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Randomized Comparison of Combination Chemotherapy With Etoposide, Bleomycin, and Either High-Dose or Standard-Dose Cisplatin in Children and Adolescents With High-Risk Malignant Germ Cell Tumors: A Pediatric Intergroup Study—Pediatric Oncology Group 9049 and Children's Cancer Group 8882

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ABSTRACT

Purpose
To determine in a randomized comparison whether combination chemotherapy with high-dose cisplatin (HDPEB) improves the event-free (EFS) and overall (OS) survival of children and adolescents with high-risk malignant germ cell tumors (MGCT) as compared with standard-dose cisplatin (PEB) and to compare the regimens' toxicity.

Patients and Methods
Between March 1990 and February 1996, 299 eligible patients with stage III and IV gonadal and extragonadal (all stages) MGCT were enrolled onto this Pediatric Oncology Group and Children's Cancer Group study. Chemotherapy included bleomycin 15 units/m^2 on day 1, etoposide 100 mg/m^2 on days 1 through 5, and either high-dose cisplatin 40 mg/m^2 on days 1 through 5 (HDPEB; n = 149) or standard-dose cisplatin 20 mg/m^2 on days 1 through 5 (PEB; n = 150). Patients were evaluated after four cycles of therapy, and those with residual disease underwent surgery. Those with malignant disease in resected specimen received two additional cycles of their assigned regimen.

Results
One hundred thirty-four eligible patients with advanced testicular (n = 60) or ovarian (n = 74) tumors and 165 with stage I to IV extragonadal tumors were enrolled. HDPEB treatment resulted in significantly improved 6-year EFS rate ± SE (89.6% ± 3.6% *v* 80.5% ± 4.8% for PEB; $P = .0284$). There was no significant difference in OS (HDPEB 91.7% ± 3.3% *v* PEB 86.0% ± 4.1%). Tumor-related deaths were more common after PEB (14 deaths *v* two deaths). Toxic deaths were more common with HDPEB (six deaths *v* one death). Other treatment-related toxicities were more common with HDPEB.

Conclusion
Combination chemotherapy with HDPEB significantly improves EFS for children with high-risk MGCT. The OS is similar in both regimens, and the significant toxicity associated with HDPEB limits its use.

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INTRODUCTION

Two-year survival for patients with malignant germ cell tumors (MGCT) rarely exceeded 20% before multiagent chemotherapy was introduced.[1-3] Cyclophosphamide-based therapy significantly improved the outcome for patients with localized MGCT, but not for those with advanced-stage disease.[4-6] Introducing cisplatin-based therapy in adults with testicular germ cell tumors dramatically improved their survival.[7]

Table 1. Staging of Testicular, Ovarian, and Extragonadal Tumors

Testicular	
I	Limited to testis, completely resected by high inguinal orchiectomy; no clinical, radiographic, or histologic evidence of disease beyond the testis; tumor markers normal after appropriate half-life decline; patients with normal or unknown markers at diagnosis must have negative ipsilateral retroperitoneal lymph node sampling to confirm stage I disease
II	Transcrotal orchiectomy; microscopic disease in scrotum or high in spermatic cord (< 5 cm from proximal end); retroperitoneal lymph node involvement (< 2 cm) and/or increased tumor markers after appropriate half-life decline
III	Tumor-positive retroperitoneal lymph node(s) > 2 cm diameter: no visceral or extra abdominal involvement
IV	Distant metastases that may include liver
Ovarian	
I	Limited to ovary, peritoneal washings negative for malignant cells; no clinical, radiologic, or histiologic evidence of disease beyond the ovaries (gliomatosis peritonei did not result in upstaging); tumor markers negative after appropriate half-life decline
II	Microscopic residual or positive lymph nodes (< 2 cm); peritoneal washings negative for malignant cells (gliomatosis peritonei did not result in upstaging); tumor markers positive or negative
III	Gross residual or biopsy only, tumor-positive lymph node(s) > 2 cm diameter; contiguous visceral involvement (omentum, intestine, bladder): peritoneal washings positive for malignant cells
IV	Distant metastases that may include liver
Extragonadal	
I	Complete resection at any site, coccygectomy included as management for sacrococcygeal site, negative tumor margins
II	Microscopic residual; lymph nodes negative
III	Gross residual or biopsy only; regional lymph nodes negative or positive
IV	Distant metastases that may include liver

