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SHORT COMMUNICATION

Central Nervous System Involvement at the Time of Allogeneic Hematopoietic Stem Cell Transplantation Is Associated with a Poor Outcome in Patients with Acute Myeloid Leukemia

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Abstract Recent reports suggested that central nervous system (CNS) involvement (CNS+) in patients with acute myeloid leukemia (AML) before allogeneic hematopoietic stem cell transplantation (allo-HSCT) is not an independent predictor of survival after allo-HSCT. However, these studies did not analyze minimal residual disease in the CNS at the time of allo-HSCT. We evaluated the effect of residual CNS+ on the transplant outcomes of 214 AML patients in a single institution. Twenty-one (10%) patients were diagnosed with CNS+ prior to allo-HSCT. Of these, 13 patients had CNS disease at the time of allo-HSCT. The patients in CNS+ AML remission at the time of allo-HSCT had better overall survival (OS) than the patients who were not in remission (2-year OS: 55% vs. 7.7%, p = 0.0001). In multivariate analyses, CNS+ at the time of allo-HSCT (hazard ratio (HR), 1.9; 95% confidence interval (CI), 1.05–3.59; p = 0.04), age over 50 years at the time of allo-HSCT, and non-complete remission disease status in bone marrow at the time of allo-HSCT were independent adverse factors for OS. However, a prior history of CNS+ before allo-HSCT did not independently affect OS (HR, 1.27; 95% CI 0.53–2.07; p = 0.6). Early diagnosis and eradication of CNS+ at the time of allo-HSCT may be necessary to improve the outcome for patients with CNS+ AML.

Keywords Central nervous system involvement · Allogeneic hematopoietic stem cell transplantation · Acute myeloid leukemia

Introduction

Central nervous system (CNS) involvement (CNS+) in acute myeloid leukemia (AML) occurs in 2–4% of patients at diagnosis [1], and is generally associated with a poor prognosis [2, 3]. Recent reports [4, 5] showed that CNS+ in patients with AML before allogeneic hematopoietic stem cell transplantation (allo-HSCT) is not an independent predictor of survival after allo-HSCT. However, Aoki et al. [4] did not evaluate CNS disease at the time of allo-HSCT, Bar et al. [5] did not include patients with CNS disease at the time of allo-HSCT, and neither group evaluated the effect of residual CNS+ on transplant outcomes. In our institution, all patients with AML undergo routine diagnostic lumber puncture for cerebrospinal fluid (CSF) sampling and prophylactic intrathecal chemotherapy prior to allo-HSCT. We hypothesized that allo-HSCT would improve the prognosis for AML patients with CNS+ at the time of allo-HSCT. To test this hypothesis, we retrospectively analyzed transplant outcomes of patients with AML in our institution.

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Patients and Methods

Patients

Initially, we investigated 245 patients with AML before allo-HSCT who underwent first allo-HSCT in our institution between July 2004 and August 2014. Ten patients who died within 4 weeks after allo-HSCT and 21 patients with insufficient CSF samples were subsequently excluded, leaving a total of 214 patients. Lumber puncture was performed at a median of 15 days before allo-HSCT. CNS+ was diagnosed as the presence of leukemic cells in the CSF. Because magnetic resonance imaging (MRI) lacks specificity for the diagnosis of CNS+ leukemia [6], we excluded the patients who had abnormal MRI findings and normal CSF. CNS remission was diagnosed based on the absence of leukemic cells in the CSF.

Intrathecal Chemotherapy and Allo-HSCT

Myeloablative conditioning mainly included intravenous busulfan (Bu; 3.2 mg/kg for 4 days) and cyclophosphamide (60 mg/kg for 2 days). The main preparative regimen for the reduced-intensity procedure consisted of fludarabine (25 mg/m^2 for 5 days), melphalan (40 mg/m^2 for 2 days), and total body irradiation (TBI) of 400 cGy in divided doses. The patients were given an intravenous infusion of donor hematopoietic stem cells derived from bone marrow, cord blood or peripheral blood on day 0. All patients received acute graft-versus-host disease (GVHD) prophylaxis with cyclosporine or tacrolimus, as well as short-term methotrexate. Engraftment in allo-HSCT is defined as the first of three consecutive days with an absolute neutrophil count of 0.5×10^9/l or greater.

