II/III	93
	≥ 11	Testis	IV	83*
	< 11	Ovary	II/III	97
	< 11	Ovary	IV	92
	≥ 11	Ovary	II/III	85
	< 11	Extragenadal	II/III	91
	< 11	Extragenadal	IV	79
Poor	≥ 11	Testis	IV	83*
	≥ 11	Extragenadal	III	61
	≥ 11	Ovary	IV	60
	≥ 11	Extragenadal	IV	40

NOTE. Adapted from Frazier et al.³⁰

Abbreviation: COG, Children's Oncology Group.

*Further assignment of this group may be modified by International Germ Cell Cancer Collaborative classification (Table 5).

node sampling than historically has been performed for ovarian GCT. The FIGO system has both similarities and differences compared with pediatric GCT staging. One example is peritoneal leakage of tumor, which would be defined as stage III disease using pediatric staging, but only stage IC using FIGO; however, on the basis of age, both cohorts of patients would receive similar therapy. Pediatric stage I would be comparable to FIGO stage IA/IB, and patients in this group might be candidates for identical treatment. It is clear that adult staging systems contain more subdivisions than does COG pediatric staging. The staging systems may be comparable if all relevant clinicopathologic data required to make such assignments are made available. A prospective trial that collects all such data may be able to answer this question.

COLLABORATION AND FUTURE APPROACHES

Despite the constraints of different staging systems and risk assignment, US and UK pediatric groups are now exploring opportunities for collab-

oration in future clinical trials with both adult and other pediatric study groups, building on the success of the MaGIC collaboration. In this setting, the next set of GCT clinical trials might be jointly sponsored by pediatric and adult clinical trial organizations. A trial for low- and intermediate-risk GCTs is currently under development. This trial will be cosponsored by COG and the newly formed US National Research Group, which includes GOG. Patients from birth to age 50 years will be eligible. According to the COG staging system (Table 1), low-risk patients are defined as any stage I patient, including testicular, ovarian, and extragonadal sites. Recommended therapy will be active surveillance, which is an accepted strategy for pediatric and adult patients with testicular cancer^{34,35} (Fig 1). In adult patients with testicular GCT, issues that affect this decision include the following: the ability of different health services to provide a comprehensive surveillance program versus the potential increased rates of retroperitoneal lymph node dissection required after such surveillance; the long-term toxicity of adjuvant abbreviated BEP; and the balance between patient education and clinical guidance.^{36,37} However, active surveillance will now be extended to all adult women with FIGO stage IA/B ovarian GCT (Appendix Table A2), after comprehensive staging according to GOG guidelines, and all patients with COG stage I extragonadal GCT (Table 1), who would currently receive chemotherapy as standard care.³⁸ In reality, most patients with localized stage I extragonadal GCTs are young pediatric patients with sacrococcygeal disease; thus, this protocol will be a significant change in clinical practice for adult women with ovarian tumors and children with stage I extragonadal GCT. In addition, this trial will allow a critical reassessment of current COG and GOG ovarian staging guidelines.

For intermediate-risk patients, the protocol will be a randomly assigned comparison of regimens containing carboplatin versus cisplatin (Fig 1). Eligibility will include all patients, except those with stage I testicular and extragonadal disease, those with FIGO stage IA/IB ovarian tumors, and patients defined as having a poor prognosis (patients ≥ 11 years with either stage IV ovarian or stage III/IV extragonadal GCT, and patients > 15 years with IGCCC intermediate- or poor-prognosis testicular GCT). In the MaGIC analysis, outcomes with carboplatin using PEb were not significantly different than outcomes with JEb, either overall or in any individual risk group.³⁹ This trial will test PEb versus JEb (area under the [concentration-time] curve of 7.9 mg/mL per minute) in children younger than 11 years and the adult regimen of BEP versus the regimen of carboplatin, etoposide, and bleomycin (administered once per week) in

Table 5. International Germ Cell Cancer Collaborative Prognosis System Before First-Line Chemotherapy

