Brief Report

CLINICAL TRIALS AND OBSERVATIONS

Long-term survival following autologous and allogeneic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm

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Key Points

- Auto-HSCT in CR1 provides long-term remission in BPDCN patients.

- RIC allo-HSCT and MAC allo-HSCT results are comparable.

We sought to clarify the role of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (auto-HSCT) and allogeneic hematopoietic stem cell transplantation (allo-HSCT) to treat blastic plasmacytoid dendritic cell neoplasm (BPDCN). We retrospectively identified 25 BPDCN patients (allo-HSCT, n = 14; auto-HSCT, n = 11) from registry data of the Japan Society for Hematopoietic Cell Transplantation and analyzed clinicopathologic data and clinical outcomes after transplantation. The median age at HSCT was 58 years (range, 17-67 years). All 11 patients who underwent auto-HSCT were in the first complete remission (CR1). With a median follow-up of 53.5 months, the overall survival rates at 4 years for patients who underwent auto-HSCT and allo-HSCT were 82% and 53% (P = .11), respectively, and progression-free survival rates were 73% and 48% (P = .14), respectively. Auto-HSCT for BPDCN in CR1 appears to provide promising results and deserves further evaluation in the setting of prospective trials. (*Blood*. 2015;125(23):3559-3562)

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare malignancy of plasmacytoid dendritic cells, as classified by the World Health Organization,[1] and was previously diagnosed as blastic natural killer cell lymphoma or CD4^{+}/CD56^{+} hematodermic neoplasm.[2-5] BPDCN is characterized by distinct clinical, pathologic, and genetic features[3,6-8] and is diagnosed based on the expression of immunophenotypic markers such as CD4, CD56, CD123, and TCL1.[9,10] BPDCN is a disease of advanced age, and BPDCN patients often initially present with cutaneous lesions.[3,8]

The optimal treatment strategy for BPDCN has not been established, and the prognosis of BPDCN is extremely poor, with a median overall survival (OS) of ~1 year.[2,3] Commonly used induction treatment of BPDCN varies from cyclophosphamide, doxorubicin, vincristine, and prednisolone to leukemia-like regimens.[3] Despite the initial response to chemotherapy with

41% to 94% complete remission (CR) rates,[2,3,11-13] almost all cases eventually develop into a fulminant chemoresistant leukemic phase. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) with myeloablative conditioning (MAC) during remission has shown encouraging results for patients with BPDCN.[3,12-17] Meanwhile, only a few small case series were described that showed the benefit of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (auto-HSCT) or reduced-intensity conditioning (RIC) allo-HSCT.[12,14,15,18,19] Because BPDCN is a disease of advanced age, clarifying the role of the RIC regimen or auto-HSCT in BPDCN is crucial.

The present study aimed to clarify the role of both allo-HSCT and auto-HSCT in treating BPDCN using registry data from the Japan Society for Hematopoietic Cell Transplantation.

Study design

All patients with a diagnosis of "BPDCN," "blastic natural killer cell lymphoma," "CD4$^+$/CD56$^+$ hematodermic neoplasm," or "dendritic cell leukemia" ≥15 years of age who underwent the first HSCT in 2002 or later were identified in the Transplant Registry Unified Management Program (TRUMP),[20] which is the registry data of the Japan Society for Hematopoietic Cell Transplantation . The initial diagnosis was made by hematopathologists in each institution. Baseline information and transplantation characteristics of the selected patients were obtained from TRUMP. Then, we sent out questionnaires to collect additional data regarding clinical presentation, histopathology, and flow cytometry reports and therapies before HSCT and follow-up updates. In addition, a central clinicopathologic review was performed by 7 of the authors to confirm the diagnosis of BPDCN in accordance with the World Health Organization classification.[1] The study protocol was approved by the Institutional Review Board at Nagoya Daini Red Cross Hospital and Shimane University where this study was organized and was performed in accordance with the Declaration of Helsinki.

Results and discussion

Of the 109 identified patients in TRUMP, additional data were obtained for 83 patients. After central clinicopathologic review, 58 patients were excluded from analysis because of a different diagnosis or the absence of important clinical data. Finally, the diagnosis of BPDCN was confirmed in 25 patients (allo-HSCT, n = 14; auto-HSCT, n = 11).

The median age at HSCT was 58 years (range, 17-67 years), and male patients were predominant (80%). Involvement of the skin and bone marrow (BM) at diagnosis was observed in 88% and 68% of patients, respectively. No significant difference was found in baseline characteristics between the auto-HSCT group and the allo-HSCT group (Table 1). The induction regimen was as follows: non-Hodgkin lymphoma (NHL)-like (eg, cyclophosphamide, doxorubicin, vincristine, and prednisolone-like or ifosfamide/etoposide based) (n = 11), acute lymphoblastic leukemia (ALL)-like (n = 10), and acute myeloid leukemia (AML)-like (n = 4) regimens. The rate of initial response to induction chemotherapy was high, with a CR rate of 96%.