Statistical Analysis

The probability of overall survival (OS) was estimated using the Kaplan-Meier product limit method. We calculated OS from the date of allo-HSCT. The cumulative incidences of non-relapse mortality (NRM), relapse, aGVHD and cGVHD were evaluated using Gray's method. For each estimation of the cumulative incidence of an event, death without event was defined as a competing risk. Univariate models for OS included prior history of CNS involvement (yes vs. no), age at allo-HSCT (age ≥ 50 years vs. < 50 years), gender (male vs. female), white blood cell (WBC) count at diagnosis (WBC ≥ 10,000/μl vs. < 10,000/μl), revised medical research council cytogenetic risk (adverse vs others), days from diagnosis to allo-HSCT (≥ 235 vs. < 235), disease status at allo-HSCT (non-complete remission (non-CR) vs. complete remission (CR)), CNS status at the time of allo-HSCT (CNS+ vs. CNS-), stem cell source (cord blood vs. others), HLA disparity (matched vs. others), and conditioning regimen (reduced intensity conditioning vs. myeloablative conditioning). Univariate analysis was performed using Cox regression models. Multivariate analysis was performed using the Cox proportional hazards regression model or the competing risk regression model as appropriate. Factors associated with at least borderline significance ($p < 0.10$) in the univariate analyses were subjected to multivariate analysis using backward stepwise proportional-hazard modeling. Fisher's exact test was used for categorical variables, and the *t*-test was used

Table 1 Patients characteristics

	CNS-AML (n = 193)	CNS + AML (n = 21)	P value
Age at allo-HSCT (median, range)	50 (16–73)	43 (19–71)	0.02
WBC at diagnosis (median, range /μl)	7350 (700–420,000)	34,500 (1500–343,700)	0.0002
Gender, n (%)			0.06
Male	82 (42)	4 (19)	
Female	111 (58)	17 (81)	
FAB classification, n (%)			0.09
M4 or M5	38 (20)	8 (38)	
Other	155 (80)	13 (62)	
Bone marrow remission, n (%)			0.2
Yes	118 (61)	9 (43)	
No	75 (39)	12 (57)	
CNS remission, n (%)			<0.0001
Yes	193 (100)	6 (29)	
No	0	15 (71)	
Cytogeentic risk, n (%)			1
Favorable	17 (9)	2 (10)	
Intermediate	135 (70)	15 (71)	
Unfavorable	40 (21)	4 (19)	
Unknown	1 (1)	0	
HLA dysparities, n (%)			1
> 1mis	19 (10)	1 (5)	
1mis	33 (17)	4 (19)	
Haplo	10 (5)	1 (5)	
Match	130 (67)	15 (71)	
Conditionig regimen, n (%)			0.1
MAC	142 (74)	19 (90)	
RIC	51 (26)	2 (10)	
High dose TBI, n (%)			0.001
Yes	23 (12)	9 (43)	
No	169 (88)	12 (57)	

Abbreviation: *allo-HSCT* allogeneic hematopoietuc stem cell transplantation, *AML* acute myeloid leukemia, *CNS* central nervous system, *FAB* French-American-British, *Haplo* haploidentical, *HLA* human leukocyte antigen, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *TBI* total body irradiation, *WBC* white blood cell

