Pediatrics and Neonatology (2015) 56, 301–306

Available online at www.sciencedirect.com

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journal homepage: http://www.pediatr-neonatol.com

ORIGINAL ARTICLE

Treatment Results of Extracranial Malignant Germ Cell Tumor with Regimens of Cisplatin, Vinblastine, Bleomycin or Carboplatin, Etoposide, and Bleomycin with Special Emphasis on the Sites of Vagina and Testis

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Received Aug 8, 2014; received in revised form Dec 1, 2014; accepted Dec 17, 2014
Available online 2 February 2015

Key Words
childhood;
germ cell tumor;
stage I testes tumor;
vaginal tumor;
yolk sac tumor

Background: The survival of children with malignant germ cell tumor (GCT) increased over the past 2 decades with platinum-based chemotherapy. This report has three objectives: (1) comparison of PVB (cisplatin, vinblastine, and bleomycin) with JEB (carboplatin, etoposide, and bleomycin) regimens; (2) treatment modality of vaginal GCT; and (3) management of stage I testicular yolk sac tumor (YST) in boys under 2 years old.
Methods: From January 1, 1987 to December 31, 2010, 81 patients with malignant extracranial GCT were treated. Two consecutive protocols, PVB followed by JEB, were used. Girls with vaginal YST received minimal surgery and chemotherapy. Boys under 2 years old with Stage I testicular YST received surgery with or without chemotherapy.
Results: As of June 30, 2012, the 10-year overall survival (OS) was 95 ± 3% (standard error) and the event-free survival (EFS) was 88 ± 4%. With PVB, 35 patients had 10-year OS of 91 ± 5% and EFS of 89 ± 5%. With JEB, 25 patients had 7-year OS of 96 ± 5% and EFS of 96 ± 5%. All five girls with vaginal YST were cured with vagina-preserved strategy. In 32 boys age under 2 years old with stage I YST, 16 with light chemotherapy were all in EFS, whereas two of 16 patients without chemotherapy relapsed. After PVB, six patients developed nephrotoxicity and one had pulmonary fibrosis.

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http://dx.doi.org/10.1016/j.pedneo.2014.12.003

Conclusion: Girls with vaginal YST who received minimal surgery and chemotherapy had excellent prognosis and sexual organs were preservable. Light chemotherapy after surgery is a treatment option for boys under 2 years old with stage I YST to decrease relapse rate. Both JEB and PVB are effective. JEB resulted in more myelosuppression but otherwise less serious long-term toxicity than PVB.

1. Introduction

The treatment outcomes for children with malignant extracranial germ cell tumor (MEGCT) have improved markedly in the past 2 decades.[1–3] This has been achieved by the introduction of platinum-containing chemotherapy regimen, effective surgical intervention, and better supportive care.[4,5] However, a degree of renal impairment or deafness attributed to cisplatin has been reported.[3,6] The substitution of carboplatin for cisplatin, reduced dose of bleomycin to avoid lung fibrosis, and administration of etoposide comprised an effective treatment for MEGCT with acceptable toxicities.[2] To the best of our knowledge, no comparison in treatment results and complications between PVB (cisplatin, vinblastine, and bleomycin) and JEB (carboplatin, etoposide, and bleomycin) was reported. This report has three objectives: (1) comparison PVB with JEB regimens; (2) the treatment modality of vaginal germ cell tumor (GCT); and (3) management of Stage I testicular yolk sac tumor (YST) in boys younger than 2 years. First, we analyzed all cases treated at our hospital and compared the outcome and complications between two consecutive protocols, PVB and JEB regimens. Second, several previous reports described successful treatment by radical surgery, radiotherapy, and chemotherapy in girls with vaginal GCT.[7–9] The complications in survivors include loss of reproductive function and/or long-term urological problems. We reported patients with vaginal GCT treated by combination chemotherapy and minimal surgery to preserve their sexual organs as far as possible. The literature showed that patients under 2 years with Stage I GCT of the testes treated with surgery alone had good survival rates but still had relapses.[2,10] In this study, we compared the outcomes between surgery alone and with the addition of light chemotherapy in boys younger than 2 years with Stage I testicular YST.