Histologic Feature	Good	Intermediate	Poor
Seminoma	Absence of nonpulmonary visceral metastasis*	Presence of nonpulmonary visceral metastasis	Not applicable
Nonseminoma	Meets all criteria below: Gonadal or RP primary site Absence of nonpulmonary visceral metastasis (S0) or S1 STM HCG < 5,000 IU/mL AFP < 1,000 ng/mL LDH < 1.5 × ULN	Meets all criteria below: Gonadal or RP primary site Absence of nonpulmonary visceral metastasis S2 STM HCG ≥ 5,000 and ≤ 50,000 IU/mL AFP ≥ 1,000 and ≤ 10,000 ng/mL LDH ≥ 1.5 × ULN and ≤ 10 × ULN	Meets any of criteria below: Mediastinal primary site Presence of nonpulmonary visceral metastasis S3 STM HCG > 50,000 IU/mL AFP > 10,000 ng/mL LDH > 10 × ULN

NOTE. Adapted from the International Germ Cell Cancer Collaborative Group.²⁸ The International Germ Cell Consensus Classification is a prognostic factor–based staging system for metastatic germ cell cancers.

Abbreviations: AFP, α-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; RP, retroperitoneal; S0, normal marker; STM, serum tumor marker; S1, S2, S3, range listed above; ULN, upper limit of normal.

*Nonpulmonary visceral metastasis refers to metastasis involving organs other than lung (lymph nodes do not count).

Fig 1. Potential strategies for future treatment of malignant extracranial germ cell tumors on the basis of risk stratification from Malignant Germ Cell International Collaborative (MaGIC) pediatric data set and adult germ cell studies. The MaGIC data set will be expanded and analyzed. In addition, all studies will emphasize coordination of the collection of tumor material for biologic studies. BEJ, carboplatin, etoposide, and bleomycin (administered once per week); BEP, cisplatin, etoposide, and bleomycin (administered once per week); CCLG, Children's Cancer and Leukemia and Cancer Group; COG, Children's Oncology Group; GOG, Gynecology Oncology Group; IGCCC, International Germ Cell Consensus Classification; JEb, carboplatin, etoposide, and bleomycin only with cycle; PEb, cisplatin, etoposide, and bleomycin only with cycle; TIGER, Randomized Phase III Trial of Initial Salvage Chemotherapy for Patients with Germ Cell Tumors.

AYA patients age 11 to 25 years (Fig 1). The number of courses of chemotherapy delivered within and between each arm will be determined by analyses of the completed COG AGCT0132 study, which are in progress.

Because outcomes in children with GCT younger than 11 years are excellent, the pediatric collaboration on this trial will be extended beyond COG and CCLG, to have sufficient power to investigate whether carboplatin is comparable to cisplatin in terms of EFS. Three large pediatric clinical centers will therefore be included: Boldrini Children's Cancer Hospital (Campinas, Brazil), TATA Memorial Hospital (Mumbai, India), and Children's Cancer Hospital (Cairo, Egypt). These three centers have appropriate approvals for participation in international pediatric clinical trials.

POOR-PROGNOSIS GCT

Through the application of the IGCCC staging system,²⁸ men with metastatic GCT can be assigned to good-, intermediate-, and poor-prognosis categories (Table 5).²⁸ The term stage IV testicular GCT has therefore been eliminated from most adult testis cancer studies. In the pediatric studies, patients with gross disease and retroperitoneal lymphadenopathy were considered as having stage III disease, and only those with distant metastatic sites were defined as having stage IV disease. In the MaGIC analysis, postpubertal males (≥ 11 years) with COG stage IV testicular GCT had LTDF survival of 83%. Even when the IGCCC risk classification was applied to all such adolescent males with metastatic testicular GCT, a group with less than 80% LTDF survival could not be identified. This may be because most patients in the MaGIC data set were younger than 15 years, with only 22 patients in the 15- to 19-year age group. In contrast, patients 11 years or older with COG stage IV ovarian GCT and COG stage III/IV extragonadal GCT had poor rates of LTDF survival in the MaGIC analysis (67%; 65% and 40%, respectively). Although the MaGIC data set is the largest GCT data set available, it lacks sufficient information to apply