Eleven of 13 patients demonstrated sustained complete responses when cisplatin was combined with bleomycin and either vinblastine or etoposide in a small pediatric trial.[8] However, concerns regarding the cumulative toxicity of regimens incorporating both cisplatin and bleomycin hindered their use in pediatric patients.[9-13] Based on these concerns, these three drugs generally were combined with cyclophosphamide-based regimens to limit total drug exposure.[14,15] Several pediatric studies suggested that the use of high-dose cisplatin and etoposide was associated with acceptable toxicity.[16,17] Additionally, several trials for adults with testicular tumors suggested that high-dose cisplatin was more effective than standard-dose cisplatin.[18-21] However, a subsequent randomized study in adults with testicular tumors demonstrated that cisplatin dose-intensification did not affect the outcome of patients with advanced testicular tumors and significantly increased toxicity.[22] Because of that trial, the standard treatment for adults with germ cell tumors has become standard-dose cisplatin combined with bleomycin and either vinblastine or etoposide.[23-29]

Pediatric germ cell tumors differ from those in adults in histology,[30-32] primary sites, cytogenetics,[33,34] and age distribution.[30] The significant differences between adult and pediatric germ cell tumor patients prompted the Pediatric Oncology Group and the Children's Cancer Group (CCG) to design a randomized trial testing the effectiveness of cisplatin dose-intensification on the outcome of patients with high-risk tumors as defined by 1990 criteria. Additional objectives included correlating initial tumor marker levels (alpha fetoprotein [AFP], beta-human chorionic gonadotropin [βHCG], and lactate dehydrogenase [LDH]) with outcome, determining patterns of relapse, and comparing toxicities between the two regimens.

PATIENTS AND METHODS

Eligibility Criteria

This randomized Intergroup study for extracranial MGCT was open to enrollment from March 1990 through February 1996. Eligibility requirements included age $\leq$ 21 years, stage III to IV MGCT of gonadal origin, or stage I to IV MGCT originating at extragonadal sites (Table 1). Additional requirements included no prior therapy other than surgical resection or biopsy. Patients with stage III or IV malignant recurrence from a previously resected stage I testicular tumor were eligible, as were children with malignant recurrence from a previously resected immature or benign teratoma. Histologically, the presence of malignant elements within the tumor was required, including yolk sac carcinoma (endodermal sinus tumor), embryonal carcinoma (EC), choriocarcinoma, or dysgerminoma (seminoma). Patients with teratoma or immature teratoma without malignant elements were excluded. Histology was confirmed by central pathology review.

Surgical Staging Procedures

If possible, all gonadal MGCT were completely excised. Biopsy was required when surgical resection was not possible. Patients with localized gonadal MGCT (stages I and II) were ineligible. In general, testicular tumors were managed with radical inguinal orchiectomy including high ligation of the spermatic cord. Retroperitoneal lymph node sampling with removal of grossly suspicious nodes was only performed when imaging abnormalities were present. Retroperitoneal lymph node dissection or sampling was otherwise not recommended.

The goal of initial surgery in patients with ovarian MGCT was to evaluate the extent of disease (staging) and resect all tumor if feasible while sparing uninvolved reproductive organs. Ascitic fluid was collected for cytologic examination; in the absence of

ascites, peritoneal washings for cytology were obtained. Pelvic viscera, pelvic and retroperitoneal lymph nodes, omentum, peritoneal surfaces, liver surface, and subphrenic spaces were also inspected and peritoneal nodules were biopsied or resected. When one ovary was involved, tumor was removed by unilateral oophorectomy; when both ovaries were involved, bilateral oophorectomy was recommended with preservation of fallopian tubes and uterus. Surgical guidelines included bivalved examination of the normal-appearing contralateral ovary, complete omentectomy, and bilateral retroperitoneal lymph node sampling of internal iliac, common iliac, low para-aortic, and perirenal chains, with debulking of all retroperitoneal lymphatic spread and peritoneal metastases.

Surgical guidelines for the initial management of extragonadal MGCT depended on the primary tumor site. Complete resection with coccygectomy through a posterior transsacral approach was recommended for presacral or sacrococcygeal tumors. Laparotomy was indicated for potentially resectable tumors with intrapelvic extension. Lateral thoracotomy or median sternotomy was recommended when mediastinal MGCT resection was possible. Resection of thymus or pericardium was done to assure adequate tumor-free margins with regional lymph node sampling. Initial biopsy was recommended in bulky extragonadal presentations, reserving definitive resection until after four chemotherapy cycles.

Pretreatment Evaluation

Standard requirements at study entry included medical history, physical examination (with documentation of congenital anomalies), CBC count with differential, absolute neutrophil count greater than 750/μL and platelet count greater than 100,000/dL, urinalysis, tumor markers (AFP, βHCG, and LDH), electrolytes, creatinine, bilirubin less than 1.5 mg/dL, ALT, alkaline phosphatase, total protein, albumin, phosphorus, magnesium, calcium, and either radionuclide glomerular filtration rate or creatinine clearance. Pulmonary function studies with diffusing capacity (if age permitted) or cutaneous oxygen saturation and audiogram or brainstem auditory evoked responses were also required. Diagnostic imaging evaluation included chest x-ray, chest/abdomen/pelvis computed tomography or magnetic resonance imaging, and bone scan. Constitutional karyotype was required for patients entered at CCG institutions.

