CASE REPORT

Effective Treatment of a Childhood Blastic Plasmacytoid Dendritic Cell Neoplasm with a Cutaneous Tumor Alone by Stem Cell Transplantation with Reduced Intensity Conditioning

Maiko Shimomura^{1,2} · Takaki Asano¹ · Aya Furue¹ · Mizuka Miki¹ · Yasuhiko Sera¹ · Hiroshi Kawaguchi¹ · Kazuhiro Nakamura¹ · Masao Kobayashi¹

Received: 6 January 2015 / Accepted: 13 April 2015 / Published online: 21 April 2015
© Indian Society of Haematology & Transfusion Medicine 2015

Abstract Pediatric blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological malignancy that has an extremely poor prognosis despite the use of intensive chemotherapy. Recently, treatment of BPDCN with bone marrow transplantation (BMT) using myeloablative conditioning has been reported to increase survival in adults. We report a 9-year-old girl with cutaneous BPDCN who was successfully treated with combination chemotherapy followed by BMT using reduced intensity conditioning (RIC), without any adverse complications. The success of this treatment regimen suggests that BMT with RIC may be a feasible option for treating children with cutaneous BPDCN.

Keywords Blastic plasmacytoid dendritic cell neoplasm (BPDCN) · Cutaneous tumor · Hematopoietic stem cell transplantation (HSCT) · Reduced-intensity stem-cell transplantation (RIST)

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological malignancy, which was previously known as blastic natural killer (NK)-cell leukemia/lymphoma, agranular CD4+ NK-cell leukemia, or CD4+/
CD56+ hematodermic neoplasm [1]. According to the 2008 revision of the World Health Organization (WHO) classification of myeloid disorders and leukemia, BPDCN is considered to be a myeloid neoplasm [1]. It is a clinically aggressive tumor known to be derived from the precursors of plasmacytoid dendritic cells (pDCs) (CD123+) with a high frequency of cutaneous and bone marrow involvement [2]. The overall prognosis is dismal, with a median overall survival of 12–14 months [3]. Recent studies suggest that the best treatment options include intensive, acute lymphoblastic leukemia (ALL)-like chemotherapy, followed by hematopoietic stem cell transplantation (SCT) in the first complete remission (CR) [4]. Recently, in adult case, it has been observed that skin-restricted BPDCN shows no better outcome than primarily disseminated, hence, aggressive management including SCT should be considered despite the fact that BPDCN may initially appear as a localized skin [5]. After all, the treatment including indication of SCT and recommended conditioning regimen of BPDCN being initially limited to the skin remain controversial and not standardized. We described a girl with BPDCN, which exclusively involved the skin at presentation. Knowledge of pediatric BPDCN is especially limited, with only a few case reports described in the literature; further, there are no clinical reports of pediatric BPDCN treated with reduced-intensity stem-cell transplantation (RIST). In this report, we describe the case of a 9-year-old girl with cutaneous BPDCN who was treated with RIST.

Case Report

A 9-year-old girl with a 2-month history of a gradually enlarging subcutaneous mass (1 × 1 cm) in her left forearm was referred to our hospital for treatment. Physical

✉ Maiko Shimomura
shimomai0105@yahoo.co.jp

¹ Department of Pediatrics, Hiroshima University Graduate School of Biomedical & Health Sciences, Hiroshima, Japan

² Department of Pediatrics, Yamaguchi University Graduate School of Medicine, 1-1-1 Minamikogushi, Ube 755-8505, Japan