the IGCCC classification to every patient.^{22,30} In addition, adolescents (age 15 to 19 years) may do less well than those slightly older or younger, when adjusted for stage and IGCCC risk group,⁴⁰ and are not well represented in clinical trials. Until further data are available, treatment assignment according to IGCCC prognostic categories seems prudent for postpubertal adolescent boys with metastatic GCT.

Answering clinically important questions in randomized clinical trials (RCTs) for poor-prognosis patients with GCT will be impossible without the inclusion of young adult patients and, in particular, patients with testicular GCT, given the 10-fold higher incidence of testicular GCT compared with ovarian GCT; therefore, collaboration with the testicular GCT community is essential for the development of RCTs in poor-risk disease. BEP has been the standard of care for adult testicular GCT for the past three decades.⁴ Patients classified as having good-prognosis metastatic GCT, according to IGCCC, achieve a durable remission (90%) with three cycles of BEP.^{41,42} Several strategies have been tested in phase II and III clinical trials for patients with poor-prognosis IGCCC disease, including the use of alternative or additional chemotherapy agents,⁴³⁻⁴⁵ more complex multidrug regimens,⁴⁶⁻⁴⁸ and high-dose chemotherapy and stem cell support.^{36,45,49,50} Unfortunately, none of these strategies has demonstrated clear improvement in cure rates.

An approach currently being investigated for poor-prognosis patients is dose intensification, a strategy that can increase the sensitivity of tumors to chemotherapy by increasing dose per unit of time. This can be attained by increasing the amount of drug per cycle (high-dose chemotherapy, unsuccessful as already noted above) or, alternatively, shortening the time between cycles (accelerated or dose-dense treatment).⁵¹ For example, accelerated timing has been used successfully in Ewing sarcoma⁵² and is currently being evaluated in hepatoblastoma by the European Societe Internationale d'Oncologie Pediatrique Epithelial Liver Tumor Study Group. For GCT, a phase I/II trial of accelerated BEP included four cycles of cisplatin and

etoposide, administered every 2 weeks (instead of every 3 weeks), with bleomycin administered once per week and growth factor support. Although the cycles with cisplatin and etoposide were compressed, patients still received all 12 bleomycin doses, administered once per week. The phase I/II data showed acceptable toxicity and promising efficacy.⁵³

Another approach for patients with poor-risk GCT is whether those patients who are likely to experience failure of standard BEP treatment can be identified early during BEP treatment and switched to more intensive therapy in real time. Retrospective reports have suggested that men with GCT and inadequate tumor marker decline (AFP) after initiation of chemotherapy are a poor-prognostic group.^{50,54} A recent randomized trial, GETUG 13,⁵⁵ intensified therapy among patients with a poor AFP marker response to one cycle of BEP. There was a 10% increase in EFS compared with those who continued to receive standard-dose BEP; however, OS was similar between the two groups. The complexity of the GETUG 13 regimen, as well as the inclusion of insufficiently active or more toxic therapy, makes widespread adoption of this strategy unlikely. However, continued investigations of potential response-based strategies should be pursued.