2. Methods

2.1. Patients

From January 1, 1987 to December 31, 2010, 81 children $\leq$ 15 years old with newly diagnosed MEGCT were treated after written informed consent was obtained from guardians. The subtypes included YST, dysgerminoma, malignant teratoma, and embryonal carcinoma. Five patients having immature teratoma with YST and greatly elevated serum alpha-fetoprotein (AFP) levels were classified as malignant teratoma and treated with chemotherapy. The treatment result of boys with Stage I testicular YST has been reported in part,[11] whereas more patients were included in this study with longer follow-up.

2.2. Pretreatment evaluation

Clinical evaluation included complete blood cell count, serum electrolytes, creatinine, bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, phosphorus, uric acid, lactate dehydrogenase, and tumor markers including serum AFP and human chorionic gonadotropin. Increased AFP was calculated as magnification of the average normal serum level of children at various ages.[12] Staging imaging evaluation included chest radiography, computed tomography of the brain, chest, and abdomen, long bone survey, and technetium-99 bone scan.

2.3. Staging

Staging was based on St. Jude Children's Research Hospital Staging System for GCTs[13] as follows: Stage I—complete surgical resection with margin free from tumor, and negative tumor markers after 1 month postoperatively; Stage II—gross resection with microscopic residual disease, negative tumor markers; Stage III—gross resection with macroscopic residual disease, $\pm$ tumor markers; and Stage IV—distant metastases $\pm$ tumor markers.

2.4. Surgery

Patients received complete surgical excision of the tumor if no major morbidity was predicted; otherwise, biopsy was performed. For those with vaginal YST, only a small biopsy was performed prior to chemotherapy in an attempt to preserve the organs. Those with residual tumors after chemotherapy underwent second-look surgery. Boys younger than 2 years old with Stage I testicular YST received radical inguinal orchidectomy including high ligation of the spermatic cord without retroperitoneal lymphadenectomy.

2.5. Chemotherapy

Two consecutive protocols, PVB (from January 1987 to December 1998) followed by JEB (after January 1999), were used for patients with MEGCT. PVB consisted of bleomycin

(15 mg/m^2/d on Days 1–3), vinblastine (6 mg/m^2 on Day 2), and cisplatin (90 mg/m^2 on Day 3). Hydration for 6 hours with mannitol and then cisplatin infusion with continuous hydration for at least 24 hours after the end of chemotherapy were given. JEB consisted of etoposide (120 mg/m^2/d on Days 1–3), carboplatin (600 mg/m^2 on Day 2), and bleomycin (15 mg/m^2 on Day 3). Chemotherapy was given with 21-day intervals. For those in whom complete surgical excision was attainable initially at diagnosis, two to four courses of chemotherapy were given. For those with unresectable disease, and four to six courses of chemotherapy were given to decrease the tumor size to make tumors resectable. Two additional courses of chemotherapy were given following second-look surgery for patients with residual disease, whereas no further therapy was given for those without residuals and with normalized AFP level (in YST). Boys younger than 2 years with Stage I testicular YST were stratified into two treatment groups after surgery, with or without light chemotherapy, according to the decision of the guardians. Those patients with chemotherapy received either four courses of PVB or two courses of JEB after January 1999. Chemotherapy dosage for infants younger than 12 months was based on kilogram where 1 m^2 of body surface area equaled a body weight of 30 kg.

2.6. Assessment of treatment response and toxicity

Patients who had elevated tumor markers at diagnosis received further measurement weekly until normal values were reached, then every 4–6 weeks for 2 years, every 3 months for 3 years, and every 6 months for further 2 years. All image abnormalities were assessed by chest radiography, abdominal ultrasonography, and/or computed tomography every 3 months. Nephrotoxicity was defined as a doubling of baseline creatinine levels after chemotherapy. Ototoxicity was evaluated by audiometry.

2.7. Statistical analysis

The duration of overall survival (OS) was defined as the time from the start of treatment to death from any cause, and event-free survival (EFS) from the start of treatment to first progression, relapse, or death from any causes. Survival rates were estimated using the Kaplan–Meier method. Univariate analyses of prognostic factors were conducted with two-sided log-rank test. The difference in the complications between PVB and JEB was tested using Fisher's exact test. A statistically significant difference was defined as $p < 0.05$. Survival rates were described as mean $\pm$ standard error.

