Int J Clin Exp Med 2016;9(9):18168-18175
www.ijcem.com /ISSN:1940-5901/IJCEM0027430

Original Article

Clinical analysis of pleuropulmonary blastoma in four larger Chinese pediatric hematology and oncology center

Xiaoli Ma[1,2,3], Xisi Wang[1,2,3], Xiaofei Sun[5], Shan Wang[6], Chao Duan[1,2,3], Mei Jin[1,2,3], Dawei Zhang[1,2,3], Ying Chen[1,2,3], Sihui Li[1,2,3], Qi Zeng[2,3], Libing Fu[2,3], Lejian He[2,3], Xiaoxia Peng[2,3,4], Jingyan Tang[7]

[1]Beijing Key Laboratory of Pediatric Hematology Oncology; National Key Discipline of Pediatrics, Ministry of Education; Hematology Oncology Center, 56 Nanlishi Road, Beijing, China; [2]Beijing Children's Hospital, 56 Nanlishi Road, Beijing, China; [3]Capital Medical University, 56 Nanlishi Road, Beijing, China; [4]Clinical Epidemiology and Evidence-Based Medicine Center, Beijing, China; [5]Sun Yat-sen University Cancer Center, Guangdong, China; [6]The Children's Hospital of Chongqing Medical University, Chongqing, China; [7]Shanghai Children's Medical Center, Shanghai Jiaotong University School of Medicine, Shanghai, China

Received March 6, 2016; Accepted August 12, 2016; Epub September 15, 2016; Published September 30, 2016

Abstract: Backgroud: Pleuropulmonary blastoma (PPB) is a very rare malignant tumor of the pleuropulmonary mesenchyme in childhood. This report retrospectively analyzed PPB in four larger Chinese pediatric oncology centers in recent years. And provide a basis for multicenter collaborative treatment of PPB in China. Methods: This analysis concerns patients aged 0-18 years with confirmed to have PPB by pathology review, registered from 1999 to 2011 in Beijing Children's Hospital, Sun Yat-Sen University Cancer Center, The Children's Hospital of Chongqing Medical University and Shanghai children's medical center. Lesions were classified as type I, type II or type III according to Dehner's classification. Results: The series included 38 patients (2 type I, 15 type II and 21 type III), 14 males, 24 females with a median age of 37.5 months (19~204 months), a median of 28 days (2-180 days) from onset to diagnosis. Most Tumors were large (97%>5 cm) and invaded the parietal pleura and pericardium. In seven patients developed with distant metastasis. 9/38 (23.7%) of the patients had lost to follow up at the time of initial diagnosis because they gave up further treatment or got treatment by a local hospital. The remaining 29/38 (76.3%) patients had follow-up information. 2 patients died of respiratory failure after biopsy. 27 patients had treated by chemotherapy/surgery or both among them, 13 patients had total resection, 6 had partial resection. And 7 patients received no further treatment after surgery, but 5 patients relapsed. Total 22 patients had chemotherapy, 1 patient had chemotherapy only. The median follow-up was 43.0 months, 6 patients had recurrences and died, For the 6 recurrent cases, 5 cases had surgery only at initial treatment, and 1 case had chemotherapy only at initial treatment. 10-year overall survival rate was 71.1±8.7%. The relations between outcome and treatment were not significantly associated (P=0.196), but treatment with combined chemotherapy and surgery may suggest better prognosis (P=0.06). Conclusions: Our study showed that achieving total resection of the tumor and combined chemotherapy at any time of treatment may resulted in a better prognosis. The patient's characteristics and pathologic features were different from the worldwide data, for the higher prevalence of type II and type III, also the higher prevalence of stage III and IV in our patients. Presumably the problem was diagnosed late for PPB in China.

Keywords: Children, pleuropulmonary blastoma, Chinese

Pleuropulmonary blastoma (PPB) is a rare intrathoracic neoplasm, occurring in young children. Three types of PPB-type I, type II, and type III have been described based on histopathology, and the prognosis are related and to type at presentation [1, 2]. This report retrospectively analyzed PPB in four larger Chinese pediatric oncology centers in recent years. And provide a basis for multicenter collaborative treatment of PPB in China.

