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

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ABSTRACT

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%. The successful introduction of cisplatin-based chemotherapy in adults with GCT from the 1970s informed the design of subsequent pediatric protocols.

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.
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 surgery was advised, which had been proven effective for those with a testis primary tumor and on the basis of experience in ovarian primary tumors.15,16 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 extragonadal 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 extragonadal disease, were enrolled onto sequential pilot studies of intensified therapy (Table 2). The COG trial P9749 treated patients with HDPEPb with the addition of the ototoxicant, amifostine, but unfortunately, rates of ototoxicity were not reduced.14 In a second pilot AGCT01P1, escalating doses of cyclophosphamide did not improve on the response of standard PEB. 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,15,21 the higher doses of carboplatin used in pediatric compared with adult trials produced promising results in children.15 In the second GCT study,
<table>
<thead>
<tr>
<th>Study</th>
<th>Age Eligibility/Site/Stage</th>
<th>No. Enrolled/Age*</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT-0106/POG9048/CCG8891 (Rogers et al9)</td>
<td>&lt; 21 years/ovary/I</td>
<td>41/median: 10.5 years</td>
<td>PEb, CDDP 20 mg/m² D 1-5, ETOPO 100 mg/m² D 1-5, BLEOMycin 15 mg/m² D 1 only, four cycles (+ 2 if PR)</td>
<td>6-year EFS and OS, 95%</td>
<td>Is surgery and observation possible for patients with ovarian GCT stage I?</td>
</tr>
<tr>
<td></td>
<td>&lt; 21 years/ovary/II</td>
<td>16/16 month to 16.7 years</td>
<td>PEb, four cycles (+ 2 if PR)</td>
<td>6-year EFS, 87.5%; 6-year OS, 93.8%</td>
<td>Can PEb be reduced in patients with stage II ovarian GCT?</td>
</tr>
<tr>
<td></td>
<td>&lt; 10 years/testis/I</td>
<td>63/median: 16 months (1 month to 6.5 years)</td>
<td>Surgery/observation/salvage PEb</td>
<td>6-year EFS, 78.5%; 6-year OS, 100%</td>
<td>Surgery and observation for &lt; 10 years of age is appropriate strategy</td>
</tr>
<tr>
<td></td>
<td>&lt; 10 years/testis/II</td>
<td>17/&lt; 10 years</td>
<td>PEb, four cycles (+ 2 if PR)</td>
<td>6-year EFS and OS, 100%</td>
<td>Most stage II patients were initially stage I with subsequent AFP elevation</td>
</tr>
<tr>
<td>US INT-0097/POG9049/CCG8882 (Cushing et al10)</td>
<td>&lt; 21 years/ovary/III</td>
<td>18/ &lt; 10 years</td>
<td>Randomized trial a. PEb, CDDP 20 mg/m² D 1-5, ETOPO 100 mg/m² D 1-5, BLEOMycin 15 mg/m² D 1 only, four cycles (+ 2 if PR), b. HDPEb, CDDP 40 mg/m² D 1-5, ETOPO 100 mg/m² D 1-5, BLEOMycin 15 mg/m² D 1 only, four cycles (+ 2 if PR)</td>
<td>6-year EFS, 94.4%; 6-year OS, 100%</td>
<td>Can PEb be reduced in patients with stage III ovarian GCT?</td>
</tr>
<tr>
<td></td>
<td>&lt; 21 years/ovary/IV</td>
<td>8/&lt; 10 years</td>
<td>10/&lt; 10 years</td>
<td>11/&lt; 15 years</td>
<td>6/&gt; 15 years</td>
</tr>
<tr>
<td></td>
<td>&lt; 21 years/EG/I-IV</td>
<td>25/0.6-13.9 years</td>
<td>HDPEb CDDP 40 mg/m² D 1-5, ETOPO 100 mg/m² D 1-5, BLEOMycin 15 mg/m² D 1 only, plus amifostine 825 mg/m² days 1-5, 4 cycles (+ 2 if PR)</td>
<td>2-year EFS, 83.5%; 2-year OS, 85.6%</td>
<td>Similar EFS and OS were observed compared to HDPEb in INT-0097, but there was no otoprotection</td>
</tr>
<tr>
<td>AGCT 01P1 (Malogolowkin et al12)</td>
<td>&lt; 21 years/EG/II/IV</td>
<td>19/0-18 years</td>
<td>PEb, CDDP 20 mg/m² D 1-5, ETOPO 100 mg/m² D 1-5, BLEOMycin 15 mg/m² D 1 only, cyclophosphamide D 1 of each cycle (escalating doses (1.2, 1.8, and 2.4 g/m²), four cycles (+ 2 if PR)</td>
<td>4-year EFS, 74%; 6-year OS, 89%</td>
<td>OS survival similar to HDPEb in INT-0097, but this was only feasibility study and numbers are too small to make any conclusions</td>
</tr>
<tr>
<td>AGCT 0132 (Billmire et al13)</td>
<td>&lt; 16 years/ovary/I</td>
<td>8/&lt; 10 years; 17/&gt; 10 years</td>
<td>Compressed PEb, CDDP 33.3 mg/m² D 1-3, ETOPO 167 mg/m² D 1-3, BLEOMycin 15 mg/m² D 1 only, three cycles (if PR)</td>
<td>4-year EFS, 52%; 4-year OS, 96%</td>
<td>Observation and salvage may be possible for stage I ovarian tumors, but perhaps a rapid surgical review is necessary to confirm stage I</td>
</tr>
<tr>
<td></td>
<td>&lt; 21 years/ovary/II/III; EG/I-IV/&lt; 15 years/testis/IV</td>
<td>NA</td>
<td>Surgery/observation/salvage compressed PEb, Compressed PEb, CDDP 33.3 mg/m² D 1-3, ETOPO 167 mg/m² D 1-3, BLEOMycin 15 mg/m² D 1 only, three cycles (+ 3 if PR)</td>
<td>NA</td>
<td>Study awaiting analysis</td>
</tr>
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</table>