Toxicity

Renal toxicity was monitored by measurement of blood urea nitrogen and creatinine before each chemotherapy course and at completion of chemotherapy. Glomular filtration rate or creatinine clearance was required before therapy and at the completion of four and six chemotherapy cycles (if two additional cycles were necessary). If abnormal, these studies were repeated at 12, 24, and 36 months. Pulmonary function tests (if age permitted) or pulse oximetry and audiograms were monitored before treatment and at the completion of therapy. Institutions were required to notify the statistical center if hearing aids were needed. Submission of audiograms was suggested but not required. All toxicity results were graded 1 to 4 according to National Cancer Institute guidelines by the treating institution. Graded toxicity scores were reported to statistical center.

Chemotherapy

Written informed consent was obtained from all patients or their guardians under the guidelines of the individual institutional review boards and in compliance with the Declaration of Helsinki. Patients were first stratified according to stage, site, and presence of metastases. Patients were randomized one to one so that each stratum was balanced for age, tumor marker, and treatment. Treatment included bleomycin 15 units/m^2 on day 1 and etoposide 100 mg/m^2 on days 1 through 5 combined with either high-dose cisplatin 40 mg/m^2 on days 1 through 5 (high-dose cisplatin [HDPEB]; n = 149) or standard cisplatin 20 mg/m^2 on days 1 through 5 (standard-dose cisplatin [PEB]; n = 150). Treatment was repeated at 21-day intervals for four cycles. Chemotherapy doses for infants younger than 12 months of age were calculated by body weight: cisplatin (0.7 mg/kg/dose or 1.3 mg/kg/dose), etoposide 3 mg/kg/dose, and bleomycin 0.5 mg/kg/dose. Vigorous pre- and postchemotherapy hydration with mannitol and continuous oral magnesium supplementation were recommended. The use of granulocyte colony-stimulating factor was left to the treating physician's discretion.

Treatment at Week 12

Patients were evaluated with diagnostic imaging and marker levels after four chemotherapy cycles. Response was determined by the treating institution. Patients with normal serum tumor markers and resolution of all imaging abnormalities were considered complete responders (CR) and received no further chemotherapy. Patients with a partial response (PR) based on residual imaging abnormalities ($>$ 50% decrease) at either the primary or metastatic sites and/or declining markers underwent attempted resection. Surgery was also done for patients with less than 50% decrease in size on imaging studies and unchanged or persistent marker elevation (classified as no response). Postsurgical treatment depended on histologic findings. If the resected specimen showed no malignant disease (only mature or immature teratoma), patients were considered to have a pathologic CR and received no further therapy. Patients with malignant residual disease in the resected specimen were considered pathologic PR and received two additional cycles of their assigned regimen. Patients with more than 25% increase in size, new lesions, or increasing tumor markers were classified as progressive disease (PD). Patients with PD were taken off study.

Study Design and Statistical Analysis

Outcome analyses were performed for event-free survival (EFS), where the time to an event was defined as the time from study entry until the first occurrence of PD, relapse, second malignancy, death, or until the last reported contact if none of these occurred. For patient overall survival (OS), survival time was defined as the time from study entry until death or until the last reported contact. Survival estimates were obtained using the Kaplan-Meier method.[35] CIs (95%) for survival rates were calculated on the basis of the SE of the log transformed cumulative hazard function as described in Kalbfleisch and Prentice.[36] Differences in survival curves were tested using a one-sided log-rank test. Prognostic factors were tested using a multivariable Cox proportional hazards model. The difference in the proportions of responders was tested using Fisher's exact test. All tests, including those used to identify factors of prognostic importance, were performed at a significance level of .05.

RESULTS

Overall Results

Between March 1990 and February 1996, 317 patients were enrolled on this Intergroup study. We describe 299

Table 2. Clinical and Pathologic Characteristics of Children With High-Risk MGCT

Characteristic	Testicular (n = 60)		Ovarian (n = 74)		Extragonadal (n = 165)		Overall (N = 299)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Sex and age								
Males								
< 15 years	29	48.3	NA		42	75.0	71	61.2
≥ 15 years	31	51.7	NA		14	25.0	45	38.3
All ages	60	100	NA		56	100	116	100
Females								
< 10 years	NA		24	32.4	106	97.3	130	71.0
≥ 10 years	NA		50	67.6	3	2.7	53	29.0
All ages	NA		74	100	109	100	183	100
Stage								
I-II	NA		NA		30	18.2	30	10
III	17	28.3	58	78.4	61	37.0	136	45.5
IV	43	71.7	16	21.6	74	44.8	133	44.5
Histology*								
YST	25	42.4	28	38.9	138	83.6	191	64.5
Mixed	28	47.4	17	23.6	15	9.1	60	20.3
Germinoma	2	3.4	25	34.7	4	2.4	31	10.5
Choriocarcinoma	1	1.8	1	1.4	7	4.3	9	3.0
Other	3	5.0	1	1.4	1	0.6	5	1.7
Unknown	1		2		0		3	
AFP at diagnosis, ng/mL								
< 1,000	33	55.9	36	51.4	32	19.8	101	34.7
1,000-10,000	14	23.7	16	22.9	31	19.1	61	21.0
> 10,000	12	20.3	18	25.7	99	61.1	129	44.3
Unknown	1		4		3		8	
βHCG at diagnosis, mU/mL								
< 5,000	40	81.6	58	95.1	129	97.7	227	93.8
≥ 5,000	9	18.4	3	4.9	3	2.3	15	6.2
Unknown	11		13		33		57	
Treatment								
HDPEB	30	50.0	37	50.0	82	49.7	149	49.8
PEB	30	50.0	37	50.0	83	50.3	150	50.2
Overall	60	20.1	74	24.8	165	55.2	299	100

