



# **Reduced and Compressed Cisplatin-Based Chemotherapy in Children and Adolescents With Intermediate-Risk Extracranial Malignant Germ Cell Tumors: A Report From the Children's Oncology Group**

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# Reduced and Compressed Cisplatin-Based Chemotherapy in Children and Adolescents With Intermediate-Risk Extracranial Malignant Germ Cell Tumors: A Report From the Children's Oncology Group

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## ABSTRACT

### Purpose

To investigate whether event-free survival (EFS) can be maintained among children and adolescents with intermediate-risk (IR) malignant germ cell tumors (MGCT) if the administration of cisplatin, etoposide, and bleomycin (PEb) is reduced from four to three cycles and compressed from 5 to 3 days per cycle.

### Patients and Methods

In a phase 3, single-arm trial, patients with IR MGCT (stage II-IV testicular, II-III ovarian, I-II extragonadal, or stage I gonadal tumors with subsequent recurrence) received three cycles of PEb. A parametric comparator model specified that the observed EFS rate should not be significantly < 92%. As recommended for trials that test a reduction of therapy, a one-sided  $P$  value  $\leq .10$  was used to indicate statistical significance. In a post hoc analysis, we also compared results to the EFS rate of comparable patients treated with four cycles of PEb in two prior studies.

### Results

Among 210 eligible patients enrolled from 2003 to 2011, 4-year EFS (EFS<sub>4</sub>) rate was 89% (95% confidence interval, 83% to 92%), which was significantly lower than the 92% threshold of the comparison model ( $P = .08$ ). Among 181 newly diagnosed patients, the EFS<sub>4</sub> rate was 87%, compared with 92% for 92 comparable children in the historical cohort ( $P = .15$ ). The EFS<sub>4</sub> rate was significantly associated with stage (stage I, 100%; stage II, 92%; stage III, 85%; and stage IV, 54%;  $P < .001$ ).

### Conclusion

The EFS rate for children with IR MGCT observed after three cycles of PEb was less than that of a prespecified parametric model, particularly for patients with higher-stage tumors. These data do not support a reduction in the number of cycles of PEb from four to three. However, further investigation of a reduction in the number of cycles for patients with lower-stage tumors is warranted.

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## INTRODUCTION

Children and adolescents with intermediate-risk (IR) malignant germ cell tumors (MGCTs) have excellent event-free survival (EFS) rates (> 90%) with standard chemotherapy but can experience significant dose-dependent toxicities.<sup>1</sup> In prior pediatric intergroup studies (INT-0106 and INT-0097),<sup>2,3</sup> children with IR MGCTs were treated with four cycles of cisplatin, etoposide, and bleomycin (PEb) every 3 weeks.<sup>4</sup> In these trials,

10% of children treated with standard-dose cisplatin (cumulative dose, 400 to 600 mg/m<sup>2</sup>) had moderate to severe ototoxicity.<sup>3,5</sup> Children who receive cumulative doses of cisplatin  $\geq 400$  mg/m<sup>2</sup> have a three times higher risk of moderate to severe ototoxicity than those receiving lower doses. Because men with testicular cancer are treated with nearly identical regimens, the late effects<sup>6</sup> observed in this population are also likely relevant to children. These include a two-fold increased risk of cardiovascular disease and second malignancies over the lifespan,<sup>7</sup> as well as peripheral neuropathy

## ASSOCIATED CONTENT



Appendix  
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Data Supplement  
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and nephrotoxicity.<sup>8</sup> Therefore, the research objective for patients with IR MGCTs is to maintain EFS while reducing toxicities.

To reduce the cumulative dose of chemotherapy and, hence, the late effects, two randomized controlled trials (RCTs) of adult men with good-prognosis MGCTs found that three cycles of bleomycin, etoposide and cisplatin led to a noninferior progression-free survival compared with four cycles.<sup>9,10</sup> One trial also found that administration of chemotherapy over 3 days per cycle was noninferior to administration over 5 days per cycle.<sup>9</sup> However, regimens for adult testicular tumors administered bleomycin once per week (BEP), whereas pediatric protocols delivered bleomycin once every 3 weeks (PEb) because of concerns about the enhanced risk of pulmonary toxicity in young children. Using three cycles of PEb, with its reduced frequency and cumulative dose of bleomycin, had never been studied in children.