The median time from diagnosis to HSCT was 6 months (range, 2-22 months). Among the patients who underwent allo-HSCT, MAC and RIC regimens were used in 8 (57%) and 6 (43%) patients, respectively. The allogeneic transplant donor was a relative in 7 patients, unrelated bone marrow in 7 patients, and cord blood in 1 patient. Regarding the disease status at transplantation, all 11 patients who underwent auto-HSCT were in CR1, whereas among patients who underwent allo-HSCT, 12 were in CR1 (n = 10; RIC allo-HSCT, n = 5; MAC allo-HSCT, n = 5)/CR2 (n = 2; RIC allo-HSCT, n = 1; MAC allo-HSCT, n = 1), and 2 (MAC allo-HSCT) were not in remission.

With a median follow-up of 53.5 months in surviving patients, OS and progression-free survival (PFS) at 4 years after HSCT were 65% and 58%, respectively. OS at 4 years for patients who underwent auto-HSCT and allo-HSCT in CR1 was 82% and 69%, respectively (P = .44), and PFS at 4 years was 73% and 60%, respectively (P = .43; Figure 1A-B). The 3 induction regimen groups (NHL-like, ALL-like, and AML-like regimens) had similar OS rates: 62%, 70%, and 67% at 4 years, respectively (P = .86). OS did not differ significantly between MAC and RIC groups (OS at 4 years: 45% vs 60%, respectively; P = .31).

Nonrelapse death within 1 year occurred in 0 and 2 (gastrointestinal bleeding and suicide) patients in the auto-HSCT and allo-HSCT groups,

Table 1. Patient characteristics

Characteristic	All		Auto-HSCT		Allo-HSCT		P value
	No.	%	No.	%	No.	%	
Patient number	25		11		14		
Age at HSCT (years)							
Median	58		57		58		.891
Range	17-67		19-67		17-64		
>60 years	9	36	3	27	6	43	.335
Sex, Male	20	80	9	82	11	79	.622
PS, ≥2 at HSCT	2	8	1	9	1	7	.697
Clinical presentation at diagnosis							
Skin	22	88	10	91	12	86	.593
Lymph nodes	12	48	4	36	8	57	.265
Peripheral blood	7	28	2	18	5	36	.496
Bone marrow	17	68	8	73	9	64	.496
Induction treatment							
NHL-like	11	44	7	64	4	29	.089
ALL-like	10	40	4	36	6	43	.534
AML-like	4	16	0	0	4	29	.079
Disease status at HSCT							
CR1	21	84	11	100	10	71	.079
CR2	2	8	0	0	2	14	
Refractory	2	8	0	0	2	14	
Time from diagnosis to HSCT, months							
Median	6		6		5		.496
Range	2-22		2-7		2-22		
Year of HSCT, median	2009		2007		2010		
Range	2003-2013		2003-2011		2004-2013		
Donor type							
Related					7	50	
Unrelated					7	50	
Stem cell source							
Peripheral blood					5	36	
Bone marrow					8	57	
Cord blood					1	7	
Myeloablative conditioning					8	57	
TBI+CY					4	29	
TBI+CY+CA					1	7	
Other TBI based					1	7	
BU based					2	14	
Reduced-intensity conditioning					6	43	
Flu+Bu+TBI					2	14	
Flu+Mel+TBI					1	7	
Flu+Bu					1	7	
Flu+Mel+TBI					1	7	
Other Flu based					1	7	
High-dose regimen for auto-HSCT							
MCEC based			4	36			
MEAM based			2	18			
TBI bases			4	36			
LEED			1	9			

BU, busulfan; CA, cytarbine; CY, cyclophosphamide; Flu, fludarabine; LEED, cyclophosphamide, etoposide, melphalan, and dexamethasone; MCEC, ranimustine, carboplatin, etoposide, and cyclophosphamide; MEAM, ranimustine, etoposide, cytarbine, and melphalan; Mel, melphalan; TBI, total body irradiation.

