

Original Article

Relative hematopoietic stem cell transplantation for the treatment of blastic plasmacytoid dendritic cell neoplasm: a case report and literature review

Zhi-Yun Niu¹, Shu-Peng Wen¹, Li-Na Xing¹, Feng-Yun Wang¹, Zhi-Yong Cheng², Zhen-Zhen Wang¹, Ying Wang¹, Fu-Xu Wang¹, Xue-Jun Zhang¹

¹Department of Hematology, The Second Hospital of Hebei Medical University, Shijiazhuang 050000, China; ²Department of Hematology, The First Hospital of Baoding, Baoding 071000, China

Received June 23, 2019; Accepted July 26, 2019; Epub September 1, 2019; Published September 15, 2019

Abstract: Objective: To report the long-term survival of a patient with maternal plasmacytoid dendritic cell tumor (BPDCN) treated by allo-HSCT. Methods: The patient was diagnosed by skin infiltration, bone marrow involvement, skin biopsy and bone marrow cytology. CD4, CD56, and CR123 were expressed in tumor cells. The first complete remission (CR1) was achieved by CHOP-E and MA regimens before transplantation. In March 2018, HLA 5/10 matched hematopoietic stem cell transplantations were performed in the paternal donors and fathers. The pretreatment regimen was FTBI (4 Gy × 2, total lung dose 6 Gy) + CY (cyclophosphamide 1.8 g/m² × 2 d) + Flu (30 mg/m² × 4 d) + ATG (10 mg/kg); CSA + MMF + MTX to prevent GVHD. MNC 6.45 × 10⁸/kg and CD34 + cells 7.40 × 10⁶/kg were transfused back. + Granulocyte and platelet were engrafted 12 days and 14 days respectively. The donor-recipient chimerism was monitored regularly, immunosuppressive agents were regulated, and minimal residual disease (MRD) was monitored by flow cytometry. No DLI. Results: Complete donor implantation and continuous remission were achieved after transplantation. After transplantation, complications such as mucositis, viral infection, hypoproteinemia, and renal dysfunction occurred. At present, the disease-free survival is 10 months. Conclusion: BPDCN combined with TBI in the CR1 phase can effectively control the disease; HLA haploidentical hematopoietic stem cell transplantation is also an alternative treatment, and complications should be treated in a timely manner.

Keywords: BPDCN, allo-HSCT, the pretreatment regimen, whole-body irradiation, GVHD, long-term survival

Introduction

Blastic plasmacytoid cell dendritic neoplasm (BPDCN) is a rare and highly invasive hematological neoplasm. It is an independent classification of a medullary tumor in the WHO (2016) classification of hematological tumors [1]. The tumor tends to invade multiple sites, preferring skin, followed by bone marrow, peripheral blood, and the lymph nodes. BPDCN is highly invasive, sensitive to chemotherapy and radiotherapy, but prone to recurrence. Its median survival time is only one year, and its prognosis is very poor. The diagnosis depends on biopsy and pathological examination. In our transplantation center, haploidentical hematopoietic stem cell transplantation (HSCT) was used to treat a case of BPDCN with skin lesions as the first manifestation. The results are reported

as follows. The progress of the treatment of BPDCN is reviewed.

Since Adachi first reported on the condition in 1994, more than 200 cases of BPDCN have been reported so far, constituting up to 0.27% of lymphoma and 0.76% of AML cases. Aged patients are common, the median age of onset ranges from 60 to 70 years old, but it can be seen in patients of any age, and children and young patients have a relatively good prognosis. Men are affected more often, and the ratio of men to women can be as high as 3:1. Skin damage is often the first symptom. About 80% to 90% of patients have skin involvement. At onset, there are no systemic symptoms. It is manifested as single or multiple plaques or nodules. The head and face are most often involved. The limbs and trunk can also be

involved. Sometimes the skin lesions can be contusion-like, some form ulcers, and sometimes the condition is misdiagnosed as hematoma. As the disease progresses, it may gradually involve other soft tissues, the lymph nodes, bone marrow, and hematopenia, and especially thrombocytopenia, and lymph node, liver and spleen enlargement, and central nervous system involvement may also occur. The median time from the onset of the first symptoms to diagnosis is 4 months, but in some cases the first symptoms may take up to 1.5 years to appear. Clinical manifestations are highly invasive, have a poor prognosis, and are sensitive to the initial treatment, but the remission period is not long-lasting, and the symptoms often recur after the relapse of drug resistance. The median survival period is 12 to 16 months.