Collaborators in pediatric oncology, medical oncology, and gynecologic oncology have discussed proposals for patients age 11 years and older with poor-risk disease. The premise was that an RCT with increased sample size, including male and female AYA with the same predicted poor outcome, was feasible. Perhaps, planning of a tentative joint RCT, simultaneously evaluating two or, perhaps, three of the most promising strategies (Fig 1), was possible. Several promising regimens, such as Accel-BEP,⁵³ carboplatin, bleomycin, vincristine, and cisplatin with BEP (CBOP-BEP),⁴⁸ and first-line paclitaxel, ifosfamide, and cisplatin (TIP),⁵⁶ are being discussed. In the interim, pediatric groups continue to explore opportunities for collaboration with adult cooperative trial groups to establish feasibility of this strategy as a means to increase accrual and expedite evaluation of new approaches, especially in AYA. One option might be joining a currently open poor-prognosis adult GCT trial. One regimen under consideration for a multiarm trial is the currently active study, ANZUP 1302 (Australia and New Zealand), a phase III RCT of standard BEP versus accelerated BEP treatment for patients with IGCCC intermediate- and poor-prognosis GCT. This approach might provide the opportunity to demonstrate that a pediatric clinical trial group and a testicular cancer trial group can collaborate successfully across international boundaries.

Fortunately, for patients with relapsed GCT, salvage therapy is often successful. Salvage therapies have included other conventional chemotherapy agents, such as the TIP regimen and high-dose chemotherapy with or without stem-cell rescue.^{50,57-61} However, the lack of RCTs in patients with relapsed GCT has not allowed for identification of the optimal salvage therapy. An international collaborative RCT, the Randomized Phase III Trial of Initial Salvage Chemotherapy for Patients with Germ Cell Tumors (TIGER) study (Alliance 0311102/EORTC 1407), will compare OS in patients with relapsed GCT treated with TIP or paclitaxel and ifosfamide, followed by high-dose carboplatin/etoposide. More important, because of the previous engagement of the pediatric and adult testicular communities through MaGIC, COG has been invited to cosponsor the Alliance trial, and the concept has been approved by the COG Science Council. The TIGER trial is expected to open in 2015.

BIOLOGICALLY-BASED TREATMENT

Advancement of biologic understanding of GCT, both pediatric and adult, is essential. Definitive pediatric GCT biologic studies have historically been hampered by the lack of available specimens, a hurdle that has been overcome by the MaGIC collaboration. Key differences in genomic changes have been identified in mediastinal tumors in children younger than 8 years and in those 8 years or older.⁶² The patterns of gains and losses were similar to age-matched GCTs at other sites. In studies of adults with GCT, a prognostic mRNA gene expression signature was identified and validated with relatively few patients with poor clinical outcome.⁶³ However, Palmer et al⁶⁴ showed that GCTs in children have a protein-coding gene expression profile distinct from GCTs occurring in adults; therefore, whether the adult prognostic mRNA signature applies to children and adolescents remains to be determined. Other biologic parameters (eg, microRNAs) seem to be universally clinically informative in GCTs.^{65,66} It is hoped that collaboration will enhance not only understanding of basic GCT biologic features in children, adolescents, and young adults, but may enhance diagnosis, disease monitoring, risk stratification, and the identification of targetable mutations across the diverse clinical spectrum of extracranial GCT disease.

CONCLUSION

For too long, the study of GCT has been hampered by arbitrary clinical divides on the basis of age and sex. We can enhance the study of GCT through the generation of large clinical trial data sets that encompass all age groups and multiple cooperative groups with different treatment strategies. The planning of joint future trials is moving forward because of the persistent efforts of many groups. These studies will include an international attempt to prospectively collect biologic specimens that may ultimately improve diagnosis, disease monitoring, and risk stratification, and identify potential targets for treatment. Well-designed RCTs should allow improvement of clinical outcomes with reduced toxicity. One more facet about the study of rare pediatric cancers should be noted: Funding limitations have particularly hampered the study of GCT. The MaGIC studies and present collaborations could not have occurred without strong support and funding from COG and CCLG, as well as the Teenage Cancer Trust (United Kingdom) and other charities, such as the Katie Walker Fund (United Kingdom), Bridging the GAP (United States), The Franklin Foundation (United States), and the Dana Farber/Boston Children's Cancer and Blood Disorders Center. Investigators and patients are indebted to these valiant people.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pediatric and Adolescent Extracranial Germ Cell Tumors: The Road to Collaboration