Patients and methods

Patients diagnosed with PPB at Beijing Children's Hospital, Sun Yat-Sen University Cancer Center, The Children's Hospital of Chongqing Medical University and Shanghai children's medical center between 1999 and 2011. The clinical features, pathological findings and outcomes of PPB cases observed from clinical data, surgical notes and summaries of treat-

Table 1. Chemotherapy regimens used for pleuropulmonary blastoma

IVADo: Ifosfamide 3 g/m^2 on days 1 and 2; Vincristine 1.5 mg/m^2 (max 2 mg) on day 1, 8, 15; Actinomycin-D 1.5 mg/m^2 (max 2 mg) on day 1; Doxorubicin 30 mg/m^2 on days 1 and 2
IVA: Ifosfamide 3 g/m^2 on days 1 and 2; Vincristine 1.5 mg/m^2 (max 2 mg) on day 1, 8, 15; Actinomycin-D 1.5 mg/m^2 (max 2 mg) on day 1
VAC: Vincristine 1.5 mg/m^2 (max 2 mg) weekly; Actinomycin-D 0.045 mg/kg (max 2.5 mg) on day 1; cyclophosphamide 1 g/m^2 on day 1
IE: Ifosfamide 1.8 g/m^2 on days 1-5; etoposide 100 mg/m^2 on days 1-5
CAV: Vincristine 1.5 mg/m^2 (max 2 mg) weekly, cyclophosphamide 1.2 g/m^2 on day 1; Doxorubicin 30 mg/m^2 on days 1 and 2
Cisplatin + etoposide: cisplatin 50 mg/m^2 on days 1-4; etoposide 150 mg/m^2 on days 1-3

ment were taken from the charts. We have two more pathologists (central path review) reviewed the slides of included patients to confirm the diagnosis.

This retrospective study was approved by the hospital ethics committee, and informed consents were provided to all the patients and/or their parents. All children were followed up to Jun 30, 2015. The medical records were reviewed for:

Patient general information: age, gender, presenting symptoms and signs, primary tumor site, pathologic subtype characters of the tumor.

Routine laboratory investigations at presentation and during treatment, for example, complete blood count, liver function tests, kidney function tests, serum electrolytes and lactate dehydrogenase (LDH), bone marrow asperiate for some patients.

Tumor staging: In all cases, staging investigations at diagnosis included: physical examination, evaluation of local tumor and other common metastatic sites extent with chest X-ray, computerized tomography (CT) scan and ultrasound. All lesions were subclassified according to the histological classification proposed by Dehner et al [1, 2]: type 1 PPB (exclusively cystic areas), type 2 PPB (with solid and true cystic areas), and type 3 PPB (a true solid tumor).

The ethical consent according to IRB approval was confirmed by their parents. We will do our best to make sure that the personal information in patients' medical record be kept private. Patients' name and other personal information will not be commercially used.

Treatment

Chemotherapy: According to stage system and pathological type for some patients treated by International Pleuropulmonary Blastoma Registry. IVADo (ifosfamide + adriamycin + vincristine + actinomycin D) and IVA (ifosfamide + vincristine + actinomycin) regimen for 12 courses. Others were treated by chemotherapy based on soft tissue sarcomas protocols, such as ifosfamide + etoposide (IE), cyclophosphamide + actinomycin + vincristine (CAV), vincristine + adriamycin + cyclophosphamide (VDC) and cisplatin + etoposide regimens (**Table 1**).

Surgery: The extent of surgical resection was estimated after detailed review of surgical and histopathologic notes as: (1) biopsy only; (2) total resection when tumors were free of surgical margins or microscopical residual disease was present at the surgical margins; (3) partial resection when macroscopic tumor remained.