The primary objective of this prospective, phase 3, single-arm trial (AGCT0132) was to determine whether a 4-year EFS (EFS<sub>4</sub>) rate of 92% could be maintained with a reduction in chemotherapy from four to three cycles of PEb and a compression of chemotherapy from 5 days to 3 days per cycle.

## PATIENTS AND METHODS

### Eligibility Criteria

Eligible patients included patients with extracranial MGCT containing yolk sac tumor, embryonal carcinoma, or choriocarcinoma. Mixed germ cell tumors and teratomas were eligible if they contained one of these histologies. Patients with pure teratomas, seminomas, or dysgerminomas, and those with a non-germ cell malignant component (eg, sarcomas) were excluded. Histology was confirmed by central pathology review. Patients with ovarian and extragonadal tumors were  $\leq 21$  years old and patients with testicular tumors were  $\leq 15$  years old at diagnosis. The IR group included patients with Children's Oncology Group (COG) stage<sup>11</sup> II-IV testicular, COG II-III ovarian, or COG I-II extragonadal tumors, and patients with stage I ovarian or testicular tumors who had recurrence of disease on surveillance after surgery alone. Results of the low-risk stratum<sup>12,13</sup> and the concurrent high-risk trial<sup>14</sup> have been reported.

The study was approved by the human investigations committees at participating institutions, conducted in accord with an assurance filed with and approved by the Department of Health and Human Services, and registered at [ClinicalTrials.gov](http://ClinicalTrials.gov) (identifier: NCT00053352).

### Study Design

All patients had an initial resection or biopsy of their tumors following specific protocol guidelines.<sup>12,15</sup> Induction chemotherapy consisted of three cycles of "compressed" PEb (cisplatin 33.3 mg/m<sup>2</sup>/d on days 1 to 3, etoposide 167 mg/m<sup>2</sup>/d on days 1 to 3, and bleomycin 15 units/m<sup>2</sup> [maximum 30 units] on day 1). Granulocyte colony-stimulating factor was only recommended in subsequent cycles if neutropenia (neutrophil count  $\leq 500/\mu\text{L}$ ) was observed. Cycles were repeated every 3 weeks contingent on neutrophil and platelet recovery. Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 3.0 (before August 2011) or 4.0 (after August 2011).<sup>16</sup>

After three cycles of compressed PEb, an evaluation of response was conducted with serum tumor markers and radiologic imaging. Second-look surgery was recommended for patients with a residual mass. A complete response was defined as normalization of tumor markers (to within five times the upper limit of the institutional normal, to allow for a low-level plateau)<sup>17,18</sup> with either no radiologic evidence of disease or a residual mass with no viable malignant tumor. Patients who achieved a complete response after three cycles received no further chemotherapy.

Patients who achieved a partial response were to receive three additional cycles of compressed PEb as consolidation. Patients with no response or progressive disease discontinued protocol therapy.

### Statistical Analysis

EFS was defined as the time from enrollment until disease progression, second malignant neoplasm (SMN), death, or last patient contact, whichever occurred first. Overall survival (OS) was defined as the time from enrollment until death or last patient contact. The survivor functions for EFS and OS were estimated by the Kaplan-Meier method.<sup>19</sup>

The IR arm was designed to accrue 180 patients over 6 years with at least 1 year of follow-up after the last enrollment. The estimated survival curve was to be compared with a piecewise exponential failure model with a failure rate in the first year of 0.07, in the second year of 0.013, in the third year of 0.0044, and zero thereafter. This was derived from fitting a piecewise exponential model with cure to comparable data from INT-0097 and INT-0106. This model has an EFS<sub>4</sub> rate of 92%. The Woolson one-sample log-rank test<sup>20</sup> was used to assess whether patients in AGCT0132 were at significantly increased risk for an EFS event compared with the hypothesized failure model. A one-sided test with  $P \leq .10$  at the time of final analysis indicated a significant departure from the target EFS model. A  $P$  value of .10 was used to be consistent with the COG practice of using a liberal type I error rate for therapeutic changes that were considered reductions in therapy intensity. The design had 80% power to detect a decrease in the 3-year EFS rate from 92% to 81%. Interim monitoring of risk of events was performed using the method of Lan and DeMets<sup>21</sup> annually with a spending function that was linear in information time.