NOTE. Unknown data not included in percentages.
Abbreviations: MGCT, malignant germ cell tumor; NA, not applicable; YST, yolk sac tumor; AFP, alpha fetoprotein; βHCG, beta-human chorionic gonadotropin; HDPEB, high-dose cisplatin; PEB, standard-dose cisplatin.
*Histology: other, testes (two pure EC, one malignant teratoma); ovarian (teratocarcinoma); EG (teratoma with neuroepithelial elements); unknown, slides were not reviewed centrally.

who were eligible in this report. Eighteen ineligible patients were excluded because of incorrect histology (n = 8), lack of institutional review board approval or informed consent (n = 5), incorrect stage (n = 2), refusal of randomization (n = 2), or prior therapy (n = 1). Table 2 lists the clinical and pathologic characteristics and clinical response for all patients. The response rates after 12 weeks (four cycles) of chemotherapy are shown in Table 3. The CR/PR rate was 96% in each treatment group. The CR rate was 58% in the HDPEB group and 51% in the PEB group. This difference was not statistically significant ($P = .1519$).

The overall 6-year (± SE) EFS was 85.0% ± 3.0% and OS was 88.8% ± 2.6%. There was a statistically significant EFS advantage for patients receiving HDPEB compared with those receiving PEB (6-year EFS, 89.6% ± 3.6% *v* 80.5% ± 4.8%, respectively; $P = .0284$). There was no statistical difference in OS between HDPEB and PEB (6-year OS, 91.7% ± 3.3% *v* 86% ± 4.1%; $P = .1756$). Figure 1 illustrates the EFS by randomized group, and Table 4 illustrates the EFS and OS according to age, primary tumor site, and stage.

Prognostic Factors

In the multivariable Cox model for EFS (n = 232 with complete data), three unfavorable prognostic factors were identified: primary mediastinal site ($P = .0186$), AFP greater than 10,000 ng/mL ($P = .0390$), and βHCG greater than 5,000 mU/mL ($P = .0285$). In the Cox model for OS (n = 232), only primary mediastinal site ($P = .0017$) and AFP greater than 10,000 mg/mL ($P = .0411$) were

Table 3. Response Rate to Induction Treatment at Week 12

	Testicular (n = 60)				Ovarian (n = 74)				Extragonadal (n = 165)				Overall (N = 299)			
	HDPEB		PEB		HDPEB		PEB		HDPEB		PEB		HDPEB		PEB	
Response	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
CR	16	53.3	16	55.2	28	82.4	28	77.8	38	49.5	30	38.0	82	58.2	74	51.4
PR	12	40.0	12	41.4	6	17.7	6	16.7	36	46.8	46	58.2	54	38.3	64	44.4
NR	1	3.3	1	3.5	0	0	2	5.6	2	2.6	1	1.3	3	2.1	4	2.8
PD	1	3.3	0	0	0	0	0	0	1	1.3	2	2.5	2	1.4	2	1.4
Unknown*	0		1		3		1		5		4		8		6	
Total	30	100	29	100	34	100	36	100	77	100	79	100	141	100	144	100

NOTE. CR and PR rate at week 12 based on imaging and tumor marker studies.
Abbreviations: HDPEB, high-dose cisplatin; PEB, standard-dose cisplatin; CR, complete response; PR, partial response; NR, no response; PD, progressive disease.
*Patients with unknown responses are not included in percentages, totals, or Fisher's exact test.

predictive of death. Metastatic site and LDH were investigated and were not prognostically important.