examination revealed a palpable solid, painless, 3×3 cm subcutaneous mass (Fig. 1). No hepatosplenomegaly or lymphadenopathy were found. Laboratory data revealed a normal complete blood count, chemistry panel, and cerebrospinal fluid cell count. The titer of soluble interleukin-2 receptor (sIL-2R) was 346 U/mL. A pretreatment whole body PET/CT scan showed increased 3H-2-fluoro-2-deoxy-D-glucose (FDG) uptake within the subcutaneous mass on the left forearm (Fig. 2). PET/CT was performed after biopsy, therefore it only showed local surgical stress and no metastasis. A biopsy specimen showed tumor cells with irregular nuclei and eosinophilic inclusion bodies diffusely invading the subcutaneous fatty tissue from the dermis. Neoplastic cells were positive for CD4, CD56, CD123, and TdT (Fig. 3), and negative for CD3, CD5, CD7, CD20, MPO, and TIA-1, indicating BPDCN. No bone marrow involvement was found morphologically. The subcutaneous mass completely resected was relapsed immediately. After local re-excision of the lesion, the patient received systemic lymphoblastic lymphoma-type chemotherapy including prednisolone, dexamethasone, cyclophosphamide, L-asparagine, cytarabine, vincristine, daunorubicin, methotrexate, and mercaptopurine according to Phase II clinical trial of limited stage lymphoblastic lymphoma (ALB-NHL03) by Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG). After four cycles of chemotherapy, bone marrow transplantation (BMT) was performed from a HLA-DR one-locus mismatched unrelated donor (allele-level, 7/8 match) due to a paucity of compatible related or unrelated donors. Since the patient underwent BMT in the state of full remission, prevention against treatment-related early and late toxicities was carried out by using RIST. Table 1 shows conditioning regimens. Graft-versus-host disease (GVHD) prophylaxis included tacrolimus and short course methotrexate. A total

Fig. 1 Subcutaneous mass in the left forearm on admission. Size 3×3 cm, color dull red, solidity hard, pain no tenderness. (Color figure online)

of 1.3×10^8 /kg BM nucleated cells were transplanted. The early post-transplantation period was uneventful, however, the patient presented with fever and rash on the face and extremities including palm on day 10. The rash was erythematous with pruritus and spread to over 50 % of the body surface. She had mild diarrhea but not icteric. It was diagnosed as grade 2 GVHD. Treatment with methylprednisolone was effective against symptoms of GVHD. Engraftment was achieved on day 19. At day 29, GVHD was improved but mild pruritus became persistent. At day 42, CMV antigenemia appeared and treated by administration of ganciclovir. Although she had mild hepatic dysfunction, it was improved immediately. At day 63, CMV antigenemia was improved and ganciclovir was stopped. She didn't have other infections. After that, she has been achieved complete donor chimerism. At day 104, she was discharged without any complication. After 29 months, the patient was found to have no GVHD and was in full remission without any apparent toxicity.

Discussion

BPDCN has been known to be an entity derived from the precursors of pDCs. However, the origin of pDCs has been controversial. It seems that both pDCs and common DCs may be derived from a common DC precursor [6]. On the other hand, some studies suggest that pDCs can originate from a common lymphoid progenitor [7]. We have described a pediatric case of BPDCN. Notably, this case with lesion restricted to the skin was treated performing BMT using RIST in the status of full remission.

BPDCN usually occurs in older patients and is characterized by a high frequency of manifestations in the skin, lymph node, and bone marrow [2, 8, 9]. The phenotypic appearance of the cutaneous lesions is variable, ranging from local to diffuse. The overall prognosis is dismal, with a median overall survival of 12–14 months [3]. To date, the treatment of BPDCN is not standardized owing to extremely poor prognosis. Classical chemotherapy regimens for acute myeloid leukemia have been disappointing, as the initial response has most often been followed by early relapse [6, 10, 11]. Several studies suggest that patients can be successfully treated with combination chemotherapy for ALL followed by hematopoietic SCT [4, 12, 13]. Dalle et al. reported a case study of BPDCN in 47 patients ranging in age from 8 to 96 years. In total, BMT was performed in ten patients. The difference in overall survival between patients with BMT (mean, 31.3 months) and those without BMT (mean, 12.8 months) was highly significant ($P = 0.0018$) [6]. The study confirmed that an aggressive treatment strategy that included BMT was necessary to ensure improved clinical outcome.