The log-rank test<sup>19</sup> was used to compare the risk of EFS events between groups defined by prognostic factors. As a post hoc analysis, the results of this trial were compared with the previous intergroup studies<sup>2,3</sup> that used four cycles of standard-dose PEb. These historical data had been consolidated in the Malignant Germ Cell Tumors International Collaborative database.<sup>1</sup> The cohort assembled for the comparison included children with the same stage, site, histologic inclusion criteria, and chemotherapy doses per cycle as patients in this study. The log-rank test<sup>19</sup> was used to compare the risk of EFS events between the two cohorts, with  $P \leq .10$  considered statistically significant.

## RESULTS

The IR arm of AGCT0132 was opened to all member institutions in November 2003. Enrollment was stopped in July 2011 because there was evidence that the EFS<sub>4</sub> was  $< 92\%$ . Data current to March 2015 were used for AGCT0132 in this analysis.

The IR arm enrolled 210 patients (Fig 1). Of these, 181 eligible patients were classified as intermediate risk at diagnosis, and 29 patients were transferred from the low-risk (LR) arm to the IR arm because of tumor recurrence after surgery and observation. All 210 patients received induction chemotherapy, and 20 patients (9.5%) additionally received consolidation chemotherapy.

The characteristics of patients are summarized in Table 1, stratified by age 11 years. Age 11 years was used because this cutoff was found to be the most prognostically significant in analyses of Malignant Germ Cell Tumors International Collaborative data.<sup>1</sup> Furthermore, the median age of patients in this trial was 11 years. The majority of patients (71%) were female, reflecting the eligibility criteria, which included boys to age 15 years and girls to age 21 years. The most common tumor site was ovary (59%), followed by testes (22%) and extragonadal (19%). The most prevalent histology was mixed MGCT (39%), followed by pure yolk sac tumor (28%).  $\alpha$ -Fetoprotein was elevated in 196 (93%) and  $\beta$ -human

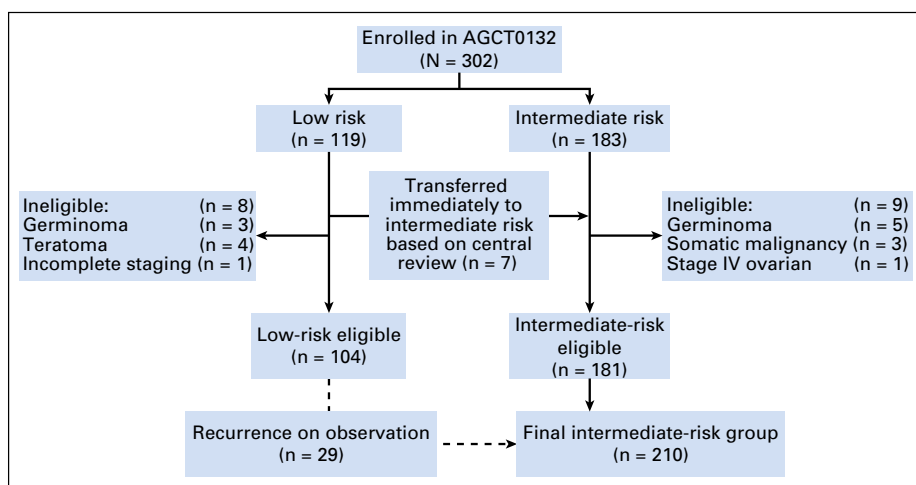


Fig 1. Flow of patients through the low-risk and intermediate-risk arms of the study.

chorionic gonadotropin in 52 patients (25%) relative to institutional age-appropriate normal values.