Although allo-HSCT can also provide long-term survival as a second-line treatment, it should be performed in the CR1 stage because of its high invasiveness and drug resistance after relapse. Data from the European Blood and Bone Marrow Transplantation Group (EBMT) in 2013 showed that 16 of 34 patients receiving allo-HSCT BPDCN survived, with a median survival of 28 (4-77) months. The 3-year non-recurrence mortality, disease-free survival and OS rates were 30%, 33%, and 41%, respectively. 11 cases (32%) had recurrence, and the median recurrence time was 8 (2-27) months. No patients with advanced recurrence (> 27 months) were found. This suggests that allo-HSCT could lead to lasting remission or even a radical cure. The disease-free survival and OS rate of patients with CR1 prior to transplantation were better than those of other patients, which again suggests that conditional patients should undergo allo-HSCT at CR1.

Materials and methods

Clinical data

A 55-year-old male patient with right hip skin sclerosis for 1 year was diagnosed as having had BPDCN for 3 months. He was admitted to our hematology department for the first time on October 6, 2017. One year earlier, the patient had an unexplained, broad bean-like painless mass on the right buttock, which was neglected. Three months before admission, the mass enlarged rapidly and protruded from the skin, and was light brown in color. The patient was

hospitalized in the local hospital. The bilateral inguinal groin could touch multiple lymph nodes, and the elder was 1 cm × 2 cm. The heart and lungs were normal, the liver was not felt, and the spleen was felt under the ribs. On the right buttock, one could feel a stiff, slidable mass about 5 cm in diameter, with a smooth purple-brown surface, a higher skin temperature, and no tenderness. Blood routine: WBC $5.77 \times 10^9/L$, Hb 159 g/L, Plt $69 \times 10^9/L$. Liver and kidney function and lactate dehydrogenase were normal. Bone marrow imaging showed that the proliferation of bone marrow was active, and the original cells were 12.5%. The cells were of medium size, with round or irregular nuclei, reticular chromatin, and nucleoli. The cytoplasm was grey-blue with no granules in the cytoplasm, and some of the cells had pseudopodal or vesicular processes in the cytoplasm. Bone marrow flow cytometry showed that abnormal cells accounted for about 4.43% of the nuclear cells, expressing HLA-DR, CD38, CD123, CD56, CD33, CD304, CD4, but not CD117, CD19, CD7, CD11b, CD10, CD20, MPO, CD303, CD13, CD34, c-kappa, c-lambda, CD64 (**Figure 1**). Diagnosis: BPDCN. In conclusion, BPDCN bone marrow invasion was considered. CT showed 1. Splenomegaly; 2. Right hip subcutaneous space (**Figure 2**); 3. Bilateral inguinal lymph node enlargement; 4. Fatty liver. Pathology of skin mass on the right buttock: Destruction of skin tissue structure, infiltration of a large number of single patches of atypical lymphoid cells in the dermis, large or medium cells, medium cytoplasm, oval or irregular nucleolus, nuclear division was easy to see, no epidermal infiltration. Immunohistochemistry: CD4, CD123, CD56, CD43, and CD33 were positive, Ki67 was about 50%, CD20, CD3, PAX5, and CD7 were a little positive, TDT, CD34, CD117, CD30, CD117, GrB, ALK, and EMA were negative; diagnosis: right hip skin BPDCN. Clinical diagnosis: 1. BPDCN bone marrow invasion; 2. Type 2 diabetes mellitus. An induction chemotherapy CHOP-E regimen was given in local hospitals for three cycles, and the hip mass disappeared gradually. After that, a hematopoietic stem cell transplantation was carried out in our department.