Tumor response criteria

Evaluation of tumor response was performed after 12 weeks of chemotherapy. Response to treatment, judged by the degree of tumor volume reduction resulting from clinical and imaging evidence, was defined as follows: complete remission (CR), that is, the complete disappearance of disease; partial response (PR), that is, a reduction in tumor volume of >50%; and minor response (MR), that is, a reduction >25% but <50%. Stable disease or a reduction in volume of <25% was recorded as no response, whereas an increase in tumor size or the detection of new lesions was considered as disease progression.

Statistical analysis

Outcome was defined by overall survival (OS). OS was calculated from the time of diagnosis of relapse or recurrent to death from any cause. Survival curves were calculated by the Kaplan-Meier method. The 10-year rates were expressed together with their standard errors. For univariate analysis, the statistical significance

Table 2. Patient characteristics, pathologic features

Patient Characteristics	No	%
Age		
Median	37.5	
Range	19-204	
<36	15	39.5
36-60	17	44.7
>60	6	15.8
Gender		
Male	14	36.8
Female	24	63.2
Tumor size		
<5	1	2.6
5-10	11	28.9
>10	17	44.7
Null	9	23.7
Tumor side		
Left	16	42.1
Right	19	50.0
Uncertainty	3	7.9
Pathotype		
I	2	5.3
II	15	39.5
III	21	55.3
Stage		
II	2	15.8
III	25	65.8
IV	7	18.4

of each variable was tested by univariate regression $P<0.05$ was considered statistically significant, unless otherwise indicated.

Results

Clinical features

The series included 38 patients (**Table 2**), with a median age of 37.5 months (19~204 months), 32/38 (84.2%) patients were less than 5 years old, 24 females, 14 males, female to male ratio was 1.7:1. Presenting symptoms included cough in 14 patients, shortness of breath and respiratory distress in 12 patients, fever in 14 patients, thoracic cavity or mediastinal mass in 12 patients, and chest pain in 4 patients, with a median of 28 (2-180) days from onset to diagnosis. At the initial diagnosis, 10 cases were misdiagnosed, including 7 cases with pneumonia, 2 cases with tuberculosis, and 1 case with congenital cystic adenomatoid malformation. Finally, 3 patients conformed to lung cysts, and one patient's grandfather had even pleural effusion.

17/38 (44.7%) of the patients had lung involvement only. 14/38 (36.9%) of the patients had adjacent tissue involvement, including mediastinal in 6 cases, pleura in 5 cases and pericardial in 3 cases. 7/38 (18.4%) of the patients had distant metastasis, including abdominal lymph nodes, cervical lymph nodes and bone marrow metastasis in 6 cases and liver involvement in 1 case. Bone marrow aspirates were done in 21 patients, and only one patient had bone marrow infiltration. Tumor size was less than 5 cm in one patient, between 5 and 10 cm in 11 patients, more than 10 cm (max 16 × 15 × 12 cm^3) in 17 patients, and unknown in 9 patients. Histological subtypes were type I in 2 patients, type II in 15 patients, and type III in 21 patients. Average serum LDH level was 438 U/L (range 121~1884 U/L), 18 patients had LDH level more than 300 U/L, 3 patients had LDH level more than 1000 U/L.

Treatment and outcome

9/38 (23.7%) of the patients had lost to follow up at the time of initial diagnosis because they gave up further treatment or got treatment by a local hospital. The remaining 29/38 (76.3%) patients had follow-up information. 2 patients died of respiratory failure after biopsy. 27 patients had treated by chemotherapy/surgery or both (**Table 3**).

Surgery: Among 27 patients, 13 patients had total resection, 6 had partial resection, 8 patients had tumor biopsy only at initial diagnosis. And 7 patients received no further treatment after surgery, but5 patients relapsed.

Chemotherapy: Total 22 patients had chemotherapy. 1 patient had chemotherapy only, but died of recurrence. 6 Patients had chemotherapy before surgery, 12 patients had chemotherapy after primary surgery, and 3 patients received chemotherapy after relapse. 5 patients received CAV/IE regimen for 3-8 courses; 5 patients received VCR + CTX + ADR + Act-D for 3-8 courses; 4 received cisplatin and VP16 regimen for 4-12 courses; 8 received IVAD and IVA regimen for 12 courses.