The trial included 14 patients with stage I extragonadal tumors (6.7%) and 13 patients with stage IV testes tumors (6.2%). The IR definition excluded all other patients with stage I and stage IV

disease. Hence, the majority of patients were categorized as having stage II (41%) or stage III (32%) disease. The 29 patients (14%) transferred from the LR to the IR arm were classified as having unstaged disease because their disease stage at the time of transfer was not collected on this protocol.

Table 1. Patient Characteristics

Characteristic	All Patients (N = 210)		Age at Enrollment			
	N	%	< 11 years (n = 93)		≥ 11 years (n = 117)	
	N	%	N	%	N	%
Sex						
Male	62	29.5	33	35.5	29	24.8
Female	148	70.5	60	64.5	88	75.2
Race						
White	138	65.7	61	65.6	77	65.8
Black	25	11.9	9	9.7	16	13.6
Asian	15	7.1	6	6.5	9	7.7
Other	18	8.6	9	9.7	9	7.7
Unknown	14	6.7	8	8.6	6	5.1
Site						
Testes	47	22.4	23	24.7	24	20.5
Ovary	124	59.1	37	39.8	87	74.4
Extragonadal	39	18.5	33	35.5	6	5.1
Stage						
I (extragonadal only)	14	6.7	10	10.8	4	3.4
II	86	40.9	41	44.1	45	38.4
III	68	32.4	25	26.9	43	36.8
IV (testicular only)	13	6.2	2	2.1	11	9.4
Unstaged (LR to IR)	29	13.8	15	16.1	14	12.0
α-fetoprotein (ng/mL) elevated at diagnosis	196	93.3	85	91.4	111	94.9
Histology						
YST	59	28.1	38	40.9	21	17.9
YST plus MT	28	13.3	17	18.2	11	9.4
YST plus IT	14	6.7	4	4.3	10	8.5
YST plus germinoma	8	3.8	2	2.1	6	5.1
Embryonal carcinoma	0	0	0	0	0	0
Choriocarcinoma	0	0	0	0	0	0
IT*	3	1.4	2	2.1	1	0.9
Germinoma*	1	0.5	0	0	1	0.9
Mixed MGCT	82	39.0	26	27.9	56	47.9
Unknown	16	7.6	4	4.3	11	9.4

Abbreviations: IR, intermediate risk; IT, immature teratoma; LR, low risk; MGCT, malignant germ cell tumor; MT, mature teratoma; YST, yolk sac tumor.

\*Histology is based on central review. Three patients with immature teratoma and one patient with germinoma were considered eligible based on institutional pathology reviews that observed malignant histology.

The EFS<sub>4</sub> rate for the 210 children in the IR arm was 89% (95% confidence interval [CI], 83% to 92%), and the 4-year OS rate was 97% (95% CI, 93% to 99%; Fig 2). The median time from enrollment to last contact for patients who had not experienced an event was 63 months. There were 23 events, of which 21 were tumor recurrences and two were SMNs. The latest recurrence occurred 1.43 years from the start of protocol therapy. Six patients died of recurrent disease. Of the two patients who developed SMNs, one developed a therapy-related acute myelogenous leukemia 2.3 years after enrollment, and the other developed a lymphangiosarcoma in the peritoneum 7 years after enrollment. The latter patient died of the SMN. There were no treatment-related or infectious deaths. The 4-year postevent survival rate was 66.8% (95% CI, 41.8% to 83.0%). Data on the type of second-line therapy used after recurrence were not available.

The observed value of the Woolson test statistic was 1.93, which is associated with a one-sided *P* value of .08. Because the level for statistical significance for this comparison was set at *P* ≤ .10, the observed EFS rate was significantly less than that expected by the hypothetical model.