Testicular Tumors

Sixty patients with stage III to IV testicular MGCT were enrolled. Forty-four patients were newly diagnosed, whereas 16 patients had recurrent disease after complete resection of a clinical stage I tumor. The age distribution was 0.6 to 19.0 years (median, 16.0 years) for newly diagnosed patients and 0.8 to 19.3 years (median, 3.1 years) for patients with recurrent disease. The predominant histologies included mixed MGCT in 25 (57%) of 44 newly diagnosed patients, whereas pure yolk sac carcinoma predominated in former stage I testicular MGCT patients with relapsed disease (11 [78%] of 14 patients). Pure yolk sac tumor was more common in male patients younger than 15 years of age (23 [82%] of 28 patients), whereas mixed MGCT predominated in male patients ≥ 15 years of age (24 [80%] of 30 patients). EC was seen with yolk sac tumor in mixed MGCT. Only two patients, ages 14 and 15 years, were classified as having pure EC. There were two patients with pure germinoma, ages 16 and 18 years.

The responses, as defined by imaging and tumor marker studies, to four chemotherapy cycles at week 12, are shown in Table 3. Response rates were quite similar in both treatment arms ($P = .875$). The PR rate at week 12 was not

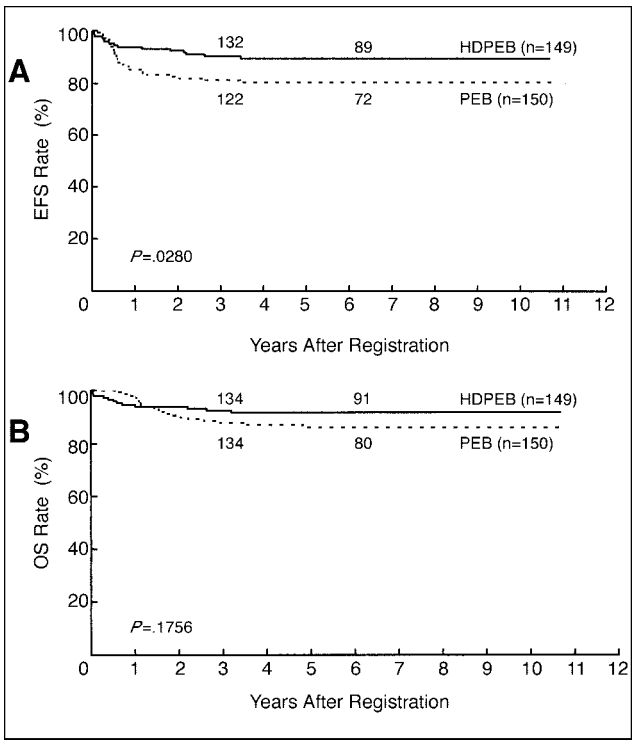

Fig 1. (A) Event-free survival (EFS) curves by treatment group: high-dose cisplatin (HDPEB, n = 149) versus standard-dose cisplatin (PEB, n = 150; $P = .0284$). (B) Overall survival (OS) curves by treatment group: High-dose cisplatin (HDPEB, n = 149) versus standard-dose cisplatin (PEB, n = 150; $P = .1756$).

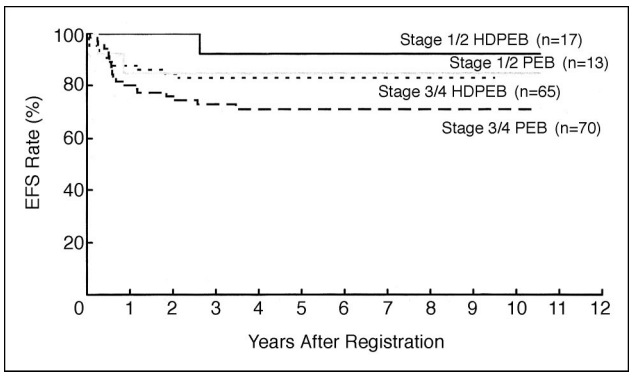

Fig 2. Event-free survival (EFS) curves for extragonadal malignant germ cell tumors (MGCT) by stage and treatment group: Stage I and II patients treated with high-dose cisplatin (HDPEB, n = 17) versus stage I and II patients treated with standard-dose cisplatin (PEB, n = 13) versus stage III and IV patients treated with HDPEB (n = 65) versus stage III and IV patients treated with PEB (n = 70).