Table 3. Patient treatment, and outcome

Patient	Treatment	Primary surgery	Chemotherapy	Time	Outcome
1	Chemo + surgery	Biopsy	VCR + CTX + ADR × 2 + CDDP + Act-D × 2	102	CR
2	Surgery + chemo	Total resection	VCR + CTX + ADR × 3	79	CR
3	Surgery only	Total resection	traditional chinese medicine	67	CR
4	Surgery + chemo	Partial resection	IVADo × 4 + IVA × 8	64	CR
5		Biopsy	Death by respiratory failure	0.5	Death
6	Surgery only	Total resection	--	48	CR
7	Surgery + chemo	Total resection	IVADo × 4 + IVA × 8	46	CR
8	Chemo + surgery	Biopsy	VCR + CTX + ADR × 4 + VCR + CTX + Act-D × 4	107	CR
9	Surgery only	Total resection	--	162	CR
10	Surgery + chemo	Total resection	CDDP + VP16 × 4	146	CR
11	Surgery + chemo	Partial resection	VCR + CTX + Act-D × 6	138	PR
12		Biopsy	Death by surgery	0.5	Death
13	Surgery + chemo	Total resection	VCR + CTX + Act-D × 3 + VCR + CTX + ADR × 3	124	CR
14	Surgery	Partial resection	VAC/VDC/IE × 5 (after relapse)	8	Death
15	Surgery only	Total resection	--	12	Death
16	Chemo + surgery	Biopsy	CAV/IE × 5	49	PR
17	Surgery + chemo	Partial excision	CAV/IE × 8	54	CR
18	Surgery	Biopsy	CAV/IE × 8 (after relapse)	19	Death
19	Surgery	Partial resection	CAV/IE × 6 (after relapse)	10	Death
20	Surgery + chemo	Total resection	DDP + VP16 + IFO + Act-D + CTX × 12	43	CR
21	Surgery + chemo	total resection	DDP + VP16 + IFO + Act-D + CTX × 7	53	CR
22	Chemo only	Biopsy	DDP + IFOd + VP16 × 1	2	Death
23	Chemo + surgery + radiotherapy	Biopsy	IVADo × 4 + IVA × 8	38	CR
24	Surgery + chemo	Total resection	IVADo × 4 + IVA × 8	21.5	CR
25	Chemo + surgery	Biopsy	IVADo × 4 + IVA × 8	14.5	CR
26	Surgery + chemo	Total resection	IVADo × 4 + IVA × 8	14.5	CR
27	Surgery only	Partial resection	--	6	Death
28	Chemo + surgery	Biopsy	IVADo × 4 + IVA × 8	14.5	CR
29	Surgery + chemo	Total resection	IVADo × 4 + IVA × 7	5.5	CR

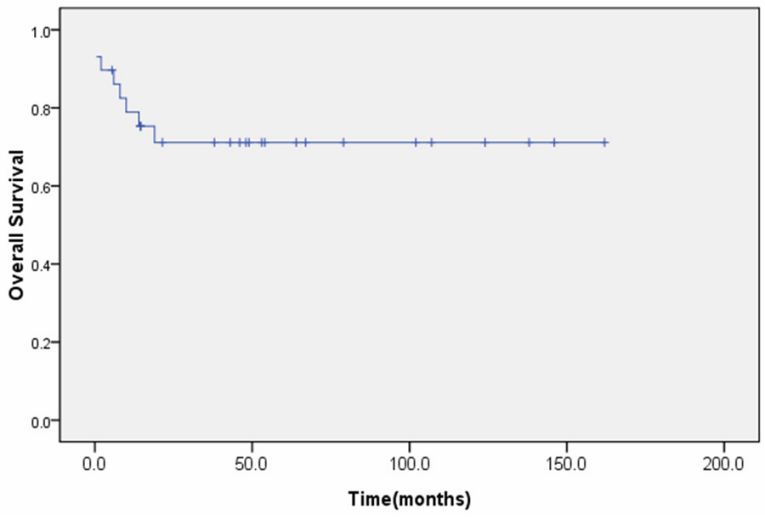

Figure 1. 8 patients were died. Ten year OS was 71.1±8.7%, 95% CI 91.32%~143.64%, while median OS time was 43.0 months.