We examined the effect on EFS of various potential prognostic factors (Table 2). EFS was not associated with an initial α-fetoprotein level (*P* = .50). The EFS rate estimate was higher for children under 11 years of age (93%) compared with children 11 years of age or older (85%), but the difference was not statistically significant (*P* = .14). The EFS rate estimate was higher for children transferred from the LR arm (97%) compared with those directly enrolled in the IR arm (87%), but the difference did not reach statistical significance (*P* = .13). Last, EFS rate was significantly affected by stage (*P* < .001), with the EFS<sub>4</sub> rate declining with higher stages (stage I, 100%; stage II, 92%; stage III, 85%, and stage IV, 54%). Although EFS was also significantly affected by site (*P* = .04), this was a function of the inclusion criteria that restricted certain sites to lower stages. Stage I tumors included only the extragonadal site and stage IV tumors included only the testes site. Of note, among the

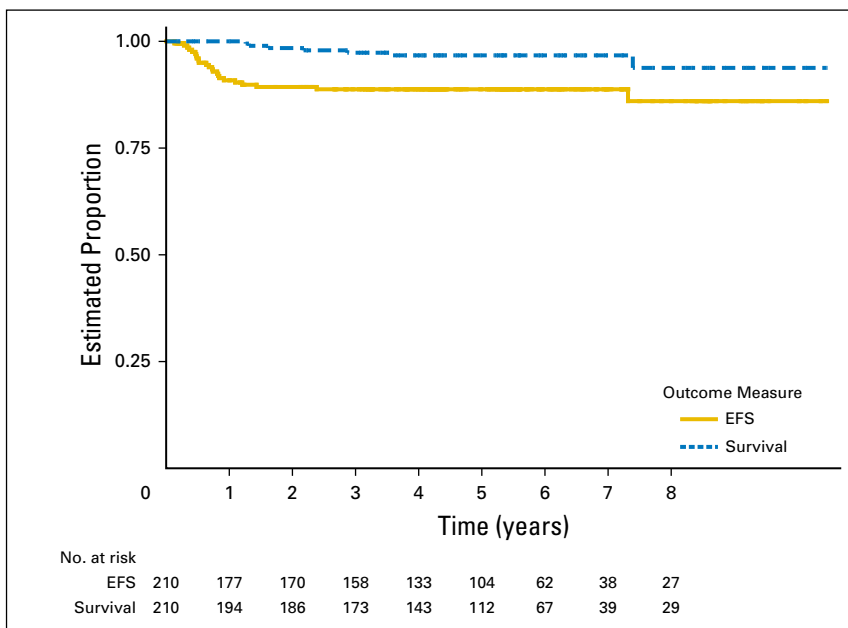
39 children with stage I or II extragonadal tumors, the EFS<sub>4</sub> rate was 100%.

In a secondary post hoc analysis, we compared the results achieved for the 181 patients with newly diagnosed IR tumors treated with three cycles of PEb ± consolidation on this trial (3PEb) with those of a matched cohort of patients treated on prior COG studies<sup>2,3</sup> with four cycles of PEb ± consolidation (4PEb; Appendix Table A1, online only). Data current to March 2006 were used for the patients enrolled in INT-0097 or INT-0106. As shown in Table 2, patients with stage I and stage II tumors had similar outcomes with either 3PEb or 4PEb. However, patients with stage III and stage IV tumors had a significantly lower EFS<sub>4</sub> rate with 3PEb. The EFS<sub>4</sub> rate for patients with stage III tumors was 85% on 3PEb therapy compared with 96% for patients receiving 4PEb therapy (*P* = .13). The EFS<sub>4</sub> rate for patients with stage IV tumors (testes site only) was 54% with 3PEb, compared with 90% for patients receiving 4PEb (*P* = .01).

The frequencies of grade 3 and grade 4 toxicities are shown in Table 3. Of note, neutropenia was observed in 50% of patients during induction in this trial, compared with 23% in INT-0106<sup>2</sup> and 36% in INT-0097<sup>3</sup> among patients who received standard-dose PEb. Two patients experienced grade 3 or 4 hearing impairment. One patient experienced severe dyspnea.

## DISCUSSION

This study evaluated whether efficacy could be maintained if the standard regimen for pediatric germ cell tumors, PEb, was reduced from four cycles to three cycles and administered over 3 days instead of 5. The EFS<sub>4</sub> rate was less than expected in the 210 patients treated with three cycles compared with a hypothetical parametric model (*P* = .08). When compared with a historical control group with identical inclusion criteria treated with four cycles,<sup>2,3</sup> the 181 patients with newly diagnosed tumors in this trial again had a lower observed EFS<sub>4</sub> rate (observed, 87%; control



**Fig 2.** EFS (event-free survival) and overall survival probability for 210 patients enrolled in the intermediate-risk arm of AGCT0132.