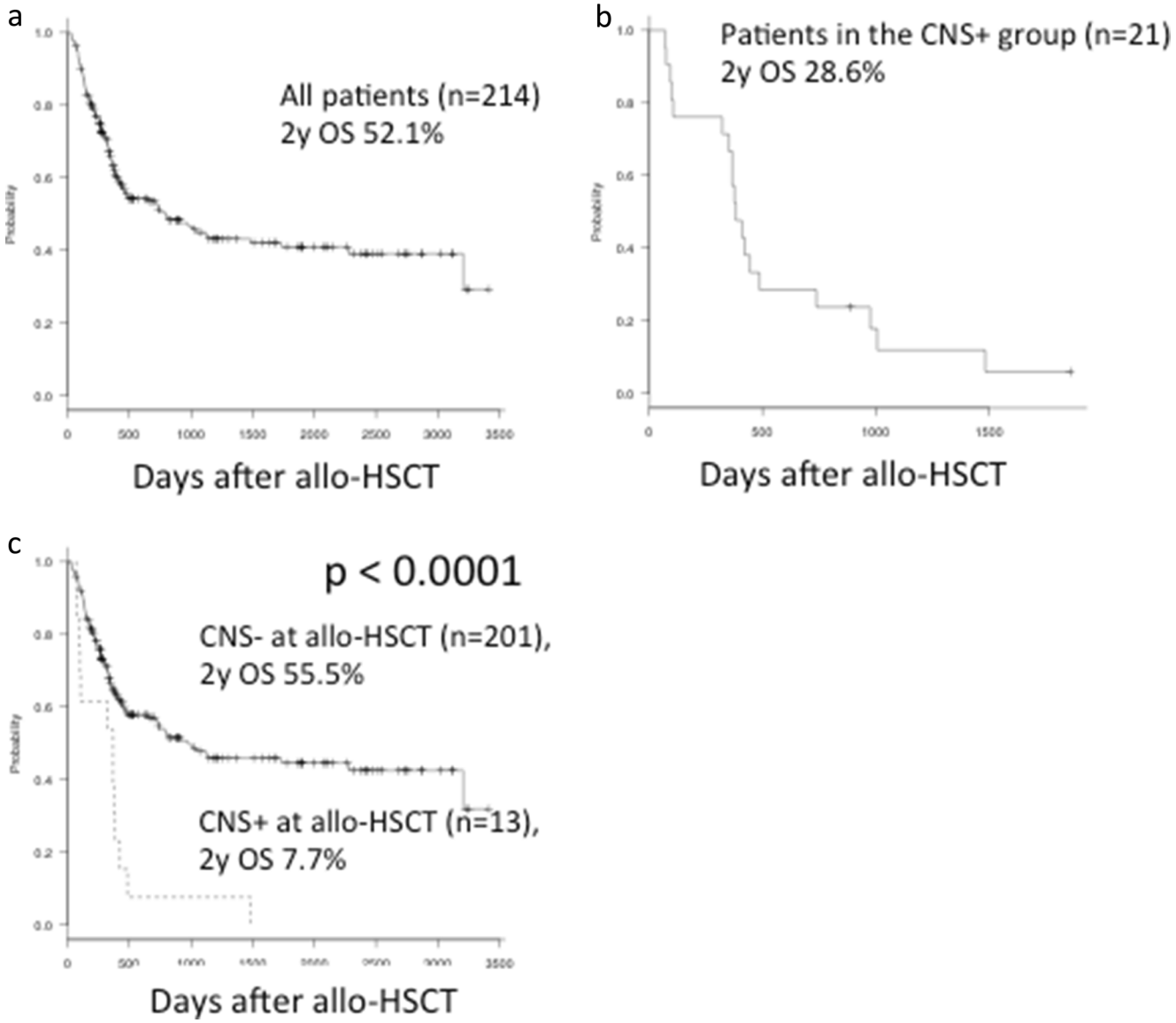

Fig. 1 Overall survival (OS) of acute myeloid leukemia (AML) patients after allogeneic stem cell transplantation (allo-HSCT). **a** OS for the entire cohort of 214 AML patients. **b**, OS for the 21 patients with central nervous system involvement (CNS+) AML prior to allo-HSCT. **c**. OS after allo-HSCT of patients with AML in CNS remission at the time of allo-HSCT, compared with those who were not in remission

for continuous variables. All statistical tests were 2-sided with $p < 0.05$ considered statistically significant. All statistical analyses were performed with EZR, a graphical user interface for R software (The R Foundation for Statistical Computing, version 2.13.0; www.r-project.org).