Radiotherapy: Only one patient (#23 on **Table 3**) had the residual mass at the right posterior mediastinal after chemotherapy and surgery, and radiotherapy (18 Gy) was given 3 months later, followed by four additional courses of chemotherapy. After 38 months of the initial biopsy, there is no evidence of recurrence.

Survival distribution of 29 patients: Total 6 patients had recurrences, there were male 1 and female 5; PPB-type I, II, III for 1, 3, 2 respectively, stage II, III, IV for 1, 3, 2 respectively. For the 6 recur-

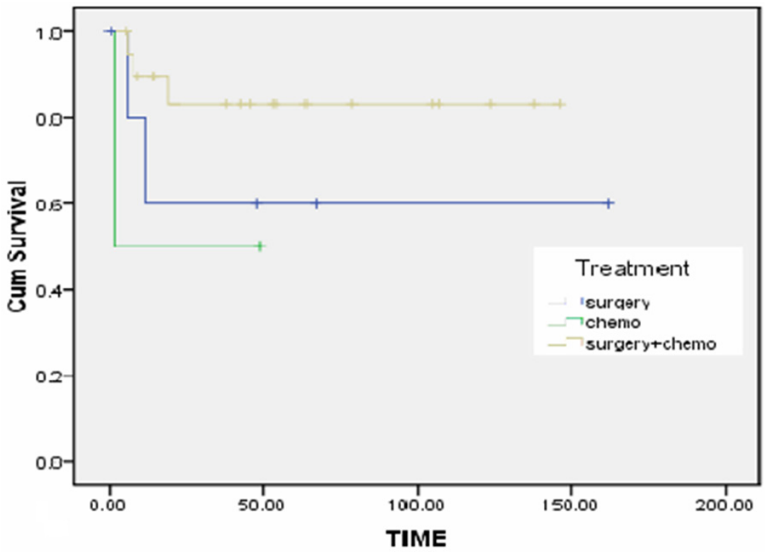

Figure 2. According to treatment, the estimated OS rate was 33.3±15.7% and 94.7±5.1%, while mean OS time was 36.5 months and 58.5 months for patients on surgery only, surgery with chemotherapy, respectively (X=18.3, P=0.196).

Table 4. Survival distribution of 29 pleuropulmonary blastoma

	Number	Survival	Death	*P* value	HR	95% CI
Age				0.36	1.57	0.60~4.06
<36	11	8	3			
36-60	11	8	3			
>60	7	5	2			
Gender				0.16	4.60	0.55~38.33
Male	10	9	1			
Female	19	12	7			
Size				0.13	2.22	0.80~6.18
<5	1	1	0			
5-10	11	8	3			
>10	9	9	0			
Null	8	4	4			
Treatment						
Surgery only	9	3	4	0.13	3.20	0.72~14.34
Chemo only	1	1	1	0.31	2.99	0.36~25.07
Surgery with chemo	19	17	4	0.06	0.24	0.05~1.07
Pathotype						
I	2	1	1	0.53	1.98	0.24~16.56
II	11	8	3	0.48	1.73	0.38~7.80
III	16	12	4	0.31	0.46	0.10~2.07
Stage				0.31	1.83	0.57~5.85
II	6	5	1			
III	19	14	5			
IV	4	2	2			

rent cases, 5 cases had surgery only at initial treatment, and 1 case had chemotherapy only at initial treatment. All recurrent patients had died. Ten year OS was 71.1±8.7%, 95% CI 91.32%~143.64%, while median OS time was 43.0 months (**Figure 1**).