**Table 2.** Outcomes According to Patient Characteristics and Comparison With Historical Control

Characteristic	3PEb (AGCT0132)		4PEb (INT Studies)		Log-Rank <i>P</i> (3PEb v 4PEb)	HR 3PEb v 4PEb* (95% CI)
	No. of Patients	EFS <sub>4</sub> (95% CI)	HR (95% CI)	No. of Patients		
Overall	210	89 (83 to 92)	—	92	92 (85 to 96)	0.61 (0.26 to 1.42)
By initial risk group						
Newly diagnosed IR pts	181	87 (81 to 92)	Reference	92	92 (85 to 96)	0.54 (0.23 to 1.26)
LR to IR pts	29	97 (78 to 100)	0.24 (0.03 to 1.80)	N/A	—	—
<i>P</i>		.13				
Age (years)						
< 11	93	93 (85 to 97)	Reference	54	96 (86 to 99)	0.38 (0.08 to 1.87)
≥ 11	117	85 (77 to 91)	1.92 (0.79 to 4.67)	38	87 (71 to 94)	0.89 (0.33 to 2.44)
<i>P</i>		.14			.10	
Initial AFP level (ng/mL)						
< 10,000	150	90 (84 to 94)	Reference	61	92 (81 to 97)	0.71 (0.26 to 1.97)
≥ 10,000	60	85 (73 to 92)	1.34 (0.57 to 3.16)	25	92 (72 to 98)	0.53 (0.11 to 2.51)
Unknown	0	—	—	6	—	—
<i>P</i>		.50			.50	
Site						
Ovary	124	88 (80 to 92)	Reference	36	92 (76 to 97)	0.57 (0.16 to 1.99)
Testes	47	83 (68 to 91)	1.42 (0.60 to 3.35)	42	95 (82 to 99)	0.25 (0.05 to 1.20)
Extragenadal	39	100	—	14	86 (54 to 96)	—
<i>P</i>		.04			.48	
Stage†						
I (extragonadal only)	14	100	—	4	100	—
II	86	92 (84 to 97)	Reference	42	90 (77 to 96)	1.00 (0.29 to 3.47)
III	68	85 (73 to 92)	1.71 (0.64 to 4.58)	27	96 (77 to 99)	0.23 (0.03 to 1.84)
IV (testicular only)	13	54 (25 to 76)	2.53 (2.53 to 22.56)	19	90 (64 to 97)	0.18 (0.04 to 0.89)
<i>P</i>		< .001			.72	
Site, stage†						
Testes, II	9	89 (43 to 98)	—	15	100	.20
Testes, III	6	80 (20 to 97)	—	8	100	.21
Testes, IV	13	54 (25 to 76)	—	19	89 (64 to 97)	.02
Ovary, II	52	90 (77 to 96)	—	17	88 (61 to 97)	.80
Ovary, III	62	85 (73 to 92)	—	19	95 (68 to 99)	.29
Extragenadal, I	14	100	—	4	100	—
Extragenadal, II	25	100	—	10	80 (41 to 95)	.03

Abbreviations: —, not estimable; 3PEb, three cycles of cisplatin/etoposide/bleomycin; 4PEb, four cycles of cisplatin/etoposide/bleomycin; AFP,  $\alpha$ -fetoprotein; EFS, event-free survival; HR, hazard ratio; IR, intermediate risk; LR, low risk; N/A, not applicable; pts, patients.  
 \*Excludes 29 unstaged LR to IR patients.  
 †Hazard ratios comparing 3PEb v 4PEb use 3PEb as the reference group.