respectively. Cumulative incidence of relapse is shown in Figure 1C. Seven patients (28%) relapsed at a median of 10 months (range, 3-21 months) after HSCT (MAC allo-HSCT, n = 2; RIC allo-HSCT, n = 3; auto-HSCT, n = 2). Notably, no relapse occurred in patients without BM infiltration at diagnosis in the auto-HSCT treatment
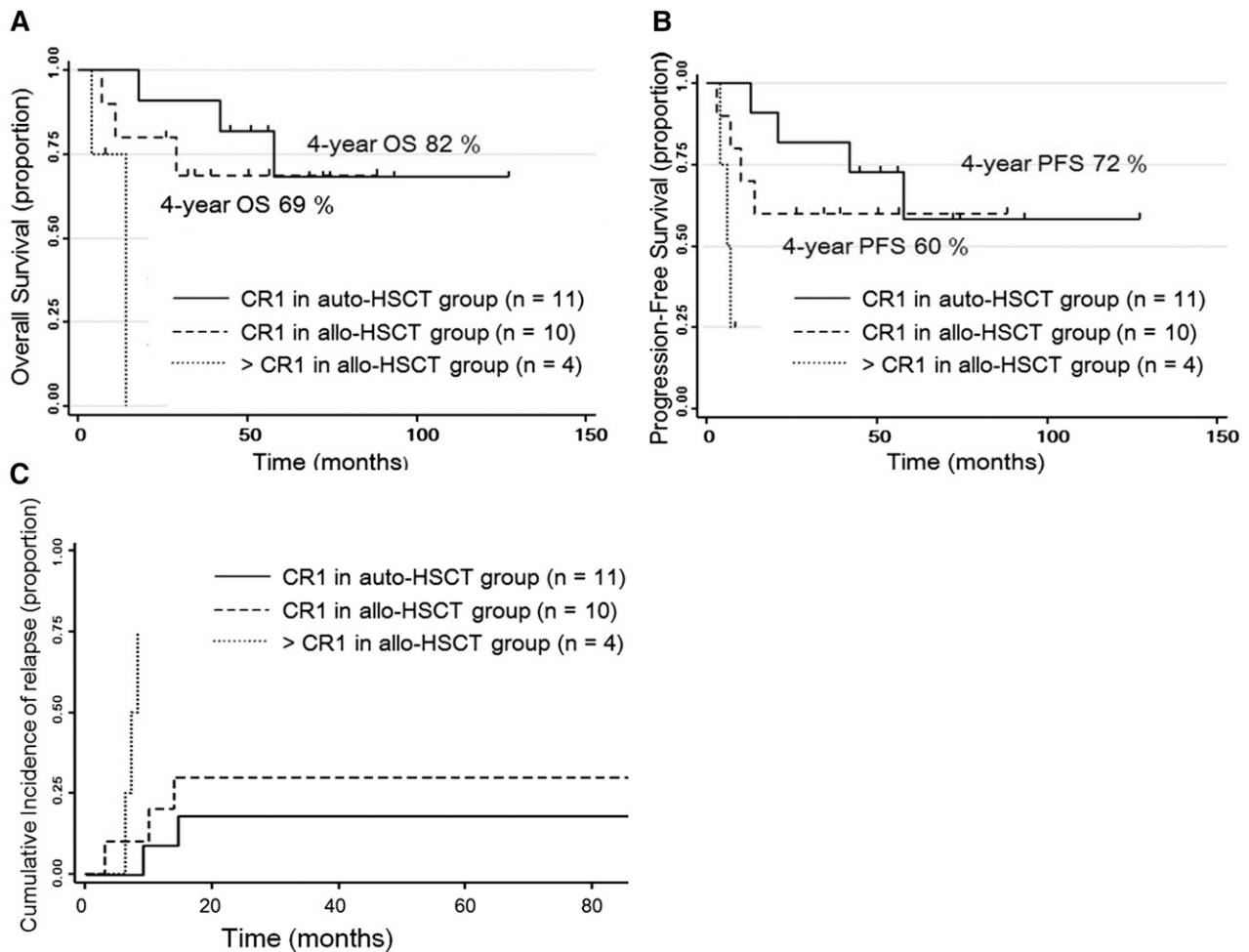
Figure 1. Survival of all patients with BPDCN after auto-HSCT or allo-HSCT according to disease status at HSCT. (A) Overall survival, (B) progression-free survival, and (C) cumulative incidence of relapse after auto-HSCT or allo-HSCT according to disease status at HSCT.

group. After allo-HSCT, grade 2 to 4 acute graft-versus-host disease was observed in 5 patients (36%). Two patients in the auto-HSCT group died because of a second malignancy at days +1282 and +1768.

With univariate analysis, HSCT beyond CR1 was an adverse prognostic factor for OS and PFS. BM infiltration was not identified as an adverse prognostic factor for survival.

To the best of our knowledge, this is the first report to demonstrate the clinical outcomes of auto-HSCT for BPDCN with a reasonably large number of patients. Auto-HSCT for BPDCN in CR1 appears to provide promising results and deserves further evaluation in the setting of prospective trials.

Several previous small case series were reported that described the outcomes of auto-HSCT for BPDCN.[3,18,21] The outcomes, especially beyond CR1, were poor.[3] Meanwhile, all patients who underwent auto-HSCT were in CR1 in our study. Taken together, these results suggest that the disease status at auto-HSCT is crucial for a better outcome.

As previous reports have shown,[3,15,22] allo-HSCT can also provide long-term survival in patients with BPDCN. Meanwhile, allo-HSCT could not overcome the poor disease status beyond CR1 in the present study. Considering the results of long-term remission without a late relapse in the auto-HSCT group, high-dose chemotherapy may play an important role in curing BPDCN independent of a graft-versus-tumor

effect of allo-HSCT. A previous large study also referred to the high-dose effect for BPDCN.[15]

Although the present study provides novel information about BPDCN, this was a retrospective study; thus, treatment outcomes may have been overestimated or underestimated with possible unrecognized biases. We could not evaluate patients who intended to undergo HSCT but failed during salvage treatment. In addition, determining statistically significant differences in survival analyses and identifying prognostic factors in this study were difficult because of the small number of patients.

In summary, our findings indicated that patients with BPDCN can achieve a durable remission with HSCT regardless of the type of induction regimen. In particular, auto-HSCT in CR1 appears to be a reasonable treatment option and may play an important role in improving the outcomes of BPDCN.

Acknowledgments

Authorship

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