Fig. 2 A pretreatment whole body PET/CT scan. This showed increased FDG uptake within the subcutaneous mass on the left forearm. Cervical and axillary adenopathy were present without significant findings. No metastasis was observed

Pediatric cases of BPDCN are rare, with only a few case reports and a small collection of cases described in the literature. For instance, Jegalian et al. reported 29 cases of childhood-onset BPDCN [14]. In children who underwent SCT, the overall survival was 67 % (4/6 cases), compared with 74 % (14/19 cases) in non-transplanted patients [14]. Importantly, the two patients who died despite receiving SCT had not received initial combination chemotherapy and concerned about the possibility of not full remission before SCT. Jegalian et al. also reported 11 of the 18 children with cutaneous BPDCN survived (61 % survival; median follow up, 60 months) [14]. Additionally, Sagashita et al. reported 3-year overall survival was 57.4 ± 10.9 % in a total of 32 cases of pediatric BPDCN for whom follow up information was available [15]. SCT was applied in first or second remission to two of eight patients who lacked skin involvement, and 6 of 23 patients with cutaneous disease [15]. For these reports of CR and long-term survival without SCT in children, in contrast to BPDCN in adults, where the long-term survival depends on SCT in the first CR, BPDCN in children may be clinically less aggressive. SCT may be reserved for children who relapse and achieve a second remission. Although, it has been reported that BPDCN cases with skin involvement had more unfavorable outcome than with leukemia and a lack of skin involvement [14–16]. Sagashita et al. also reported the overall survival in eight children with BPDCN without cutaneous disease at presentation was significantly higher than the value in children with skin involvement

[15]. But this report included not only BPDCN with lesion restricted to the skin. A summary of eight cases of pediatric BPDCN being initially limited to the skin is shown in Table 2 [17–21]. With only a few case reports of pediatric BPDCN being initially limited to the skin, treatment remains controversial and not standardized, especially. SCT has been considered as an alternative treatment strategy in case of failure of chemotherapy. But we selected SCT following combination chemotherapy due to early local relapse and poor prognosis of BPDCN in adults and with lesion restricted to the skin. Since BPDCN in children is rare, the efficacy and necessity of SCT for treating pediatric BPDCN has also been controversial. Our current case study suggests that consecutive treatment of combination chemotherapy following SCT may be effective for pediatric patients with BPDCN. In addition, we used RIST for the possibility of prevention of treatment-related early and late toxicities. In recent years, reduced intensity conditioning (RIC) regimens have been demonstrated to be safe and efficacious for adult hematologic malignancies [22]. Since most RIC regimens use relatively low doses of chemotherapy, transplant-related morbidity and mortality are low [23]. Whereas relapse rates after RIC may be higher, reductions in transplant-related morbidity and mortality have generally compensated for this, and several studies have shown outcomes comparable with myeloablative conditioning (MAC) [24]. Dietrich et al. suggested that allogeneic (allo) SCT with RIC may be an effective treatment against BPDCN in elderly patients up to 70 years

Fig. 3 A histological examination showed tumor cells with irregular nuclei and eosinophilic inclusion bodies diffusely invading the subcutaneous fatty tissue from the dermis. Hematoxylin and eosin stained tumor cells (**a** magnification $\times 100$ and **b** magnification $\times 400$). Tumor cells were positive for CD4 (**c** magnification $\times 400$), CD56 (**d** magnification $\times 400$), CD123 (**e** magnification $\times 400$), and TdT (**f** magnification $\times 400$)

of age [3]. To date, there have been no clinical reports of pediatric BPDCN cases treated with RIST. Recently, a study of 34 patients with BPDCN who underwent allo-SCT between 2003 and 2009 was reported [19]. In this study, a MAC regimen was used in 74 % ($n = 25$) and RIC regimen was used in 26 % of the cases ($n = 9$) [3]. Disease free survival, and overall survival was significantly better in patients who received the MAC regimen than in those who received the RIC regimen. The poor outcome of patients treated with RIC was largely due to a high non-relapse mortality (NRM) rate; none of the patients treated with RIC were able to achieve prolonged disease control owing to early relapse or death. However, patients treated with RIC were significantly older than those treated with MAC (median age, 62 vs. 36 years; $P = 0.005$), and the

high mortality rate in the RIC group was due to NRM, rather than relapse [3]. In this study two groups has significant difference of median age, therefore, we can't make a simple comparison of outcome between MAC and RIC. It is also difficult to conclude the efficacy of using RIC to treat BPDCN, especially in children. The results of a phase 2 trial of RIC transplantation concluded that favorable outcomes could be achieved for children and adolescents with hematologic malignancy in remission at ransplantation [25].