**Table 3.** Grade 3 and 4 Toxicities

Toxicity	During Induction (n = 210)		During Consolidation (n = 20)	
	No.	%	No.	%
Nausea	6	2.9	1	5.0
Vomiting	7	3.3	1	5.0
Oral mucositis	1	0.5	0	0
Anaphylaxis	3	1.4	0	0
Neutrophil count decreased	105	50.0	4	20.0
Febrile neutropenia	14	6.6	3	15.0
Anemia	15	7.1	1	5.0
Platelet count decreased	12	5.7	4	20.0
Hypokalemia	2	1.0	0	0
Hypomagnesemia	1	0.5	0	0
Acute kidney injury	1	0.5	0	0
Infections	28	13.3	1	5.0
Dyspnea	1	0.5	0	0
Hearing impairment	2	1.0	0	0

group, 92%), although the difference did not reach statistical significance ( $P = .15$ ). We thus recommend that four cycles should remain the standard treatment when PEb is used in the treatment of childhood MGCTs.

Some patient subgroups in this study had excellent EFS rates when treated with three cycles of PEb, including patients with stage I and II extragonadal tumors (EFS<sub>4</sub> rate, 100%) and those with stage I gonadal tumors transferred from the LR arm for subsequent recurrence after surgery alone (EFS<sub>4</sub> rate, 97%). These patients typically had minimal residual disease evidenced by microscopic positive margins or rising tumor markers; therefore, reduced therapy may have been sufficient to achieve remission. It may be argued that such patients could henceforth be treated with three cycles. However, these results should be considered hypothesis generating alone because this study was not powered for subgroup comparisons and should be validated by future research before being considered for standard practice. They may provide support for further refinements in risk stratification and selection of patients for reduced therapy in future trials.

Outcomes were significantly worse for patients with stage III gonadal tumors (EFS<sub>4</sub> rate, 85%) and stage IV testicular tumors (EFS<sub>4</sub> rate, 54%) compared with the historical control group. In reduction-of-therapy studies, a negative result allows conclusive delineation of the minimally sufficient treatment. Therefore, for patients with stage III or IV MGCTs, this study showed that treatment with three cycles of PEb is clearly insufficient and a minimum of four cycles of PEb are required.

In medical oncology, metastatic testicular germ cell tumors (defined as any disease outside of the testis, including adenopathy) is risk stratified using the International Germ Cell Consensus Classification Group (IGCCCG) system.<sup>22</sup> The standard treatment of men with good-risk metastatic disease is three cycles of BEP<sup>23</sup> (or four cycles of cisplatin and etoposide (PE) for men who cannot receive bleomycin). The standard treatment of men with IR or poor-risk metastatic disease is four cycles of BEP. An assessment of adult RCT evidence provides insight into why our trial failed to maintain efficacy after reduction to three cycles of PEb. In a trial of patients with good-risk testicular cancer who were randomly

allocated to 3BEP versus 4PEb, the EFS and OS were significantly inferior in the group receiving reduced bleomycin despite the use of an extra cycle.<sup>24</sup> Interpretation of this result is somewhat confounded by the fact that patients in the reduced bleomycin arm also received a reduced dose of etoposide per cycle (360 mg/m<sup>2</sup> instead of 500 mg/m<sup>2</sup>), although the cumulative dose of etoposide was similar on the two strategies (1,440 mg/m<sup>2</sup> and 1,500 mg/m<sup>2</sup>, respectively). In another RCT of adult men with testicular cancer comparing 3BEP with 4PE, there was no statistically significant difference in the 4-year EFS rate, although the trend favored 3BEP (91% v 86%;  $P = .135$ ).<sup>25</sup> Last, in a trial comparing 3BEP with 3PE, the 3-year failure-free survival rate was markedly inferior in the group receiving no bleomycin (86% v 69%;  $P = .01$ ).<sup>26</sup> The reasonable conclusion from all these studies is that the use of weekly bleomycin helps compensate for the reduction in the number of cycles to three, but when weekly bleomycin is not used, a minimum of four cycles is required.