According to treatment, the estimated OS rate was 33.3±15.7% and 94.7±5.1%, while mean OS time was 36.5 months and 58.5 months for patients on surgery only, surgery with chemotherapy, respectively (*X*=18.3) (**Figure 2**). The relations between outcome and treatment were not significantly associated (*P*=0.196, **Figure 2**), but treatment with combined chemotherapy and surgery may suggest better prognosis (P=0.06, **Table 4**). No significant association with age (*P*=0.76), gender (*P*=0.08), tumor size (*P*=0.25), pathologic subtype (*P*=0.46), stage (*P*=0.57) (**Table 4**).

Discussion

PPB is a very rare malignant tumor of the pleuropulmonary mesenchyme in childhood, often involving the pleural and lung. Histologically, the tumor was with a high degree of malignancy and invasiveness [1, 2]. Patients diagnosed with PPB have a heritable predisposition to dysplastic or neoplastic disease, such as lung cysts, cystic nephroma, Wilms tumor and rhabdomyosarcoma. Pulmonary cyst is the most common, and about 25% of children with family history [3, 6].

Genetic linkage analysis of familial PPB and related disor-

ders identified loss-of-function mutations in DICER1. It has been hypothesized that loss of heterozygosity of DICER1 in lung epithelium is a non-cell autonomous etiology of PPB and a critical pathway that regulates lung development. Serum levels of the representative microRNAs were not elevated in DICER1 germline-mutated relatives. In the PPB case, serum levels of the microRNAs increased before chemotherapy, and then showed an early reduction following treatment. The microRNAs may offer future utility as serum biomarkers for screening patients with known germline DICER1 mutations for early detection of PPB, and for potential disease-monitoring in cases with confirmed PPB [1, 7-9].

In our study, 3/38 (7.8%) of the patients had lung cyst. Only one patient had a positive family history. we speculated that this might be due to the fact that this was a retrospective study and only included 4 larger Chinese pediatric hematology and oncology centers.

In our study, the average age was 3.1 years old, and the male to female ratio of children with 1:1.7. The initial clinical manifestation included cough, fever, dyspnea, or chest pain, with or without pneumothorax or pleural effusion, pleural empyema, so some of the patients were inevitably misdiagnosed as pneumonia, tuberculosis or congenital cystic adenomatoid malformation. These results are similar to Messinger YH and Bisogno G report [1, 2] that the clinical manifestations of PPB in children is not specific, the tumor has no characteristic findings on imaging studies. The majority of children in the age of 6 years old, the average age of 2.9~3.2 years old, male and female incidence rate is no obvious difference.

Different from other childhood common malignant solid tumor, distant metastasis is rare in PPB, usually at the time of recurrence, often occurs within 2 years after diagnosis; type I PPB with distant metastasis is rare; the brain and the skeletal system is type II and III PPB, the probability of occurrence was up to 30% [1, 11, 12]. But in our study, 18.4% patients had distant metastasis, such as abdominal lymph nodes and liver. These results were not the same.to Messinger YH and Bisogno G report [1, 2]. Their reports showed that 5.7-6% patients had distant metastasis of PPB.

According to tumor cystic and solid components in different proportions, Dehner et al [1, 2, 11, 12] divided PPB into three types: Type I consists of multilocular cysts containing primitive small mesenchymal cells within the cyst wall, more common in infants, account for 15% to 20% of all PPB; type II tumors have a combination of solid and cystic components, Type II is a type of polycystic with solid nodular type. Type III tumors have proliferating mesenchyma without any cysts, resulting in a solid tumor. In our study, only 2 patients with type I, type II and III account for 95% of all PPB, for the higher prevalence of type III, the fewer prevalence of type I in our patients. These results were different from the worldwide data. Messinger YH and Bisogno G et al show that type I, type II and type III accounting for 20-33%, 35-38%, 32-43% of all PPB. This may be due to the late diagnosis of PPB in China [13].