Physical examination

There was a 4 × 5 cm round pigmentation on the right hip, with small superficial lymph nodes. No abnormality was found in the cardiac

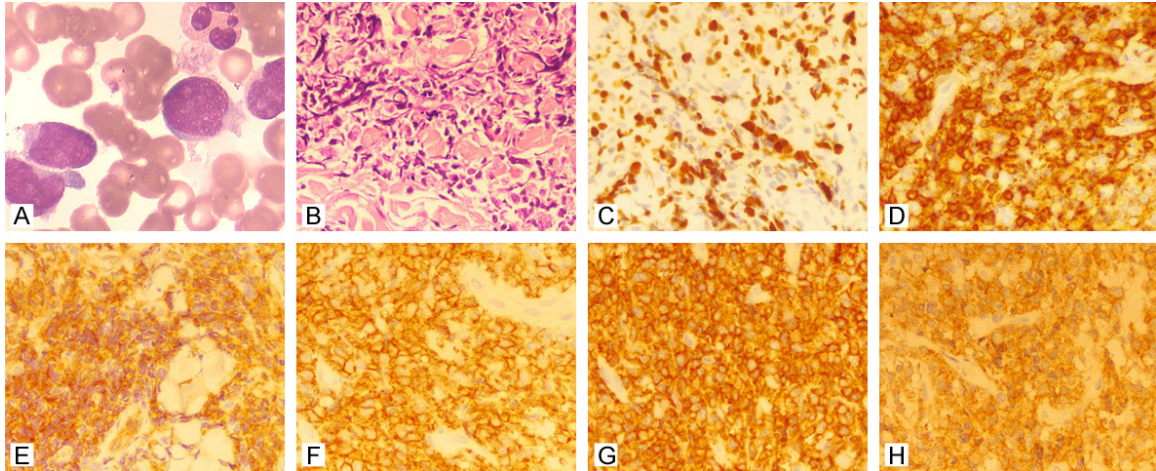


Figure 1. A. Bone marrow image of the patient (Rayleigh-Jimsa staining; *100). B. The HE images of patients (Hematoxylin-Eosin staining; *40). C-H. The immunohistochemical results of different markers (*40); The markers of C-H image are ki67, CD4, CD123, CD56, CD43 and CD33, respectively.