Results

Patient Characteristics

Twenty-one (10%) patients were diagnosed with CNS+ prior to allo-HSCT (Table 1). There were no significant differences between CNS+ and CNS- groups in a range of clinical characteristics including gender, French-American-British classification, cytogenetic risk, HLA disparities, or conditioning regimens. However, compared to the CNS- group, the patients in the CNS+ group were significantly younger, had higher WBC counts at diagnosis, presented with active CNS disease status at the time of allo-HSCT, and received more than 12 Gy TBI as a conditioning regimen. The characteristics of patients with CNS+ AML are shown in Supplementary Table 1, and the cytogenetics are shown in Supplementary Table 2. CNS+ AML patients were diagnosed with CNS+ at the time of the primary diagnosis ($n = 1$), at bone marrow relapse before allo-HSCT ($n = 5$), and with routine lumbar puncture just before allo-HSCT ($n = 15$). Of the 21 patients with CNS+, 13 patients had CNS disease at the time of allo-

HSCT. The median follow-up period for survivors was 791 days (range, 29–3412 days).

Transplantation Outcomes

The 2-year overall survival (OS) after allo-HSCT was 52.1% for the 214 patients with AML, and 28.6% for those in the CNS+ group (Fig. 1a, b). The patients in CNS leukemia remission at the time of allo-HSCT had better OS than the patients who were not in CNS leukemia remission (2-year OS: 55% vs.7.7%, $p < 0.0001$; Fig. 1c).

Table 2 shows the results of risk factor analyses for OS among the 214 patients who underwent allo-HSCT. In the univariate analyses, prior history of CNS+ before allo-HSCT (hazard ratio (HR), 2.10; 95% confidence interval (CI), 1.26–3.50; $p = 0.004$), age over 50 years at allo-HSCT (HR, 1.68; 95% CI, 1.15–2.48; $p = 0.008$), cytogenetic risk (HR, 2.55; 95% CI, 1.12–5.83; $p = 0.03$), non-CR disease status at allo-HSCT (HR, 3.32; 95% CI, 2.24–4.92; $p < 0.0001$), and CNS+ at the time of allo-HSCT (HR, 3.12; 95% CI, 1.74–4.37; $p = 0.0001$) were adverse factors for OS. In the multivariate analyses, CNS+ at the time of allo-HSCT (HR, 1.94; 95% CI, 1.05–3.59; $p = 0.04$), age over 50 years at the time of allo-HSCT (HR, 2.07; 95% CI, 1.40–3.07; $p = 0.0003$), and non-CR disease status at the time of allo-HSCT (HR, 3.29; 95% CI, 2.17–4.97; $p < 0.0001$) were independent adverse factors for OS. However, a prior history of CNS+ before allo-HSCT did not independently affect OS (HR, 1.27; 95% CI 0.53–2.07; $p = 0.6$). Moreover, a conditioning regimen including 12 Gy TBI was not an independent factor for OS (data not shown). All 13 patients with CNS+ at the time of allo-HSCT died. The causes of death were recurrence (11 patients), infection (one patient), and engraftment failure (one patient).

Discussion

This analysis showed that prior history of CNS+ before allo-HSCT did not significantly affect OS, similar to previous studies [4, 5]. It was reported that prophylactic intrathecal chemotherapy before allo-HSCT does not affect CNS relapse [7, 8]. However, these studies did not address CNS residual disease at the time of allo-HSCT. We demonstrated that CNS+ at the time of allo-HSCT was an independent prognostic factor for OS, and allo-HSCT did not improve the prognosis of these patients. Mayadev et al. showed that a cranial irradiation boost in addition to intrathecal chemotherapy improves the outcome in patients with CNS+ AML [3]. Although controversial, extramedullary disease, including CNS+, is considered to be a poor target for the graft-versus-leukemia effect [8], [1], whereas pre-transplant intervention for CNS+ AML may decrease the incidence of relapse after allo-HSCT.

Our analysis has some limitations. First, this was a small retrospective study. Second, molecular analysis was not undertaken at the time of diagnosis. To clarify the characteristics CNS+ AML, we would need further investigation including molecular abnormalities.

