Treatment and prognosis of pleuropulmonary blastoma: A Single-Center Report of 31 Cases

Feng Wang¹, Lin Zhuang², Jianghua Liang¹, Le Li¹, Hui Wang², Jue Tang¹, Jia Zeng¹, and Wei Liu¹

¹Guangzhou Women and Children's Medical Center

²Guangzhou Women and Children's Medical Center

September 4, 2021

Abstract

Objectives: Pleuropulmonary blastoma (PPB) is a very rare, characteristic and highly aggressive neoplasm occurring in children, most under 6 years of age. We assessed the clinical characteristics, treatment modalities, treatment outcomes, and prognostic factors affecting survival in patients with PPB treated at our institution over a 10-year period to improve the prognosis of PPB. **Methods:** From November 2008 to November 2019, 31 children (21 boys and 10 girls) with a median age of 30 months (range, 22 days-54 months) were treated at our institution. Here, we describe the patient characteristics, treatment modalities and treatment outcomes. The Kaplan-Meier method was used to estimate the progression free survival probability (PFS) and overall survival (OS). Log-rank test was performed for comparison between groups. **Results:** 3 children were lost to follow-up and 2 were dead of postoperative complications. Of the 26 patients included in the follow-up, 16 PPB patients displayed tumor-free survival. The 6-month, 1-, 3-, and 5-year PFS were 80.8%, 69.0%, 60.4% and 60.4%, respectively. Accordingly, the 6-month, 1-, 3-, and 5-year OS were 84.6%, 72.7%, 60.1% and 60.1%, respectively. Sex, extent of surgery and chemotherapy/irradiation appeared to affect the survival, while age and pathology type appeared not to do. **Conclusions:** PPB is an aggressive neoplasm. To improve the prognosis of PPB, we should promote radical resection and improve the auxiliary treatment measures.

Introduction

Pleuropulmonary blastoma (PPB) is a very rare, highly aggressive neoplasm occurring in the lung or pleura and presenting in children, most under 6 years of age. It was initially proposed to be a distinct entity in 1988 as a dysembryonic malignancy.¹ PPB is histologically characterized by primitive blastema and a malignant mesenchymal stroma that often shows multidirectional differentiation (rhabdomyosarcomatous, chondrosarcomatous, liposarcomatous, etc.). The tumor is usually located in the lung periphery, but may be extrapulmonary, involving the parietal pleura, mediastinum and diaphragm. Despite the introduction of multimodal therapy, the overall prognosis for PPB patients remains poor. Venkatramani et al² studied a series of 12 PPB cases and found that the 5-year overall survival was 42%. In this report, we retrospectively summarized and analyzed the clinical characteristics and living conditions in children with PPB who were admitted to our medical center from November 2008 to November 2019.

Patients and methods

The study have been approved by the Committee on Human Research at our medical center. PPB cases were included if the pathology confirmed PPB by two different pathologists. The PPB cases included in this report were diagnosed from November 2008 to November 2019 at our medical center. Altogether, 31 children were pathological diagnosis of pleuropulmonary blastoma. All of the 31 children underwent CT and chest radiography, 8 underwent echocardiography, 3 underwent thoracic ultrasonography. However, only 15 children were diagnosed with pleuropulmonary blastoma before operation. As for others, 6 were diagnosed

with lung cyst, 6 with other thoracic tumors, 2 were diagnosed with encapsulated effusion and 2 with chest wall tumor. Data of the 31 children were abstracted from medical records after participant-informed consent. SAS9.4 was used for statistical analysis. More concretely, count data were described by the number and rate of cases. Comparison between groups was performed using Fisher's exact test and Kaplan-Meier method to calculate the cumulative survival rate and draw the survival curve. Log-rank test was performed for comparison between groups. Bilateral $P < 0.05$ was considered statistically significant.

Results

2.1 Clinical features

Of the thirty-one children included in this analysis, 21 were male and 10 were female. The youngest patient was 22 days at the time of diagnosis and the oldest was 70 months (median age, 30 months). Presenting symptoms included respiratory distress in 23 patients, cough in 22, fever in 12, poor appetite in 5, chest pain in 3, abdominal pain in 2, chest wall mass in 1, hemoptysis in 1 and facial swelling in 1. Six of the 31 patients were admitted to the pediatric intensive care unit (PICU) because of their critical condition. Four patients were previously diagnosed with pulmonary cystic lesions and another 3 patients had a history of pneumothorax.

Histology was type I PPB in 5 (no type Ir PPB), type II in 5, and type III in 21 patients. Fourteen patients had primary tumors in the left lung and 15 in the right lung, while 2 patients had their primary tumors in the chest wall. Of the 31 patients, 15 patients had extrapulmonary involvement (mediastinum, parietal pleura, and diaphragm) and no one had any evidence of tumor metastasis.