3. Results

3.1. Patients' characteristics

Overall, 81 patients (consisting of 46 boys and 35 girls) were enrolled. The primary sites and their histologic diagnoses are summarized in Table 1. They consisted of 39 Stage I, six Stage II, 25 Stage III, and 11 Stage IV. The 22 patients with primary extragonadal tumors included five vaginal, five sacrococcygeal, seven retroperitoneal, four posterior mediastineal, and one diaphragmatic tumors.[14] The predominant histology was YST. Serum AFP levels were elevated in all YST patients with a median level of 3301 ng/mL (range, 64–232,340 ng/mL). Patients with Stages I or II disease had lower AFP levels (510 ng/mL) than those with Stages III and IV disease (1035 ng/mL). There were differences in neither AFP levels between gonadal (570 ng/mL) and extragonadal (758 ng/mL) tumors, nor outcomes between survivors (602 ng/mL) and nonsurvivors (671 ng/mL). Two patients with dysgerminoma had elevated human chorionic gonadotropin levels (193 IU/L and 994 IU/L).

3.2. Overall outcome

The 10-year OS and EFS rates for all patients were 95 $\pm$ 3% (standard error) and 88 $\pm$ 4%, respectively. The survival probability is shown in Figure 1. Thirty-five patients treated with PVB had 10-year OS rate of 91 $\pm$ 5%, and 10-year EFS of 89 $\pm$ 5%. The 7-year OS and EFS rates for 25 patients treated with JEB were 96 $\pm$ 5% and 96 $\pm$ 5%, respectively. A total of 32 boys younger than 2 years had Stage I testicular YST. After the surgery, nine of them received short-term PVB, seven received short-term JEB, and 16 had observation alone. Patients who received chemotherapy had 10-year OS and EFS rates of 100%, whereas patients without chemotherapy had a 10-year OS rate of 100%, and a 10-year EFS of 88 $\pm$ 8%.

3.3. Outcome according to clinical and biologic factors

The outcomes based on the clinical and biologic features of patients are shown in Table 2.

3.3.1. Stages I and II

Generally, the outcomes were good. Two boys younger than 2 years with Stage I testicular YST did not receive chemotherapy and had intrathoracic and intra-abdominal relapses at 6 months and 18 months after orchiectomy, respectively. They then received six courses of PVB and surgical resection of the relapsed tumors. The patient with intra-abdominal relapse that was complicated with adhesion ileus received surgery.

3.3.2. Stages III and IV

Thirteen patients without any residual tumors had no further surgery after chemotherapy. Ten patients with Stage III disease who had residual tumors underwent a second-look surgery after a median of five courses of chemotherapy. Fibrosis was found in nine patients, and the remaining patient with a viable malignant tumor received further chemotherapy including an additional four courses of JEB, three courses of cisplatin, vinblastine, and ifosfamide, and one course of vincristine, cyclophosphamide, and epidoxorubicin. One 1-year-old girl with Stage III malignant teratoma developed pulmonary fibrosis and pneumonia with respiratory failure after five courses of PVB and died. Of 11 patients with Stage IV disease, second-look surgery revealed eight complete fibrotic tissues and one without any residual tumor. After a median of six courses of

Table 1 Tumor sites and histology in patients with malignant germ cell tumor.

Sites	Histologic classification				
	Yolk sac tumor	Malignant teratoma	Dysgerminoma	Embryonal carcinoma	Total *n* (%)
Testis	42	2			44 (54)
Ovary	6	4	4	1	15 (19)
Vagina	5				5 (6)
Sacrococcyx	4	1			5 (6)
Retroperitoneum	5	2			7 (9)
Mediastinum	4				4 (5)
Diaphragm	1				1 (1)
Total *n* (%)	67 (83)	9 (11)	4 (5)	1 (1)	81

chemotherapy, eight continued to have long-term EFS. The remaining two patients, one dysgerminoma and the other YST, died from progressive disease despite five courses of PVB and radiotherapy. One 3-year-old girl with Stage IV YST who had multiple relapsed tumors died despite 4 years of chemotherapy.

3.3.3. Vaginal YST

Five patients' diagnoses were made from minimal vaginal wall biopsy, including three with lower pelvic YST with extensive vaginal invasion and two with primary vaginal YST. Three patients received a second-look biopsy after six courses of chemotherapy and showed only fibrotic tissue. Two patients without any residual tumor received no further surgery after four courses of chemotherapy. One 2-year-old girl had elevated AFP levels 2 months after six courses of JEB without demonstrable tumors on computed tomography. She received two further courses of JEB because the AFP level reached 100 ng/mL. All five patients were free of disease after 66—153 months.