(continued on following page)
<table>
<thead>
<tr>
<th>Study</th>
<th>Age Eligibility/Site/Stage</th>
<th>No. Enrolled/Age*</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK GC1 (Mann et al\textsuperscript{14})</td>
<td>&lt; 16 years</td>
<td>42 testis/all but 1 &lt; 6 years</td>
<td>Observation and salvage</td>
<td>Testis 5-year OS, 100% (n = 41); 12 testis stage I and 1 ovary stage I not included here had chemotherapy as markers rose</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>&lt; 16 years</td>
<td>2 ovary</td>
<td>1 EG/4 years; 16 stage II</td>
<td>5 different strategies settled on BEP; CDDP 120 mg/m\textsuperscript{2} D 1-3, BLEO 15 mg/m\textsuperscript{2} 1 only, cycles to marker normalization then n + 2</td>
<td>Testis 5-year OS, 100% (n = 2); Ovary 5-year OS, 100% (n = 1); 5-year OS, 75%</td>
</tr>
<tr>
<td></td>
<td>&lt; 16 years</td>
<td>23 stage III</td>
<td>20 stage IV</td>
<td></td>
<td>Ovary 5-year OS, 100% (n = 1); 5-year OS, 62%</td>
</tr>
<tr>
<td></td>
<td>&lt; 16 years</td>
<td>16 stage II</td>
<td></td>
<td></td>
<td>5-year OS, 55%</td>
</tr>
<tr>
<td>UK GC2 (Mann et al\textsuperscript{15})</td>
<td>&lt; 16 years</td>
<td>20/&lt; 10 years; 3/&gt; 10 years</td>
<td>Observation and salvage for stage I, Jeb, J 600 mg/m\textsuperscript{2} day 2, ETOP 120 mg/m\textsuperscript{2} days 1-3, BLEO 15 mg/m\textsuperscript{2} day 3, n cycles to marker normalization + 2</td>
<td>Testis 5-year OS, 100%</td>
<td>Difficult to combine site and stage from this article but 5-year EFS for stage III and IV for all groups was 84.8% and 78%; retrospectively, the question was raised about how many Jeb cycles are necessary</td>
</tr>
<tr>
<td></td>
<td>&lt; 16 years</td>
<td>17/&lt; 10 years; 31/&gt; 10 years</td>
<td></td>
<td></td>
<td>Ovary 5-year OS, 92.3%</td>
</tr>
<tr>
<td></td>
<td>&lt; 16 years</td>
<td>37/&lt; 10 years</td>
<td></td>
<td></td>
<td>SCT 5-year OS, 87.6%</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, \(\alpha\)-fetoprotein; BEP, similar to PBp 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, PBp with high-dose cisplatin; INT, intergroup study; J, carboplatin; NA, analysis not available or published; OS, overall survival; PBp, pediatric BEP (four cycles of standard adult doses of cisplatin [20 mg/m\textsuperscript{2} per day administered for 5 days] and etoposide [100 mg/m\textsuperscript{2} per day administered for 5 days], but bleomycin [15 mg/m\textsuperscript{2}] 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. 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. 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 Keimzellmomen studies, to use neoadjuvant chemotherapy before definitive surgery. 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 biological 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), 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 model 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 boot-strapping method (Table 4). 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.