PPB, like other solid tumors, required a multimodality treatment approach including surgery, and chemotherapy. It's very important to have a complete excision of primary surgery. The key to cure is complete surgical resection, chemotherapy and radiation therapy can be used for those cannot be completely removed or type II and III. Systematic use of ifosfamide and doxorubicin-based regimens for type II/III PPB is suggested with the aim of enabling delayed complete tumor resection and improving survival. In our study, 8 patients received IVAD and IVA regimen for 12 courses. Growth factors were not used systematically in this study. One patient suffered from one hemorrhagic cystitis and two episodes of seizures, this seemed to be related more to the administration of ifosfamide [15, 16].

Messinger YH and Bisogno G et al [1, 2] showed that, in the largest series of PPB published, 5-year overall survival rates were 83~91% for type I PPB and 71~42% for type II and type III PPB. And survival differences on the basis of pathologic subtype. In our study, ten year overall survival rates was 71.1%, there was no significant difference on the basis of pathologic subtype because of some patients had surgery only. The relations between outcome and treatment were associated significantly with overall survival.

In summary, our study showed that PPB is an aggressive neoplasm. Achieving total resection

of the tumor and combined chemotherapy at any time of treatment resulted in a significantly better prognosis. The clinical characteristics and pathologic features were different from the worldwide data, for the higher prevalence of type II and type III, also the higher prevalence of stage III and IV in our patients. We suspected that may be related to the smaller number of patients included, and the diagnosis delay. Therefore, we suggested multi-center and large-scale collaborative study, as well as early diagnosis and early treatment.

Acknowledgements

This work was granted by: 1. Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (No. ZY201404). 2. Beijing Municipal Commission of Science and Technology Capital Clinical Medicine Applied Research and Popularization Special Funding Support (No. Z15110000-4015159).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jingyan Tang, Shanghai Children's Medical Center, Shanghai Jiaotong University School of Medicine, 1678 Dongfang Road, Shanghai 200127, China. Tel: 86-21-58815377; E-mail: yantfk@gmail.com; Xiaoxia Peng, Clinical Epidemiology and Evidence-Based Medicine Center, Beijing Children's Hospital, Capital Medical University, Beijing, China. Tel: 86-13370110038; Fax: +86-10-59617600; E-mail: pengxiaoxia@bch.com.cn

References

[1] Messinger YH, Stewart DR, Priest JR, Williams GM, Harris AK, Schultz KA, Yang J, Doros L, Rosenberg PS, Hill DA, Dehner LP. Pleuropulmonary blastoma: a report on 350 central pathology-confirmed pleuropulmonary blastoma cases by the International Pleuropulmonary Blastoma Registry. Cancer 2015; 121: 276-285.

[2] Bisogno G, Brennan B, Orbach D, Stachowicz-Stencel T, Cecchetto G, Indolfi P, Bien E, Ferrari A, Dommange-Romero F. Treatment and prognostic factors in pleuropulmonary blastoma: an EXPeRT report. Eur J Cancer 2014; 50: 178-184.

[3] Pai S, Eng HL, Lee SY, Hsaio CC, Huang WT, Huang SC, Hill DA, Dehner LP, Priest JR. Correction: Pleuropulmonary blastoma, not rhabdomyosarcoma in a congenital lung cyst. Pediatr Blood Cancer 2007; 48: 370-371.

[4] Boman F, Hill DA, Williams GM, Chauvenet A, Fournet JC, Soglio DB, Messinger Y, Priest JR. Familial association of pleuropulmonary blastoma with cystic nephroma and other renal tumors: a report from the International Pleuropulmonary Blastoma Registry. J Pediatr 2006; 149: 850-854.

[5] Priest JR, Watterson J, Strong L, Huff V, Woods WG, Byrd RL, Friend SH, Newsham I, Amylon MD, Pappo A, Mahoney DH, Langston C, Heyn R, Kohut G, Freyer DR, Bostrom B, Richardson MS, Barredo J, Dehner LP. Pleuropulmonary blastoma: a marker for familial disease. J Pediatr 1996; 128: 220-224.