3.3.4. Toxicity

Table 3 lists the complications. Nephrotoxicity was only found in PVB. Loss of magnesium from urine and neutropenia were similar in each regimen. Patients treated with JEB developed higher rate of febrile neutropenia than those treated with PVB. Of the six patients treated with PVB, hearing loss was found in one patient, pulmonary fibrosis in two patients, cerebral and renal arterial thrombosis in one patient, and syndrome of inappropriate antidiuretic hormone secretion in two patients.

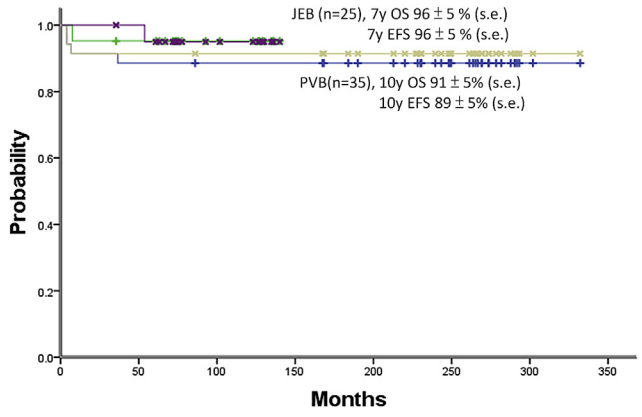

Figure 1 Overall survival (OS) and event-free survival (EFS) of 35 patients treated with PVB (cisplatin, vinblastine, bleomycin) and 25 patients treated with JEB (carboplatin, etoposide, bleomycin).

4. Discussion

PVB for the treatment of GCT at Mackay Memorial Hospital, Taipei, Taiwan, from 1987 to 1998 demonstrated a 91% survival rate, which was at least comparable to the successful study groups worldwide.[1,2] Because the survival rates had approached 90%, an optimized treatment protocol was aimed at minimizing the late effects such as cisplatin-induced ototoxicity and renal impairment.[3,15—18]

In patients treated with PVB, six patients experienced renal impairment (causing delay of chemotherapy), one pulmonary fibrosis causing death, one syndrome of inappropriate antidiuretic hormone secretion, one hearing loss after complete treatment, and one arterial thrombosis. The United Kingdom Children's Cancer Study Group (UKCCSG) study showed that JEB, substitution of carboplatin for cisplatin, greatly reduced the occurrence of both ototoxicity and nephrotoxicity.[2] Accordingly, we have used JEB since 1999. The complications were reduced whereas the frequency of febrile neutropenia increased, which was similar to the results of the UKCCSG study.[2] JEB was associated with more myelotoxicity, but there was no septic event in our patients. The JEB protocol was very effective with acceptable toxicity. In this retrospective study, there can be only historical comparison between PVB and JEB without randomization.

Vaginal YST is a rare neoplasm, ranging from 3% to 8% of GCT and develops almost exclusively in children younger than 2 years. Therapy was historically based on the combination of chemotherapy, radical surgery involving extended hysterectomy, vaginectomy, and/or lymph node dissection, and radiotherapy. However, the prognosis was dismal.[7] Survivors may lose their reproductive function and/or suffer urological complications after extensive surgery and radiotherapy. After the introduction of cisplatin-based chemotherapy, the survival rate improved significantly. The current survival rate at 2 years for vaginal malignant GCT has been reported to be 90%.[19—21] A conservative biopsy was performed instead of extensive surgery to minimize lifelong side effects. In our study, three

Table 2 Patient characteristics and treatment outcome.