**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. 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, 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).

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>
<thead>
<tr>
<th>Publication</th>
<th>Eligibility/Age</th>
<th>Protocol</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baranzelli et al(^{24})</td>
<td>Ovarian secreting GCT/median, 12 years (range, 3 months to 18 years)</td>
<td>TGM 85</td>
<td>A: 10 μg/mL (\times) 5 D; C: 300 mg/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)</td>
<td>49 Patients from both studies; 5-year EFS, 74%; OS, 85%</td>
<td>Several regimens were explored, but there were too few patients per regimen to make significant conclusions</td>
</tr>
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<td></td>
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<td>TGM 90</td>
<td>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 mg/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 mg/m(^2) (\times) 5 D; E: 100 mg/m(^2) (\times) 5 D; I, 1.8 g/m(^2) (\times) days</td>
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<tr>
<td>Schneider et al(^{25})</td>
<td>Mediastinal secreting GCT</td>
<td>MAKEI 83/86</td>
<td>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</td>
<td>26 Patients secreting tumors (16 were &lt; 10 years and 10 were &gt; 10 years); 5-year EFS, 87%; OS, 87%</td>
<td>The most important factor was resection; this group stresses that neoadjuvant therapy can improve resection</td>
</tr>
<tr>
<td>Göbel et al(^{26})</td>
<td>Sacrococcygeal teratoma (malignant)/median, 17.4 months (range, 7 to 119 months)</td>
<td>MAKEI 83/86</td>
<td>Doses as detailed above for MAKEI, 4 (\times) PVB, surgery, 4 (\times) PEI</td>
<td>66 Patients were evaluable; 5-year EFS, 76%; OS, 81%</td>
<td>Neoadjuvant therapy aided in resection</td>
</tr>
<tr>
<td>Lopes et al(^{27})</td>
<td>IR/EG stage I/II, testis stage II, ovary VII, and FIGO IC (latter would be stage III in COG)</td>
<td>GCT-91</td>
<td>P: 20 mg/m(^2) (\times) 5 D; E: 100 mg/m(^2) (\times) 5 D, two cycles, if CR + two cycles of PE, &lt; CR two cycles of I, &lt; 1.5 g/m(^2) (\times) 3 D; V: 3 mg/m(^2) (\times) D; B: 15 mg/m(^2) (\times) 1 D</td>
<td>5-year OS, 88.9%; 54 CR after two cycles; 5-year OS, 75.9%; 17 &lt; CR after two cycles, 5-year OS, 56.8%</td>
<td>This study included many dysgerminomas (low stage); it is known that these patients respond well to less therapy</td>
</tr>
<tr>
<td></td>
<td>HR/stage III/IV all sites</td>
<td>GCT-91</td>
<td>HPE: P: 30 mg/m(^2) (\times) 5 D; E: 120 mg/m(^2) (\times) 5 D, follow with three cycles of NVB</td>
<td>5-year OS, 73.5%; 36 CR after two cycles, 5-year OS, 83.3%; 17 &lt; CR 5-year OS, 58.8%</td>
<td>PE is probably inadequate induction therapy; some patients will avoid bleomycin, but increased numbers may be exposed to ifosfamide and cisplatin</td>
</tr>
</tbody>
</table>

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.
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 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
Potential collaborative strategies

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate 1</th>
<th>Intermediate 2</th>
<th>Poor prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0-50 yrs stage I (all sites)</td>
<td>Age 0-10 yrs stage II-IV (all sites)</td>
<td>Age 11-25 yrs ovarian stage II/III; testicular stage II/III</td>
<td>Age &gt; 11 yrs ovarian stage IV; testicular stage IV</td>
</tr>
</tbody>
</table>

Surgery and observation

Randomized trial COG v CCLG / GOG

Randomized trial BEP v BEJ

Response to BEP and testing multiple strategies simultaneously

Potential options

Accelerated BEP if age and sex eligibility can be extended (or other regimens)

Analysis of growing MaGIC dataset

Coordinated biologic material collection

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: Baldrini 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, men with metastatic GCT can be assigned to good-, intermediate-, and poor-prognosis categories (Table 5).

The term stage IV testicular GCT has been added to the IGCCC system to accommodate the increased incidence of metastatic disease in postpubertal adolescent patients. 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, more complex multidrug regimens, and high-dose chemotherapy and stem cell support. Unfortunately, none of these strategies have 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). For example, accelerated timing has been used successfully in Ewing sarcoma 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/I1 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),56 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.