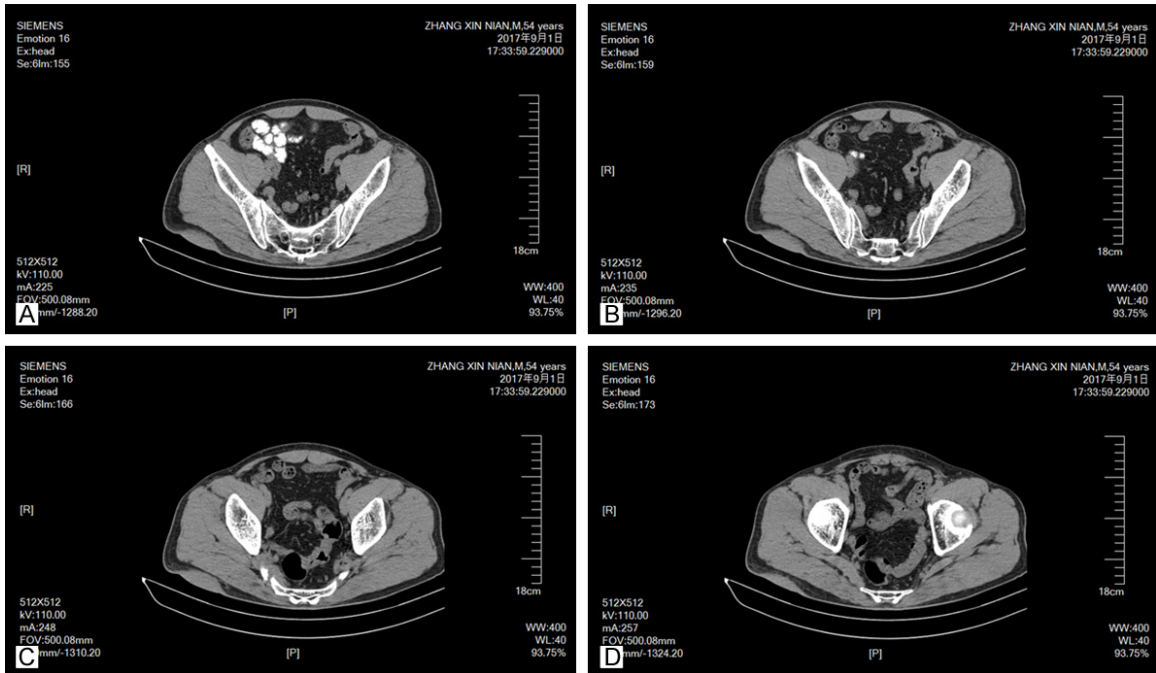


Figure 2. CT of a subcutaneous tumor of the hip in patients. A-D are the results of four levels from top to bottom, respectively.

examination, and the liver and spleen did not feel enlarged. Auxiliary examination: WBC $1.35 \times 10^9/L$, Hb 124g/L, Plt $58 \times 10^9/L$. Fasting blood glucose: 12.61 mmol/L, no abnormalities were found in other biochemical examinations. Bone marrow smear: The proliferation of the nucleated cells was obviously active. About 2% of the abnormal large cells were found in the smear. The cells were large and irregular in

shape. The nuclei were round or oval. Some of the cells were pitted and distorted. There were 1 to 2 nucleoli in the nucleus. The cells were abundant in quality and stained blue. Some cells had tails. However, the flow cytometry of the bone marrow cells showed that the BPDCN residual cells were less than 10^{-4} . Diagnosis: 1. BPDCN bone marrow invasion CR1 2. Type 2 diabetes.

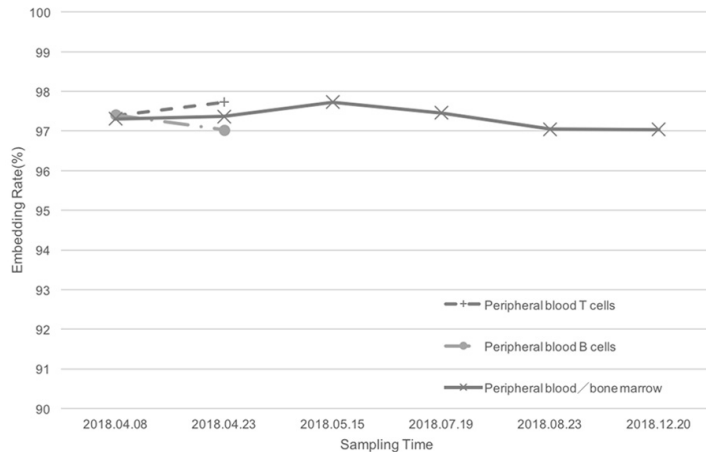


Figure 3. Donor-recipient DNA chimerism rate.

Allo-HSCT

After two cycles of intensive treatment of MA regimen (methotrexate 1.5 g/m² d1; cytarabine 1.0 g/m², d2-3.), the bone marrow images showed a complete remission and the minimal residual disease detected by flow cytometry was negative. The patient and his family strongly desired transplantation, but they had no compatible HLA donors. On March 23, 2018, a paternal HLA 5/10 matched bone marrow + peripheral blood stem cell transplantation was performed.

Results

Pretreatment regimen: total body irradiation (TBI) FTBI (4 Gy × 2, total lung dose 6 Gy) + CY (cyclophosphamide 1.8 g/m² × 2 d) + Flu (30 mg/m² × 4 d) + ATG (10 mg/kg); CSA + MMF + MTX to prevent GVHD. MNC 6.45 × 10⁸/kg and CD34 + cells 7.40 × 10⁶/kg were transfused. Granulocyte and platelet were implanted at +12 d and +14 d respectively. An oral mucosal ulcer and perioral herpes appeared on the +17 d, and HSV-DNA was positive. The symptoms improved after antiviral treatment. Bone marrow phenomena at +32 d showed remission. The DNA chimerism rate of the donor and the recipient bone marrow cells was 97.37%, The T cell chimerism rate of the peripheral blood was 97.73%, and the B cell chimerism rate of the peripheral blood was 97.03%. Beta 2-microglobulin: 4.20 mg/L, urea: 548.0 mmol/L, creatinine: 158.0 mmol/L were examined at +42 d. The above indexes returned to normal after adrenal glucocorticoids were administered.