Category	No. of patients	10-y EFS (SE)	*p*	10-y OS (SE)	*p*
Sex			0.87		0.39
Male	46	91 (5)		97 (3)	
Female	35	90 (6)		93 (5)	
Age (y)			0.41		0.46
<1	23	87 (7)		97 (4)	
1–5	39	92 (4)		95 (4)	
>5	19	85 (10)		91 (8)	
Stage			0.19		0.11
I	39	92 (4)		97 (2)	
II	6	83 (15)		83 (15)	
III	25	93 (6)		97 (4)	
IV	11	75 (15)		83 (13)	
Sites			0.79		0.27
Gonadal	59	89 (4)		96 (3)	
Extragonadal	22	91 (7)		91 (8)	
Histology			0.11		0.08
Yolk sac tumor	67	94 (4)		98 (2)	
Malignant teratoma	9	80 (13)		80 (13)	
Dysgerminoma	4	60 (22)		80 (18)	
Embryonal carcinoma	1	100		100	
AFP level (ng/mL)			0.48		0.52
<150	16	88 (8)		94 (6)	
150–670	20	96 (6)		96 (6)	
670–2000	16	88 (8)		88 (8)	
>2000	16	100		100	
Chemotherapy			0.27		0.37
PVB	35	89 (5)		91 (5)	
JEB	25	96 (5)*		96 (5)†	
Stage I testes, <2 y old			0.15		
Light chemotherapy	16	100		100	
No chemotherapy	16	88 (8)		100	

AFP = alpha-fetoprotein; EFS = event-free survival; JEB = carboplatin, etoposide, bleomycin; OS = overall survival; PVB = cisplatin, vinblastine, bleomycin.
* Seven-year EFS.
† Seven-year OS.

patients had residual mass shadow after six courses of chemotherapy that were later proven to be fibrotic residuals through biopsy. The other two children without any residual tumors after chemotherapy did not require second-look surgery. As all patients with vaginal YST responded well to chemotherapy, extensive surgery and radiotherapy were spared and long-term complications minimized. One patient had undulant AFP elevation without demonstrable tumors on a series of image studies and received two more courses of JEB. She was free of disease 96 months after the cessation of chemotherapy. Our findings of excellent results confirm that initial biopsy alone followed by platinum-containing chemotherapy and vaginal preservation in patients is the ideal approach for vaginal YST. In our study, all patients with vaginal YST survived without evidence of disease at follow-up of 66–153 months with intact vagina and uterus.

Table 3 Complications in PVB and JEB regimens.

Complication	PVB, *n* (%)	JEB, *n* (%)
Neutropenia	8 (23)	8 (32)
Febrile neutropenia	5 (3)	10 (40)
Nephrotoxicity	6 (17)	0 (0)
SIADH	2 (6)	0 (0)
Magnesium loss	4 (11)	1 (4)
Pulmonary fibrosis	1 (3)	0 (0)
Hearing loss	1 (3)	0 (0)
Cerebral and renal artery thrombosis	1 (3)	0 (0)

JEB = carboplatin, etoposide, bleomycin; PVB = cisplatin, vinblastine, bleomycin; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

For boys younger than 2 years with resected Stage I testicular YST, the evolution and difference in the management modes, in the 1990s and at present, bring up two strategies—wait-and-see and light chemotherapy. Patients with stage I GCTs of the testes have good survival rates with surgery alone.[10] To minimize the toxicities of chemotherapy and to keep high cure rates in < 2-year-old children with completely resected Stage I testicular GCTs, a wait-

and-see policy is generally followed.[2,10,22–25] However, 10–25% of patients who received orchiectomy alone had a later relapse. Even with rescue chemotherapy, some died. Furthermore, the strict follow-up schedule required for those with surgery alone may cause stress or result in noncompliance.[23,24] We initiated the treatment modality that offered four courses of PVB from 1987 to 1998 and two courses of JEB after 1999 in boys younger than 2 years with Stage I resected testicular tumor. The courses of chemotherapy were decreased to reduce toxicity. There are relatively few published reports of adjuvant chemotherapy for children younger than 2 years with testicular GCT.[25] We aimed to decrease the relapse rates, diminish the cost, as well as lessen the anxiety about the risk of relapse and the inconvenience of scrupulous follow-up. In our study, all children who received chemotherapy were event-free without significant treatment-related toxicity at a median follow-up of 126 months. One patient experienced febrile neutropenia and required 5-day hospitalization. There was no sepsis, nephrotoxicity, ototoxicity, hypomagnesemia, or lung fibrosis in the chemotherapy group. Two children who received orchiectomy alone relapsed, but they were alive after surgical resection and adjuvant chemotherapy. Among them, one patient had adhesion ileus 1 year later and underwent surgery for intestinal lysis with anastomosis. Our results suggest that PVB or JEB are similarly safe and tolerable for Stage I YST of testis in children $<$ 2 years old. Light chemotherapy with two courses of postorchiectomy JEB is sufficient to control as one of the treatment options.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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