Indeed, if BPDCN in children was clinically less aggressive than that in adults, RIST may be an effective treatment option for prevention against treatment-related early and late toxicities, especially in patients who are in remission. Treatment related late toxicities such as infertility and growth

Table 1 Conditioning regimen

Day		−7	−6	−5	−4	−3	−2	−1	0
Fludarabine	25 mg/m ²		↓	↓	↓	↓	↓		
Melphalan	70 mg/m ²		↓				↓		
Rabbit antithymocyte globulin	2.5 mg/kg					↓	↓		
Total body irradiation	3 Gy	↓							

Conditioning regimens included 3 Gy total body irradiation (day 7), fludarabine 25 mg/m² (×5 days, from day 6 to day 2), melphalan 70 mg/m² (×2 days, day 6 and day 2), and rabbit antithymocyte globulin 2.5 mg/kg (×2 days, day 3 and day 2)

Table 2 Summary of reported pediatric BPDCN cases with lesion restricted to the skin

Patient no.	Age/sex	Treatment	Response	Survival	Reference
1	4/F	NHL	CR	Alive 132mo	[14]
2	7/F	NHL, ALL → alloSCT	CR → relapse	Dead 23mo	[14]
3	5/F	ALL	CR	Alive 12mo	[17]
4	17/F	CHOP → alloSCT	CR	Alive 24mo	[18]
5	15/M	AML → alloSCT	CR	Alive 12mo	[19]
6	7/M	NA	CR	Alive 20mo	[20]
7	9/M	NA	CR	Alive 18mo	[21]
8	9/F	ALL → alloSCT(RIST)	CR	Alive 29mo	Current

ALL acute lymphoblastic leukemia, AML acute myeloid leukemia, CHOP cyclophosphamide, doxorubicin, vincristine, and prednisolone, CR complete remission, SCT stem cell transplantation, M male, F female, NA not available

deficiency and secondary malignant neoplasms have been reported in patients who received BMT with MAC. RIC regimens might be the preservation of fertility and the reduced risk of secondary malignant neoplasms [18]. Hence, the MAC regimen is preferably best avoided in children as for late toxicities. Although the role of RIC regimens in pediatric cancer treatment remains unclear [25], the possibility of prevention against treatment-related early and late toxicities is considerable. Further studies are required to determine the necessity of BMT and the efficacy of BMT with RIST, as well as the most appropriate treatments for children with BPDCN, particularly being initially limited to the skin.

Acknowledgments We thank Atsuko Nakagawa, MD, Department of pathology, National Center for Child Health and Development, Tokyo, Japan, for the histological examination and the immunohistochemical staining.