[6] Nasr A, Himidan S, Pastor AC, Taylor G, Kim PC. Is congenital cystic adenomatoid malformation a premalignant lesion for pleuropulmonary blastoma? J Pediatr Surg 2010; 45: 1086-1089.

[7] Murray MJ, Bailey S, Raby KL, Saini HK, de Kock L, Burke GA, Foulkes WD, Enright AJ, Coleman N, Tischkowitz M. Serum levels of mature microRNAs in DICER1-mutated pleuropulmonary blastoma. Oncogenesis 2014; 3: e87.

[8] Slade I, Bacchelli C, Davies H, Murray A, Abbaszadeh F, Hanks S, Barfoot R, Burke A, Chisholm J, Hewitt M, Jenkinson H, King D, Morland B, Pizer B, Prescott K, Saggar A, Side L, Traunecker H, Vaidya S, Ward P, Futreal PA, Vujanic G, Nicholson AG, Sebire N, Turnbull C, Priest JR, Pritchard-Jones K, Houlston R, Stiller C, Stratton MR, Douglas J, Rahman N. DICER1 syndrome: clarifying the diagnosis, clinical features and management implications of a pleiotropic tumour predisposition syndrome. J Med Genet 2011; 48: 273-278.

[9] Hill DA, Ivanovich J, Priest JR, Gurnett CA, Dehner LP, Desruisseau D, Jarzembowski JA, Wikenheiser-Brokamp KA, Suarez BK, Whelan AJ, Williams G, Bracamontes D, Messinger Y, Goodfellow PJ. DICER1 mutations in familial pleuropulmonary blastoma. Science 2009; 325: 965.

[10] Miniati DN, Chintagumpala M, Langston C, Dishop MK, Olutoye OO, Nuchtern JG, Cass DL. Prenatal presentation and outcome of children with pleuropulmonary blastoma. J Pediatr Surg 2006; 41: 66-71.

[11] Priest JR, Magnuson J, Williams GM, Abromowitch M, Byrd R, Sprinz P, Finkelstein M, Moertel CL, Hill DA. Cerebral metastasis and other central nervous system complications of

pleuropulmonary blastoma. Pediatr Blood Cancer 2007; 49: 266-273.
[12] Priest JR, Williams GM, Hill DA, Dehner LP, Jaffé A. Pulmonary cysts in early childhood and the risk of malignancy. Pediatr Pulmonol 2009; 44: 14-30.
[13] Zhang N, Fu L, Zhou C, Wang L, Lang Z, He L. Childhood pleuropulmonary blastoma: A clinicopathologic study of 16 cases. Zhonghua Bing Li Xue Za Zhi 2014: 43: 747-752.
[14] Priest JR, Williams GM, Manera R, Jenkinson H, Bründler MA, Davis S, Murray TG, Galliani CA, Dehner LP. Ciliary body medulloepithelioma: four cases associated with pleuropulmonary blastoma-a report from the International Pleuropulmonary Blastoma Registry. Br J Ophthalmol 2011; 95: 1001-1005.
[15] Bisogno G, Ferrari A, Bergeron C, Scagnellato A, Prete A, Alaggio R, Casanova M, D'Angelo P, Di Cataldo A, Carli M. The IVADo regimen-a pilot study with ifosfamide, vincristine, actinomycin D, and doxorubicin in children with metastatic soft tissue sarcoma: a pilot study of behalf of the European pediatric Soft tissue sarcoma Study Group. Cancer 2005; 103: 1719-1724.
[16] Priest JR, Andic D, Arbuckle S, Gonzalez-Gomez I, Hill DA, Williams G. Great vessel/cardiac extension and tumor embolism in pleuropulmonary blastoma: a report from the International Pleuropulmonary Blastoma Registry. Pediatr Blood Cancer 2011; 56: 604-609.