The patient got a fever on +65 d, and his temperature was 38.2°C. He also developed the symptoms of abdominal distension. An abdominal examination showed both positive mobile voice and edema of both lower limbs. A laboratory examination displayed glutamic-oxaloacetic aminotransferase: 54.0 U/L glutamic-alanine aminotransferase: 50.8 U/L albumin: 27.2 g/L, LDH 288 U/L, and serum CMV and EBV DNA were positive. The lung CT showed that there was a small amount of effusion in the pericardium and the right thoracic cavity. Abdominal CT findings: 1. Hydrocele in abdominal

cavity, multiple exudation in the abdominal and pelvic cavities; 2. Splenomegaly. Based on the above results, the following diagnosis was considered: Thrombotic microangiopathy? Hypoproteinemia; CMV; EBV. Biapenem combined with caspofungin acetate and other antibiotics were given successively for the anti-infection treatment. Cyclosporine, MMF and methylprednisolone were given for anti-GVHD, and ganciclovir and foscarnet were given for antiviral treatment. Meanwhile, a plasma infusion, and an intravenous injection of human immunoglobulin, albumin, and diuretics were given intermittently. His symptoms improved after about 90 days. The virus was undetectable again.

At present, the patient is in good condition and his organ function is normal. Now it is ten months after the transplantation. The donor and recipient DNA chimerism tests indicated a complete chimerism. At present, the patient is in the process of gradual reduction of immunosuppressive agents, without cGVHD (**Figure 3**).

Discussion

BPDCN is a rare disease. It has been found that the tumor cells, like plasmacytoid dendritic cells (PDC), have a strong expression of CD123 [interleukin (IL) - 3 receptor alpha chain]. The other immune phenotypes and the biological behavior of BPDCN and PDC are similar. So, it is believed that they are precursor cells derived from PDC. BPDCN is predominant in the elderly, but cases occurring at all ages have been reported. The average age of onset is 61-67

years old, and the ratio of male to female is 3.3:1 [2]. Skin lesions are often the first clinical manifestations of BPDCN. The skin lesions may present as erythema, plaques, nodules or acne, and some cases have ulcer formation. The disease can involve the peripheral blood, the bone marrow, and the lymph nodes at the same time. It is highly invasive and has a poor prognosis. The markers for BPDCN are CD4+, CD56+ and CD123+, but the markers for other B cells, T cells, and myeloid line cells are negative.

Because of the low morbidity of this disease, there is no standard clinical treatment. Earlier studies have reported that treatments including radiotherapy, such as ALL-like, AML-like, NK/T-like, and CHOP-like regimens with different intensities had higher remission rates, but the recurrence rate was also higher, and the median survival time was about one year [3-6]. High-intensity treatment can effectively prolong the remission time, so most advocate that hematopoietic stem cell transplantation at the early stage of remission can prolong the duration of remission and even achieve a cure [4]. A study by Reimer [6] analyzed 97 patients with BPDCN retrospectively. The results showed that the response rates of different chemotherapy regimens were similar in the initial treatment, but the patients with a reduced intensity regimen had a rapid relapse. DFS and OS in the acute leukemia regimen group and in the transplantation group had obvious advantages. The median survival time of 6 patients receiving allo-HSCT was 38.5 months, and the median survival time of the 4 patients receiving auto-HSCT was 16.5 months. The results showed that the intensity of treatment was proportional to the CR time, and the overall survival rate was significantly improved by HSCT in the CR1 phase. Roos-Weil [7] suggested that the probabilities of 3 year RFS, OS, and DFS of 34 BPDCN patients who received transplant were 32%, 41%, and 33% respectively. And the 3 year DFS and OS probabilities of patients with CR1 were 45% and 60% respectively. The results from Pagano's work [8] also showed that the OS of patients receiving chemotherapy alone was significantly different from those receiving allo-HSCT after disease remission (7.1 m vs 22.7 m). Most patients died from disease progression. The patients underwent hematopoietic stem-to-fine transplantation after obtaining CR1.