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Appendix

Table A1. NCCN Guidelines Version 1.2015 Staging Testicular Cancer

Stage	Primary Tumor	Stage	Pathologic (pN)	
pTX	Primary tumor cannot be assessed	pNX	Regional lymph nodes cannot be assessed	
pT0	No evidence of primary tumor (eg, histological scar in testis)	pN0	No regional lymph node metastasis	
pTis	Intratubular germ cell neoplasia (carcinoma in situ)	pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to five nodes positive, none > 2 cm in greatest dimension	
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis	pN2	Metastasis with a lymph node mass > 2 cm but not > 5 cm in greatest dimension; or more than five nodes positive, none > 5 cm; or evidence of extranodal extension of tumor	
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis	pN3	Metastasis with a lymph node mass > 5 cm in greatest dimension	
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion			
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion			
Stage	Regional Lymph Nodes (N): Clinical	Stage	Distant Metastasis (M)	
NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis	
N0	No regional lymph node metastasis	M1	Distant metastasis	
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none > 2 cm in greatest dimension	M1a	Nonregional nodal or pulmonary metastasis	
N2	Metastasis with a lymph node mass, > 2 cm but not > 5 cm in greatest dimension; or multiple lymph nodes, any one mass > 2 cm but not > 5 cm in greatest dimension	M1b	Distant metastasis other than to nonregional lymph nodes and lung	
N3	Metastasis with a lymph node mass > 5 cm in greatest dimension			
Anatomic Stage/Prognostic Groups				
Group	T	N	M	Serum Tumor Markers
Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	PT3	N0	M0	S0
	PT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S
(continued on following page)				

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Pediatric and Adolescent GCTs, Staging, and Risk Stratification

Table A1. NCCN Guidelines Version 1.2015 Staging Testicular Cancer (continued)

Stage	Serum Tumor Markers
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH $< 1.5 \times N^*$ and hCG (mIU/mL) $< 5,000$ and AFP (ng/mL) $< 1,000$
S2	LDH $1.5-10 \times N$ or hCG (mIU/mL) 5,000-50,000 or AFP (ng/mL) 1,000-10,000
S3	LDH $> 10 \times N$ or hCG (mIU/mL) $> 50,000$ or AFP (ng/mL) $> 10,000$

NOTE. Used with the permission of the American Joint Committee on Cancer (AJCC; Chicago, IL). The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer-Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit <http://www.springer.com>). Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC. All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Abbreviations: AFP, α -fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; NCCN, National Comprehensive Cancer Network.

*N indicates the upper limit of normal for the LDH assay.

Table A2. FIGO Ovarian Staging

Stage	FIGO Criteria*
I	Tumor confined to ovary
IA	Limited to one ovary, capsule intact, no tumor on surface, negative washings
IB	Both ovaries, otherwise like IA
IC1	Surgical spill
IC2	Capsule rupture before surgery, or tumor on ovarian surface
IC3	Malignant cell in ascites or peritoneal washings
II	Both ovaries or extension lower than pelvic rim or peritoneal primary
IIA	Extension and/or implant on uterus and/or fallopian tubes
IIB	Extension to other pelvic intraperitoneal structures
III	Positive RP LN and/or microscopic metastasis beyond pelvis
IIIA1	Positive RP LN only (IIIA1i < 10 mm) (IIIA1ii > 10 mm)
IIIA2	Microscopic, extrapelvic (higher than pelvic brim), peritoneal involvement with or without positive RP LN
IIIB	Macroscopic, extrapelvic peritoneal metastasis ≤ 2 cm with or without RP LN, includes extension to capsule of liver/spleen
IIIC	Macroscopic, extrapelvic peritoneal metastasis > 2 cm with or without RP LN, includes extension to capsule of liver/spleen
IV	
IVA	Pleural effusion with positive cytologic features
IVB	Metastasis to liver/spleen parenchyma and extra-abdominal organs (including inguinal LN and outside abdominal cavity)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; RP, retroperitoneal.

*Adapted from Prat et al.⁸