2.2 Treatment

The extent of surgical resection was estimated after detailed review of surgical notes as follows: 1) biopsy; 2) partial resection, when a macroscopic tumor remained; and 3) macroscopic total resection, when the surgeon reported a total resection. Upfront surgical resection was attempted in 30 patients and macroscopic total resection was achieved in 19 patients, while the remaining one tumor in the chest wall was considered unresectable and only a biopsy was performed.

Chemotherapy with IVADo (vincristine $1.5\text{mg}/\text{m}^2$, D1; actinomycin D $1.5\text{mg}/\text{m}^2$, D1; Theprubicin $30\text{mg}/\text{m}^2$, D1-2 and ifosfamide $3\text{g}/\text{m}^2$, D1-2) and irradiation ($30\text{Gy} \sim 36\text{Gy}$) were recommended for all type II/III patients after operation. However, only 17 patients received chemotherapy and irradiation.

2.3 Outcome

Three patients were lost during follow-up. One type III PPB patient died of pneumonia and another died of heart failure just after the operation. At last, 26 patients were included in the follow-up. The shortest follow-up time was 1 month and the longest was 136 months. The median follow-up time was 29.5 months.

A type III PPB patient succumbed one month later because of an intra-atrial tumor thrombus after the operation. A patient who was diagnosed with type III PPB by biopsy gave up on treatment and succumbed to PPB 20 days later. Five patients had a relapse 2 to 18 months after the operation, 4 of whom received chemotherapy and irradiation after the operation and 1 who did not. Two patients who received chemotherapy and irradiation had a bone/brain metastasis 9 to 11 months after the operation, while 1 without chemotherapy/irradiation suffered from bone/renal metastasis within 3 months. All 5 patients with tumor relapse underwent a second operation; however, it was difficult to perform macroscopic total resection and they suffered disease progression soon after and succumbed within 2 to 6 months after the second operation. The 3 patients with tumor metastasis gave up on treatment and succumbed to PPB 1 to 4 months later. The other 16 PPB patients displayed tumor-free survival. Among the 16 patients, 2 suffered from cystic lung lesions at 1 and 3 months respectively after completing primary treatment. Neither of these patients received further treatment and they remained stable at 93 or 120 months after the initial diagnosis.

On the whole, a total of 10 children died and the other 16 survived. The comparison of baseline characteristics between the dead and the alive children is shown in Table 1. By calculating, the 6-month, 1-, 3-, and 5-year

progression free survival probability (PFS) were 80.8%, 69.0%, 60.4% and 60.4%, respectively.(Table 2) Two years is a rapid period of disease progression. The PFS of girls was higher than that of boys and of children who accepted chemotherapy/irradiation was higher than that of children who didn't ($P<0.05$).Furthermore, the PFS of children with complete tumor resection was higher than that of children with partial tumor resection (the difference was statistically significant on the margin, $P=0.077$). However, age and pathology type did not affect the PFS (Fig 1).

Accordingly, the 6-month, 1-, 3-, and 5-year overall survival probability (OS) were 84.6%,72.7%,60.1% and 60.1%,respectively.(Table 2) Two years is a rapid period of death. The OS of girls was higher than that of boys and of children who accepted chemotherapy/irradiation was higher than that of children who didn't ($P<0.05$).Furthermore, the OS of children with complete tumor resection was higher than that of children with partial tumor resection (the difference was statistically significant on the margin, $P=0.073$). However, age and pathology type did not affect the OS (Fig 2).

Discussion

PPB is a characteristic tumor in children. Its histology can manifest as cystic, substantial or mixed. Accordingly, Dehner et al classified PPB into three types as follows: Type I, tumor composed of cystic elements; Type II, tumor composed of both cystic and substantial elements; and Type III, tumor composed of substantial elements.³ The three PPB pathologies form a dynamic continuum. While Type I PPB tends to be a low-grade malignancy, it can progress to the more malignant type II or III. Three patients in the present study had a history of pulmonary cystic lesions, and when they were operated on, the tumor filled the thorax. Two of the 3 patients suffered from tumor relapse soon after the operation, while the other patient was lost during follow-up. We can deduce that the cystic lesions in the lungs of the 3 patients are type I PPB. If the three patients had been operated on when they were diagnosed with pulmonary cystic lesions, their results would have been much better. It is difficult to distinguish type I PPB from a benign cyst by radiography. Thus, we suggest resecting asymptomatic lung cysts in children.

It has been reported that the prognosis of PPB is related to the pathological type. While the prognosis for type I PPB is good, the prognosis for type II and type III PPB is very poor. Messinger et al⁴, who are members of the International Pleuropulmonary Blastoma Registry (IPBR), studied a series of 350 PPB cases and calculated the 5-year overall survival rate to be 91% for type I, 71% for type II, and 53% for type III patients. Bisogno et al⁵, who are members of the European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT), studied a series of 65 PPB cases and found that the overall survival was 91.7% for type I patients and 57.5% for type II and type III patients. In the present study, all 5 type I PPB patients are alive without tumors, with the longest survival time as 136 months. By calculation, the PFS at 5 year for type I PPB is 100%, but for type II PPB is 75% and for type III PPB is 43.7%. However, there was no significant difference in survival curve among the three pathological types. It may be related to the uneven and small number of specimens.