There is no randomized controlled study on the efficacy of allo-HSCT or auto-HSCT in the treatment of BPDCN. More studies have shown that allogeneic transplantation has an advantage in prolonging the survival of BPDCN patients [9]. A retrospective study done by Kharfan-Dabaja was conducted on 45 BPDCN patients from 8 transplantation centers in the United States and Canada (allo-HSCT 37 cases, auto-HSCT 8 cases). The 1-year and 3-year OS rates in the allo-HSCT group were 68% and 58% respectively, while those in the CR1 stage were 88% and 74% respectively, and the 1-year OS of the auto-HSCT patients was only 11% (the pre-treatment was the BEAM scheme). The CR1 patients were predominant in both the auto-HSCT and allo-HSCT groups (75.7% and 62.5%). Univariate and multivariate analyses showed that disease status before allogeneic transplantation was the main factor affecting patient prognosis. Japanese scholars reported different results. Aoki [10] reported 25 cases of BPDCN. The 4-year OS rates of the allo-HSCT group (14 cases) and the auto-HSCT group (11 cases) were 53% and 82%, respectively. All the patients in the auto-HSCT group and 10 patients in the allo-HSCT group were in the CR1 stage before transplantation. Therefore, auto-HSCT can also be attempted in patients without suitable donors after obtaining CR1. We reported that patients treated with the CHOP-E regimen had no definite complete remission after 3 courses of chemotherapy. Allo-HSCT was used to reduce the recurrence rate after transplantation.

Transplantation schemes and donor selection are different. The efficacy of myeloablation pre-conditioning (MAC) and intensity reduction pre-conditioning (RIC) has also been reported differently. Roos-Weil [7] reported that TBI/Cy-based pulp-clearing pretreatment (17/25 cases, TBI > 10 Gy), DFS and OS were significantly better than RIC-based pretreatment (3/9 cases included TBI, TBI < 2 Gy). Dietrich [11] reported 4 patients with an average age of 66.7 years (56-70 years). Using the RIC protocol, the donors were HLA 8/10-9/10 matched and were unrelated. Two patients survived for a long time. It seems that older patients can benefit from RIC regimens.

Relative haploidentical transplantation has been widely carried out in China, including in our transplantation centers. But there are few

reports of BPDCN haploidentical transplantation. In the case series of Kharfan-Dabaja, 3 half-matched donors were transplanted, but the therapeutic effect was not analyzed separately [9]. Cao Honggang reported a case of CR1 HLA maternal-female haplotype hematopoietic stem cell transplantation [12]. The pre-treatment scheme was Cladribine + Bu + Ara-C + ATG, which survived for 15 months without transplantation-related complications. Zhou Hongsheng [13] reported that a 26-year-old BPDCN patient died of thrombotic microangiopathy and diffuse intraalveolar hemorrhage after CR1 HLA 7/10 matched brother BM + PBSCT transplantation including a TBI-containing super pretreatment, +6mDLI. There are few studies on the effect of GVHD on long-term remission after transplantation. EBMT data show that the incidence of aGVHD is about 50%. Among them, 3-4 degree GVHD was 14%, cGVHD was 41%, and extensive cGVHD was 16% [7]. In North America, the average occurrence time of aGVHD was over 35 days, with an incidence of 37%. In one year, the occurrence rate of cGVHD was 61%, and that of moderate and severe cGVHD was 28% [9]. However, the effect of DLI on the prevention and treatment of recurrence has only been reported in a few cases, and the effect is quite different [13, 14]. Flow cytometry was used to detect minimal residual disease in bone marrow cells and the DNA chimerism of donors and recipients. Cyclosporin was adjusted according to the results and clinical manifestations of GVHD. Up to now, no DLI was performed, and no severe GVHD occurred.