The frequency of grade 3 and grade 4 toxicities in this trial were similar to those in previous intergroup trials,<sup>2,3</sup> with the exception of a higher observed rate of neutropenia. It is possible that the compression of chemotherapy from 5 days to 3 days resulted in the higher rate, possibly because of higher daily doses of chemotherapy. We thus recommend returning to 5-day PEb administration as standard practice. Only two children in this trial experienced grade 3 or 4 hearing impairment, compared with an incidence of moderate-severe ototoxicity of 10.5% in INT-0097.<sup>5</sup>

Our study had important limitations. First, as a single-arm study with a historical comparator, the attribution of effects was weaker than would be available from an RCT. We presented univariate analyses of known prognostic factors and did not adjust for possible confounders or interactions. As a rare tumor, the available sample size of children with MGCTs precluded us from designing this trial as an RCT. Another limitation was the heterogeneity of outcomes, indicating that the collecting of patients into a single risk group was imprecise. For example, we included all patients with stage IV testicular tumors into the IR group, whereas adult trials use the IGCCCG criteria to further discriminate these patients into three groups.<sup>22</sup> We did not collect information needed to accurately assign patients to IGCCCG risk groups. Because patients with stage IV testicular tumors had the lowest EFS, use of the IGCCCG grouping might have been beneficial, especially for adolescent patients.

We have recently developed a revised risk classification system<sup>1</sup> for pediatric MGCTs, using pooled outcome data from seven clinical trials, including this trial. Future studies of pediatric germ cell tumors will use the revised risk classification system to reduce heterogeneity within subgroups. An upcoming clinical trial, AGCT1531, will compare the EFS of a carboplatin-based regimen<sup>18</sup> versus that of a cisplatin-based regimen in a randomization. Patients older than 11 years will receive regimens containing weekly bleomycin. Biologic aims of the study will include assessing the utility of circulating microRNAs and identifying or validating genetic variants associated with an increased risk of platinum-associated ototoxicity.<sup>27</sup> Most importantly, the trial will represent a collaboration across the disciplines of pediatric, medical, and gynecologic oncology and across international borders. In addition to providing collective insights from across the field, this

collaboration will also allow accruing the sample size needed to design the study as an RCT.

In summary, the reduction in chemotherapy to three compressed cycles of PEB for children with IR MGCT resulted in an EFS rate that was less than targeted. Although some subgroups had excellent outcomes, this study was not powered for conclusive subgroup comparisons. Therefore, four cycles of PEB remain the current standard treatment of children with IR extracranial MGCTs.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org](http://jco.org).

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**Reduced and Compressed Cisplatin-Based Chemotherapy in Children and Adolescents With Intermediate-Risk Extracranial Malignant Germ Cell Tumors: A Report From the Children's Oncology Group**

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**Appendix****Table A1.** Chemotherapy Comparison for Four Cycles of Standard PEb compared With Three Cycles of Compressed PEb

Dosing Characteristic	Four-Cycle Standard PEb	Three-Cycle Compressed PEb	Comparison
Doses per cycle	Cisplatin 20 mg/m <sup>2</sup> per dose for 5 days Etoposide 100 mg/m <sup>2</sup> per dose for 5 days Bleomycin 15 units/m <sup>2</sup> per dose for 1 day (max., 30 units)	Cisplatin 33 mg/m <sup>2</sup> per dose for 3 days Etoposide 167 mg/m <sup>2</sup> per dose for 3 days Bleomycin 15 units/m <sup>2</sup> per dose for 1 day (max., 30 units)	Identical doses per cycle, given over fewer days on 3PEb therapy
Cumulative doses	Cisplatin 400 mg/m <sup>2</sup> Etoposide 2,000 mg/m <sup>2</sup> Bleomycin 60 units/m <sup>2</sup> (max., 120 units)	Cisplatin 300 mg/m <sup>2</sup> Etoposide 1,500 mg/m <sup>2</sup> Bleomycin 45 units/m <sup>2</sup> (max., 90 units)	25% lower cumulative doses given on 3PEb therapy
Days of chemotherapy administration, No.	20	9	55% fewer days of chemotherapy on 3PEb therapy

Abbreviations: 3PEb, three cycles of cisplatin, etoposide, and bleomycin; max, maximum, PEb, cisplatin, etoposide, and bleomycin.