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

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### Table A1. NCCN Guidelines Version 1.2015 Staging Testicular Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Tumor</th>
<th>Stage</th>
<th>Pathologic (pN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTX</td>
<td>Primary tumor cannot be assessed</td>
<td>pNX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>pT0</td>
<td>No evidence of primary tumor (eg, histological scar in testis)</td>
<td>pN0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>pTis</td>
<td>Intratubular germ cell neoplasia (carcinoma in situ)</td>
<td>pN1</td>
<td>Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to five nodes positive, none &gt; 2 cm in greatest dimension</td>
</tr>
<tr>
<td>pT1</td>
<td>Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis</td>
<td>pN2</td>
<td>Metastasis with a lymph node mass &gt; 2 cm but not &gt; 5 cm in greatest dimension; or more than five nodes positive, none &gt; 5 cm; or evidence of extranodal extension of tumor</td>
</tr>
<tr>
<td>pT2</td>
<td>Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis</td>
<td>pN3</td>
<td>Metastasis with a lymph node mass &gt; 5 cm in greatest dimension</td>
</tr>
<tr>
<td>pT3</td>
<td>Tumor invades the spermatic cord with or without vascular/lymphatic invasion</td>
<td>pN4</td>
<td>Metastasis with a lymph node mass &gt; 5 cm in greatest dimension</td>
</tr>
<tr>
<td>pT4</td>
<td>Tumor invades the scrotum with or without vascular/lymphatic invasion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Regional Lymph Nodes (N): Clinical</th>
<th>Stage</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none &gt; 2 cm in greatest dimension</td>
<td>M1a</td>
<td>Nonregional nodal or pulmonary metastasis</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis with a lymph node mass, &gt; 2 cm but not &gt; 5 cm in greatest dimension; or multiple lymph nodes, any one mass &gt; 2 cm but not &gt; 5 cm in greatest dimension</td>
<td>M1b</td>
<td>Distant metastasis other than to nonregional lymph nodes and lung</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis with a lymph node mass &gt; 5 cm in greatest dimension</td>
<td></td>
<td></td>
</tr>
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</table>

**Anatomic Stage/Prognostic Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Serum Tumor Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>pTis</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage I</td>
<td>pT1-4</td>
<td>N0</td>
<td>M0</td>
<td>SX</td>
</tr>
<tr>
<td>Stage IA</td>
<td>pT1</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>pT2</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>PT3</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>PT4</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage IS</td>
<td>Any pT/TX</td>
<td>N0</td>
<td>M0</td>
<td>S1-3</td>
</tr>
<tr>
<td>Stage II</td>
<td>Any pT/TX</td>
<td>N1-3</td>
<td>M0</td>
<td>SX</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Any pT/TX</td>
<td>N1</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>Any pT/TX</td>
<td>N1</td>
<td>M0</td>
<td>S1</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Any pT/TX</td>
<td>N2</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>Any pT/TX</td>
<td>N2</td>
<td>M0</td>
<td>S1</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>Any pT/TX</td>
<td>N3</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>Any pT/TX</td>
<td>N3</td>
<td>M0</td>
<td>S1</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any pT/TX</td>
<td>Any N</td>
<td>M1</td>
<td>SX</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Any pT/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>Any pT/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>S1</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any pT/TX</td>
<td>N1-3</td>
<td>M0</td>
<td>S2</td>
</tr>
<tr>
<td></td>
<td>Any pT/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>S2</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>Any pT/TX</td>
<td>N1-3</td>
<td>M0</td>
<td>S3</td>
</tr>
<tr>
<td></td>
<td>Any pT/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>S3</td>
</tr>
<tr>
<td></td>
<td>Any pT/TX</td>
<td>Any N</td>
<td>M1b</td>
<td>Any S</td>
</tr>
</tbody>
</table>

(continued on following page)
### Table A1. NCCN Guidelines Version 1.2015 Staging Testicular Cancer (continued)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Tumor Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>SX</td>
<td>Marker studies not available or not performed</td>
</tr>
<tr>
<td>S0</td>
<td>Marker study levels within normal limits</td>
</tr>
<tr>
<td>S1</td>
<td>LDH &lt; 1.5 × N* and hCG (mlu/mL) &lt; 5,000 and AFP (ng/mL) &lt; 1000</td>
</tr>
<tr>
<td>S2</td>
<td>LDH 1.5-10 × N or hCG (mlu/mL) 5,000-50,000 or AFP (ng/mL) 1,000-10,000</td>
</tr>
<tr>
<td>S3</td>
<td>LDH &gt; 10 × N or hCG (mlu/mL) &gt; 50,000 or AFP (ng/mL) &gt; 10,000</td>
</tr>
</tbody>
</table>

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

### Table A2. FIGO Ovarian Staging

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

*Adapted from Prat et al.*

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