References

- Vardiman JW, Thiele J, Arber DA et al (2009) The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* 114:937–951
- Petrella T, Bagot M, Willemze R et al (2005) Blastic NK cell lymphomas (agranular CD4+ CD56+ hematodermic neoplasms). *Am J Clin Pathol* 123:662–675
- Roos-Weil D, Dietrich S, Boumendil A et al (2013) Stem cell transplantation can provide durable disease control in blastic plasmacytoid dendritic cell neoplasm (BPDCN). *Blood* 121:440–446
- Yamaguchi M, Maekawa M, Nakamura Y et al (2005) Long-term remission of blastic natural killer-cell lymphoma after autologous peripheral blood stem-cell transplantation. *Am J Hematol* 80:124–127
- Margo CM, Porcu P, Schaefer J et al (2010) Cutaneous CD4⁺ CD56⁺ hematologic malignancies. *J Am Acad Dermatol* 63:292–308
- Dalle S, Beylot-Barry M, Bagot M et al (2010) Blastic plasmacytoid dendritic cell neoplasm: is transplantation the treatment of choice? *Br J Dermatol* 162:74–79
- Chicha L, Jarrossay D, Manz MG (2004) Clonal type I interferon-producing and dendritic cell precursors are contained in both human lymphoid and myeloid progenitor populations. *J Exp Med* 200:1519–1524
- Herling M, Jones D (2007) CD4+/CD56+ hematodermic tumor: the features of an evolving entity and its relationship to dendritic cells. *Am J Clin Pathol* 127:687–700
- Cota C, Vale E, Viana I et al (2010) Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm-morphologic and phenotypic variability in a series of 33 patients. *Am J Surg Pathol* 34:75–87
- Rossi JG, Felice MS, Bernasconi AR et al (2006) Acute leukemia of dendritic cell lineage in childhood: incidence, biological characteristics and outcome. *Leuk Lymphoma* 47:715–725
- Borchiellini D, Ghibaud N, Mounier N et al (2013) Blastic plasmacytoid dendritic cell neoplasm: a report of four cases and review of the literature. *J Eur Acad Dermatol Venereol* 27:1176–1181

12. Murashige N, Kami M, Kishi Y et al (2005) Allogeneic haematopoietic stem cell transplantation as a promising treatment for natural killer-cell neoplasms. *Br J Haematol* 130:561–567
13. Suzuki R, Suzumiya J, Nakamura S et al (2006) Hematopoietic stem cell transplantation for natural killer-cell lineage neoplasms. *Bone Marrow Transplant* 37:425–431
14. Jegalian AG, Buxbaum NP, Facchetti F et al (2010) Blastic plasmacytoid dendritic cell neoplasm in children: diagnostic features and clinical implications. *Haematologica* 95:1873–1879
15. Sakashita K, Saito S, Yanagisawa R et al (2013) Usefulness of Allogeneic hematopoietic stem cell transplantation in first complete remission for pediatric blastic plasmacytoid dendritic cell neoplasm with skin involvement: a case report and review of literature. *Pediatr Blood Cancer* 60:140–142
16. Rauh MJ, Rahman F, Good D et al (2012) Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation, lacking cutaneous involvement: case series and literature. *Leuk Res* 36:81–86
17. Hashikawa K, Niino D, Yasumoto S et al (2012) Clinicopathological features and prognostic significance of CXCL12 in blastic plasmacytoid dendritic cell neoplasm. *J Am Acad Dermatol* 66:278–291
18. Karube K, Ohshima K, Tsuchiya T et al (2003) Non-B, non-T neoplasms with lymphoblast morphology: further clarification and classification. *Am J Surg Pathol* 27:1366–1374
19. Gambichler T, Pantelaki I, Stücker M (2013) Childhood blastic plasmacytoid dendritic cell neoplasm treated with allogeneic stem cell transplantation. *Pediatr Dermatol* 30:142–144
20. Dijkman R, van Doorn R, Szuhai K et al (2007) Gene-expression profiling and array-based CGH classify CD4+ CD56+ hemodermic neoplasm and cutaneous myelomonocytic leukemia as distinct disease entities. *Blood* 109:1720–1727
21. Julia F, Petrella T, Beylot-Barry M et al (2013) Blastic plasmacytoid dendritic cell neoplasm: clinical features in 90 patients. *Br J Dermatol* 169:579–586
22. Slavin S, Nagler A, Naparstek E et al (1998) Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood* 91:756–763
23. Bitan M, He W, Zhang MJ et al (2014) Transplantation for children with acute myeloid leukemia: a comparison of outcomes with reduced intensity and myeloablative regimens. *Blood* 123:1615–1620
24. Sorror ML, Sandmaier BM, Storer BE et al (2007) Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. *J Clin Oncol* 25:4246–4254
25. Pulsipher MA, Boucher KM, Wall D et al (2009) Reduced-intensity allogeneic transplantation in pediatric patients ineligible for myeloablative therapy: results of the Pediatric Blood and Marrow Transplant Consortium Study ONC0313. *Blood* 114:1429–1436