Table 4. Event-Free Survival and Survival Rates by Patient Characteristics

	No. of Patients	6-Year EFS Rate		6-Year OS Rate	
		%	SE	%	SE
Treatment					
HDPEB	149	89.6	3.6	91.7	3.3
PEB	150	80.5	4.8	86.0	4.1
Tumor type					
Testicular	60	89.8	5.3	93.3	4.4
Ovarian	74	94.5	3.7	97.3	2.6
Extragonadal	165	79.0	4.9	83.4	4.4
Sex and age					
Males					
< 15 years	71	88.5	5.2	89.3	5.0
≥ 15 years	45	70.2	10.2	75.4	9.7
All ages	116	81.4	5.1	83.8	4.8
Females					
< 10 years	130	82.9	5.1	89.7	4.0
≥ 10 years	53	98.1	2.7	98.1	2.7
All ages	183	87.2	3.7	92.1	3.0
Tumor type and stage					
Testicular stage III	17	94.1	6.9	100	
Testicular stage IV	43	88.3	7.1	90.6	6.4
Ovarian stage III	58	96.6	3.5	98.3	2.5
Ovarian stage IV	16	86.7	10.5	93.3	7.6
Extragonadal stage I-II	30	89.4	7.0	92.8	5.9
Extragonadal stage III	61	75.1	9.4	80.9	8.3
Extragonadal stage IV	74	78.0	8.0	81.5	7.3
Tumor type, stage, and age, years					
Testicular stage III < 15	11	100		100	
Testicular stage III ≥ 15	6	83.3	24.1	100	
Testicular stage IV < 15	18	94.4	7.9	100	
Testicular stage IV ≥ 15	25	84.0	10.6	84.0	10.6
Ovarian stage III < 10	18	94.4	8.4	100	
Ovarian stage III ≥ 10	40	97.5	3.5	97.5	3.5
Ovarian stage IV < 10	6	66.7	22.2	83.3	17.0
Ovarian stage IV ≥ 10	10	100		100	
Overall	299	85.0	3.0	88.8	2.6

Abbreviations: EFS, event-free survival; OS, overall survival; HDPEB, high-dose cisplatin; PEB, standard-dose cisplatin.

correlated with histology. Seven patients with pure yolk sac tumor (n = 4), pure EC (n = 1), and pure germinoma (n = 2) were classified as PR by imaging and tumor marker studies at week 12. Six patients were found to have achieved CR after second-look surgery showed no viable residual tumor. One patient with pure germinoma had viable tumor in specimen from second-look surgery. He received two additional cycles of PEB and remains in CR. Male patients older than 15 years had a high PR rate similar to that of patients with extragonadal primaries, although most patients achieved CR after second-look surgery. The 6-year EFS and OS rates for patients with testicular primaries who were younger than 15 years, ≥ 15 years of age, and overall are shown in Table 4. Five of six treatment failures occurred in boys older than 15 years with mixed MCGT. Four patients died of tumor progression. Five stage IV patients had recurrence or progression in distal abdominal lymph nodes or the initial metastatic site, the lungs.

Ovarian Tumors

Table 2 outlines the clinical and pathologic characteristics of 74 patients with stage III to IV ovarian MGCTs. These patients had a median age of 11.9 years (range, 1.4 to 20.1 years). The response of patients with ovarian tumors at week 12 is shown in Table 3, and both treatment arms are similar ($P = .2609$). Two patients randomized to PEB (two of 36 patients) did not respond, compared with no patients treated with HDPEB (0 of 34 patients). The 6-year EFS and OS rates for patients younger than 10 years, ≥ 10 years of age, and overall are shown in Table 4. Four events (days 154 to 265 postregistration) were caused by PD or tumor recurrence. Two occurred in contralateral ovary, whereas two patients developed pulmonary metastases.

Extragonadal Tumors

Clinical and pathologic characteristics for the 165 children and adolescents with MGCT of extragonadal sites are

Table 5. Grade 3 and 4 Toxicities by Treatment Arm

	HDPEB (n = 148)		PEB (n = 147)	
	No. of Patients	%	No. of Patients	%
Neutropenia	57	39	53	36
Thrombocytopenia	20	14	8	5
Infection	30	20	25	17
Nausea and vomiting	34	23	11	7
Diarrhea	5	3	4	3
Reduced creatinine clearance	10	7	0	0
Renal magnesium loss	19	13	0	0
Renal potassium loss	13	9	2	1
Pulmonary	5	3	6	4
Subjective hearing loss	5	3	0	0
Objective hearing loss	21	14	0	0

Abbreviations: HDPEB, high-dose cisplatin; PEB, standard-dose cisplatin.

listed in Table 2. Tumor distribution included 87 (53%) patients with sacrococcygeal/presacral, 39 (23%) with mediastinal, 26 (16%) with abdominal/retroperitoneal/pelvic, and 13 patients (8%) with genitourinary tumors. Age at diagnosis ranged from 0.0 to 18.5 years (median, 1.9 years). Fifty-two percent (86 of 165) of those with extragonadal tumors were younger than 2 years at diagnosis. The 39 children with mediastinal primary tumors were older (range, 1.3 to 18.5 years; median, 12.3 years) than those with other primary sites.

Responses at week 12 are shown in Table 3, and there was no difference between treatment arms ($P = .6714$). The 6-year EFS and OS rates are shown in Table 4. Events among 165 patients with extragonadal primary tumors were mostly related to tumor progression or recurrence in 24 of 34 patients. Six of 20 patients whose tumors progressed after PEB were effectively treated with salvage therapy, and two of four patients whose disease recurred after HDPEB were effectively treated with salvage therapy. Seven (18%) of 39 patients with mediastinal MGCT developed progressive or recurrent tumor, and 10 (11%) of 87 patients with sacrococcygeal primaries had tumor events. Local and regional recurrence/progression accounted for 95% of tumor events. Metastatic spread to the lungs eventually occurred in 16% of these patients. One patient with a mediastinal primary experienced relapse in a testis and lungs 3 years after completion of therapy.