Except the pathological type, the present study found that the extent of surgery and chemotherapy combined with irradiation appeared to be related to PPB prognosis. If the tumor can be macroscopically completely resected and the PPB patients accept chemotherapy as well as irradiation in addition to the operation, the results would be better. What interesting is that, girls in the study seem to have a better prognosis than boys, which has not been reported before. Why? The question needs further study. Several other studies also studied the factors related to PPB prognosis. Invasiveness, complete tumor resection, type I PPB, chemotherapy and tumor size were the main factors.^{5, 6} To achieve better results for PPB patients, we need to strive for complete tumor removal combined with chemotherapy. Unfortunately, PPB progresses rapidly such that when patients arrive at the hospital, most of the tumors are too large to be completely resected. For example, in the present series, of the 26 type II/III PPB patients, 12 had large tumors invading vital structures that resulted in incomplete resection. Therefore, some specialists suggest that patients with unresectable tumors be initially treated with core needle biopsy and neoadjuvant chemotherapy to reduce the tumor size and make it resectable.⁷⁻¹⁰ Following the protocol, the five-year overall survival was elevated from 44% to 68%.¹¹However, core needle biopsy cannot always yield the correct diagnosis because it may

penetrate necrotic tissue. Furthermore, PPB progresses very rapidly and patients may not be able to wait for pathological results; for example, Xi Chai described how four of six patients developed adverse events while waiting for pathological results after core needle biopsy.¹² For these reasons, we have not adopted core needle biopsy, rather upfront excision.

PPB is sensitive to chemotherapy, but there is no standard regimen. In 2007, following communication with sarcoma experts in Europe and North America, the IPBR recommended that chemotherapy for type II/III PPB consist of IVADo and that it consist of VAC (vincristine, actinomycin D, and cyclophosphamide) for type I.¹³ We adopted the recommendation for type II/III PPB, similar to many other medical centers,^{14, 15} and we have proven it to be effective. It should be noted that patients in the present series received irradiation in addition to chemotherapy. However, we cannot prove the effectiveness of chemotherapy alone or chemotherapy combined with irradiation. For type I PPB, some experts believe it can be cured by radical resection alone and that chemotherapy does not improve its prognosis^{4, 16}. Consistently, 5 type I PPB patients in the present study did not receive chemotherapy or irradiation after the operation. None of them suffered from tumor relapse or metastasis during the follow-up period. It appears that operation is enough for type I PPB. Of course, rigorous surveillance after the operation is needed for early detection of recurrence.

Metastases occur in up to 30% of patients with type II/III PPB, and the most common metastatic site is the brain^{17, 18}. Inconsistently, there were only 3 metastases in the present study, though relapse was more common. If patients suffer from tumor relapse or metastasis, the outcome is generally very bad because we have no effective treatment for progressive tumors. Some experts have introduced new treatments for progressive PPB via their experiences. Behery et al¹⁹ reported a PPB case with brain metastasis that was treated with surgery followed by chemotherapy and irradiation. After that, the patient underwent high-dose chemotherapy and blood stem cell transplantation. Since completing these therapies, the patient has done well without any evidence of tumors. Ohta et al²⁰ adopted a protocol with irinotecan and vincristine to treat a PPB patient with lung metastases. After the third course, the metastases disappeared and there was no recurrence. Nakano et al²¹ described two PPB cases with brain metastasis that were treated with gross total resection of the

metastatic tumors. Afterwards, one patient received 1 course of CDDP/CPT-11 (cisplatin and irinotecan), 2 courses of TMZ/ETP (temozolomide, and etoposide) and 6 courses of intrathecal methotrexate while undergoing whole-brain radiation. The other case received radiotherapy to the tumor bed followed by one course of ICE (ifosfamide, carboplatin, and etoposide) and an antiangiogenic multidrug regimen over a 22-month period. Both of the patients are currently alive and in complete remission. These methods appear effective to treat progressive PPB. However, these are just case reports. More effective treatments for recurrent and metastatic PPB are still under investigation.

In conclusion, the overall survival for type II/III patients is still low, leading us to wonder how to improve the prognosis of PPB. The problem can be dissected into determining how to completely resect the tumor and improve the auxiliary treatment measures. Prospective large sample studies are needed to achieve this goal.

Declarations of interest: none.

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Fig1 Progression free survival curve of children with different characteristics. (*Total sample size: 21)

Fig2 Overall survival curve of children with different characteristics. (*Total sample size: 21)

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