Acknowledgements

We sincerely thank all involved for their support of our research.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xue-Jun Zhang, Department of Hematology, The Second Hospital of Hebei Medical University, 215 West Heping Road, Shijiazhuang 050000, China. Tel: 86-13722781112; E-mail: zhxjhbmu@126.com

References

- [1] Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Ca-

- zzola M and Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127: 2391-2405.
- [2] Jegalian AG, Facchetti F and Jaffe ES. Plasmacytoid dendritic cells: physiologic roles and pathologic states. *Adv Anat Pathol* 2009; 16: 392-404.
- [3] Pagano L, Valentini CG, Grammatico S and Pulsoni A. Blastic plasmacytoid dendritic cell neoplasm: diagnostic criteria and therapeutical approaches. *Br J Haematol* 2016; 174: 188-202.
- [4] Dalle S, Beylot-Barry M, Bagot M, Lipsker D, Machet L, Joly P, Dompormartin A, d'Incan M, Maubec E, Grange F, Dereure O, Prey S, Barete S, Wetterwald M, Fraïtag S and Petrella T. Blastic plasmacytoid dendritic cell neoplasm: is transplantation the treatment of choice? *Br J Dermatol* 2010; 162: 74-79.
- [5] Han X, Ouyang MQ, Pei Q, Duan MH, Jiang XY and Zhou DB. Clinical characteristics of 6 patients with blastic plasmacytoid dendritic cell neoplasm. *Zhonghua Xue Ye Xue Za Zhi* 2017; 38: 700-705.
- [6] Reimer P, Rüdiger T, Kraemer D, Kunzmann V, Weissinger F, Zettl A, Müller-Hermelink HK and Wilhelm M. What is CD4+ CD56+ malignancy and how should it be treated? *Bone Marrow Transplant* 2003; 32: 637-646.
- [7] Roos-Weil D, Dietrich S, Boumendil A, Polge E, Bron D, Carreras E, Atienza AI, Arcese W, Beelen DW and Cornelissen JJ. Stem cell transplantation can provide durable disease control in blastic plasmacytoid dendritic cell neoplasm: a retrospective study from the European group for blood and marrow transplantation. *Blood* 2013; 121: 440-446.
- [8] Pagano L, Valentini CG, Pulsoni A, Fisogni S, Carluccio P, Mannelli F, Lunghi M, Pica G, Onida F and Cattaneo C. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. *Haematologica* 2013; 98: 239-246.
- [9] Kharfan-Dabaja MA, Al Malki MM, Deotare U, Raj RV, El-Jurdi N, Majhail N, Cherry MA, Bashir Q, Darrah J and Nishihori T. Hematopoietic cell transplantation for blastic plasmacytoid dendritic cell neoplasm: a North American multicentre collaborative study. *Br J Haematol* 2017; 179: 781-789.
- [10] Aoki T, Suzuki R, Kuwatsuka Y, Kako S, Fujimoto K, Taguchi J, Kondo T, Ohata K, Ito T and Kamoda Y. Long-term survival following autologous and allogeneic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm. *Blood* 2015; 125: 3559-3562.
- [11] Dietrich S, Andrulis M, Hegenbart U, Schmitt T, Bellos F, Martens UM, Meissner J, Krämer A, Ho AD and Dreger P. Blastic plasmacytoid den-

- dritic cell neoplasia (BPDC) in elderly patients: results of a treatment algorithm employing allogeneic stem cell transplantation with moderately reduced conditioning intensity. *Biol Blood Marrow Transplant* 2011; 17: 1250-1254.
- [12] Cao HG, Wu T, Guo M, Xi R, Liu TT, Xue F, Wang CB and Bai H. Haploidentical allogeneic hematopoietic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm: a case report and literatures review. *Zhonghua Xue Ye Xue Za Zhi* 2018; 39: 674-675.
- [13] Zhou H, Na X, Sun J, Deng Y, Jiang Q, Guopang Y and Liu Q. Allogeneic hematopoietic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasms. *Journal of Leukemia & Lymphoma* 2012; 21: 659-662.
- [14] Steinberg A, Kansal R, Wong M, Lopez A, Lim S, Lopategui J and Lill M. Good clinical response in a rare aggressive hematopoietic neoplasm: plasmacytoid dendritic cell leukemia with no cutaneous lesions responding to 4 donor lymphocyte infusions following transplant. *Case Rep Transplant* 2011; 2011: 651906.