Toxicity

Toxicities by regimen are listed in Table 5. Magnesium and potassium loss, reduced creatinine clearance, nausea and vomiting, and thrombocytopenia were reported more frequently with HDPEB than with PEB. Rates of infection, diarrhea, and pulmonary dysfunction were similar in each regimen. However, fatal infections accounted for seven deaths; six in patients treated with HDPEB. Objective hearing loss (grade 3/4 toxicity according to standard National Cancer Institute criteria) was reported in 21 patients (14%) treated with HDPEB and none treated with PEB. The need for hearing aids was documented in 67% of patients treated with HDPEB.

Three patients with mediastinal MGCT developed secondary hematologic disorders and died (two with acute myelocytic leukemia [AML] at 5 and 22 months after diagnosis and one with erythrophagocytic syndrome). Neither patient with AML had the 11q23 abnormalities usually associated with etoposide administration. One patient received HDPEB and one received standard PEB. The two patients with secondary AML died 39 and 29 months after AML diagnosis. One patient developed an erythrophagocytic syndrome after four HDPEB cycles and died 6 months after diagnosis.

DISCUSSION

Despite preliminary evidence suggesting that high-dose cisplatin could improve response rates over standard-dose cisplatin,[18-21] a randomized study in adults with advanced testicular tumors failed to show differences in response rates or outcome and produced significantly increased toxicity.[22] On the basis of the differences between adult and pediatric MGCT,[30-34] the Pediatric Oncology Group and CCG developed an Intergroup study to evaluate the effect of cisplatin dose-intensity on outcome. Initial concerns regarding the cumulative toxicity of cisplatin combined with bleomycin[9-13] were lessened by reports that the use of high-dose cisplatin and etoposide in other childhood tumors was associated with acceptable toxicity.[16,17] Unlike the study in adults,[22] this Intergroup study demonstrated a statistically significant EFS advantage for pediatric patients with germ cell tumors, although OS was similar in both treatment regimens. Unfortunately, excessive toxic deaths and significant ototoxicity associated with the high-dose regimen limits its utility in a group of patients with an excellent outcome. Strategies to either minimize toxicity or improve the efficacy of the standard regimen will be important to improve outcome and maintain an excellent quality of life in these patients.

Our study design differs from that used in studies of adults with testicular tumors, both in chemotherapy delivery and surgical strategies. First, the surgical treatment did not include the use of lymph node sampling. Although it is well known that adults with clinical stage I testicular tumors may develop lymph node recurrences,[37] surgery followed by close observation has become a more common strategy when patients comply with observation.[38-46] The second difference in our treatment strategy was the bleomycin dose, which was reduced because of concerns regarding pulmonary toxicity. Pediatric patients received bleomycin 1 of every 3 weeks. Thus the total bleomycin dose was 33% of that administered to adults with testicular tumors,[47] although it was similar to that used for adults with ovarian

tumors.[24] Despite the significantly reduced bleomycin dose, our results are comparable to those of adult trials in patients with advanced testicular or ovarian tumors.[22,24] Although a randomized study in adults demonstrated that three cycles of standard PEB were equivalent to four cycles,[47-49] we do not know how bleomycin affects outcome in our patients, because this question has not been evaluated prospectively in pediatric trials.

One additional objective of our study was to compare CR and PR between cisplatin regimens. It seems that the response of advanced testicular and ovarian tumors to HDPEB and PEB was similar. Although the CR rate in patients with extragonadal tumors was greater after HDPEB, the combined response rates (CR plus PR) were similar. A high PR rate was also noted for patients with stage III and IV testicular MGCT. The high PR rate in testicular MGCT reflected findings on imaging studies. Most patients had no residual viable tumor at second-look surgery, suggesting that patients were rendered CR by chemotherapy alone. The majority of testicular MGCT patients (75%) were older than 13 years of age. Most had mixed MGCT, some with both yolk sac tumor and EC elements. There were only two cases each of pure EC and germinoma in this study. The small number of patients with each histologic subtype makes meaningful comparisons regarding response and histology difficult.

Although the study was not designed to have sufficient sample size and power to test for differences within each of the smaller subsets (ovarian, testicular, and extragonadal), there was a trend toward improved EFS and OS favoring high-dose cisplatin in each subset. The trend for an EFS advantage for HDPEB was most pronounced in the stage III/IV extragonadal MGCT patients, where the difference was of borderline statistical significance. Several international pediatric MGCT trials have suggested that tumor marker elevation was a significant prognostic predictor.[50-53] An AFP value of greater than 10,000 mg/mL[52,53] was a predictor of poor outcome in European pediatric MGCT studies. In this trial, we found a significant association between tumor marker elevation (AFP and βHCG) and EFS. We were not able to demonstrate correlation of outcome and initial tumor marker (above normal) or appropriate decline. This may have been due to insufficient measurement points. The factor with the greatest effect on outcome (EFS and OS) was the presence of a primary mediastinal tumor.