In this study, most patients in the CNS+ group were asymptomatic immediately before allo-HSCT, suggesting that a comprehensive investigation of the CNS prior to allo-HSCT is warranted. This may be particularly important if early diagnosis and eradication of CNS+ at the time of allo-HSCT is necessary to improve the outcome for CNS+ AML patients.

Table 2 Results of uni-and multivariate analysis of overall survival

	Overall survival			
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Prior history of CNS involvement (Yes vs. no)	2.10 (1.26–3.50)	0.0004	1.27 (0.53–2.07)	0.6
Age at allo-HSCT (≥50 vs <50)	1.68 (1.15–2.48)	0.0008	2.07 (0.53–2.07)	0.0003
Gender (Male vs Female)	1.21 (0.81–1.79)	0.4	NE	NE
WBC at diagnosis (≥10,000/μl vs <10,000/μl)	1.11 (0.74–1.66)	0.6	NE	NE
Cytogenetic risk ()Adverse vs. others	2.55 (1.12–5.83)	0.03	2.25 (0.96–5.28)	0.07
Days between diagnosis and allo-HSCT (≥235 vs <235)	1.02 (0.68–1.52)	0.9	NE	NE
Disease status at allo-HSCT (non-CR vs CR)	3.32 (2.24–4.92)	<0.0001	3.29 (2.17–4.97)	<0.0001
CNS status at allo-HSCT (CNS+ vs. CNS-)	3.12 (1.74–5.60)	0.0001	1.94 (1.05–3.59)	0.04
Stem cell source (CB vs. others)	1.65 (0.94–2.88)	0.08	NE	NE
HLA (Match vs. others)	0.84 (0.44–1.59)	0.06	NE	NE
Conditioning regimen (RIC vs. MAC)	1.35 (0.86–2.10)	0.2	NE	NE

Abbreviations: *allo-HSCT* allogeneic stem cell transplantation, *CB* cord blood, *CNS* central nervous system, *CI* confidence interval, *CR* complete remission, *HLA* human leukocyte antigen, *MAC* myeloablative conditioning, *NE* not evaluated due to lack of significance in univariate analysis, *RIC* reduced intensity conditioning, *WBC* white blood cell

Compliance with Ethical Standards

Financial Disclosure The authors have nothing to disclose.

Conflict of Interest The authors have no conflicts of interest.

References

1. Bommer M, von Harsdorf S, Döhner H, Bunjes D, Ringhoffer M (2010) Neoplastic meningitis in patients with acute myeloid leukemia scheduled for allogeneic hematopoietic stem cell transplantation. Haematologica 11:1969–1972
2. Sanders KE, Ha CS, Cortes-Franco JE, Koller CA, Kantarjian HM, Cox JD (2004) The role of craniospinal irradiation in adults with a central nervous system recurrence of leukemia. Cancer 100:2176–2180
3. Mayadev JS, Douglas JG, Storer BE, Appelbaum FR, Storb R (2011) Impact of cranial irradiation added to intrathecal conditioning in hematopoietic cell transplantation in adult acute myeloid leukemia with central nervous system involvement. Int J Radiat Oncol Biol Phys 80:193–198
4. Aoki J, Ishiyama K, Taniguchi S et al (2014) Outcome of allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia patients with central nervous system involvement. Biol Blood Marrow Transplant 20:2029–2033
5. Bar M, Tong W, Othus M, Loeb KR, Estey EH (2015) Central nervous system involvement in acute myeloid leukemia patients undergoing hematopoietic cell transplantation. Biol Blood Marrow Tranplant 21:546–551
6. Pui CH, Thiel E (2009) Central nervous system disease in hematologic malignancies: historical perspective and practical applications. Semin Oncol 36:S2–S16
7. Ruutu T, Corradini P, Gratwohl A et al (2005) Use of intrathecal prophylaxis in allogeneic haematopoietic stem cell transplantation for malignant blood diseases: a survey of the European Group for Blood and Marrow Transplantation EBMT. Bone Marrow Transplant 35:121–124
8. Oshima K, Kanda Y, Yamashita T et al (2008) Central nervous system relapse of leukemia after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 14:1100–1107