The main causes of treatment failure included tumor recurrence and fatal infection, which differed by treatment arm. Only four patients treated with HDPEB developed tumor progression or recurrence compared with 20 patients treated with PEB. In contrast, only one patient treated with PEB died of infection, compared with six patients treated with HDPEB. Tumor events were related to site. Patients with gonadal primaries had excellent outcomes, despite advanced disease. Ovarian stage III and IV MGCT recurred rarely. The sites of recurrence from ovarian MGCT were lungs and contralateral ovaries. Failures in stage IV testicular MGCT were also rare, occurring in distal abdominal nodes and lungs (original metastatic site). The small number of tumor events in patients with gonadal MGCT make conclusions about tumor progression patterns difficult. The extragonadal tumor MGCT events were predominately caused by local failure. It is difficult to obtain clear surgical margins at mediastinal and sacrococcygeal sites. Most patients had stage III and IV disease, and initial surgical resections were minimal. Subsequent second-look surgeries were often inadequate. Eventually, 16% of patients with progressive localized extragonadal MGCT had their disease metastasize to the lungs. Unfortunately, this study was not designed to collect data from salvage treatments. It is difficult to draw meaningful conclusions about the effectiveness of chemotherapy in these patients who experienced relapse. Treatment of pediatric extracranial MGCT with radiation therapy has been reported[15] but not prospectively studied in this population. Given the small number of pediatric patients with MGCT who develop local tumor progression, the role of radiation would be difficult to define.

The use of HDPEB was associated with more hematologic and nonhematologic toxicities. In future studies, consistent use of granulocyte colony-stimulating factor might reduce hematologic toxicity and serious infection. Three patients with mediastinal primary tumors died of secondary hematologic disorders. Two patients with AML received HDPEB and PEB, respectively. The increased incidence of secondary hematologic disorders in patients with primary mediastinal germ cell tumor has been reported previously and is believed to be associated with MGCT.[54-56]

The most significant nonhematologic toxicity associated with HDPEB was ototoxicity, which necessitated hearing amplification. This complication might alter speech development, especially in children treated at young ages. In this study there seemed to be a low incidence of grade 3 to 4 ototoxicity as reported by the treating institutions. However, review of audiograms was not required. After longer follow-up, it was noted that approximately 67% of patients who received HDPEB required hearing amplification, making it evident that ototoxicity was underreported. Li et al[57] reviewed a subset of audiograms from this study and graded hearing loss using the National Cancer Institute Common Toxicity Criteria and the Brock criteria. This review confirmed a higher incidence of ototoxicity in HDPEB-treated patients (67% of patients with HDPEB and 10.5% treated with PEB).[58] In future studies, stringent assessment of ototoxicity with central review of audiograms will be required. The United Kingdom Children's Cancer Study Group has substituted carboplatin for cisplatin consistently in an effort to minimize nephrotoxicity and ototoxicity.[50,59] In their most recent study, the 5-year EFS for 137 patients was 84.8% in those with stage III disease and 78.0% in those with stage IV tumors.[50] The carboplatin dose was 600 mg/

m^2, which is significantly higher than that used in other studies that reported carboplatin was less effective than cisplatin.[52,60,61] Although the total number of extragonadal patients in the United Kingdom Children's Cancer Study Group study is small (n = 42), the 5-year EFS of 85.0% ± 3.0% is similar to the 6-year EFS of 83.4% ± 4.4% for extragonadal tumors in our trial.

Reports from the German Cooperative studies (Maligne Keimzelltumoren 83/86 and 89) show a 5-year EFS of 76.0% in 66 children with sacrococcygeal or extragonadal primary tumors (30 of whom had distant metastases) when treated with cisplatin combined with etoposide, bleomycin, vinblastine, and ifosfamide.[62] Total cumulative cisplatin and etoposide doses are similar to those in our patients who had four HDPEB cycles. The outcome for patients with mediastinal germ cell tumors treated on German and French germ cell studies was inferior to that of patients with extragonadal MGCT at other sites.[52,63]

In conclusion, the administration of HDPEB resulted in a significant EFS advantage for patients with high-risk MGCT, and only a slight, but not clinically or statistically significant, difference in OS. However, the significant toxicity associated with this regimen precludes its use. For patients classified as high-risk stage III/IV extragonadal MGCT, the Children's Oncology Group germ cell tumor subcommittee is exploring strategies to either minimize the toxicity of HDPEB or improve the efficacy of standard-dose PEB.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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