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CLINICAL RESEARCH

Central Nervous System Relapse of Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation

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Little information is available regarding central nervous system (CNS) relapse of adult leukemia after allogeneic hematopoietic stem cell transplantation (HSCT). Therefore, we reviewed the data of 1226 patients with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelogenous leukemia (CML) who received first allogeneic HSCT between 1994 and 2004, using the database of the Kanto Study Group for Cell Therapy (KSGCT), and analyzed the incidence, risk factors, and outcome of patients with CNS relapse. Twenty-nine patients developed CNS relapse at a median of 296 (9-1677) days after HSCT with a cumulative incidence of 2.3%. Independent significant factors associated with CNS relapse included ALL as the underlying diagnosis (relative risk [RR] = 9.55, 95% confidence interval [CI] = 1.26-72.2, P = .029), nonremission at HSCT (RR = 2.30, 95% CI = 1.03-5.15, P = .042), the history of CNS invasion before HSCT (RR = 5.62, 95% CI = 2.62-12.0, $P = 9.2 \times 10^{-6}$), and the prophylactic intrathecal chemotherapy after HSCT (RR = 2.57, 95% CI = 1.21-5.46, P = .014). The 3-year overall survival (OS) after CNS relapse was 18%. In 7 of 29 patients with CNS relapse, leukemia was observed only in CNS. Three of 7 patients were alive without systemic relapse, resulting in 3-year survival after CNS relapse of 46%. Although the outcome of patients with CNS relapse was generally poor, long-term disease-free survival could be achieved in some patients.

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KEY WORDS: Leukemia, Central nervous system, Relapse, Allogeneic hematopoietic stem cell transplantation

INTRODUCTION

Relapse of the original disease remains 1 of the most important causes of failure after allogeneic hematopoietic stem cell transplantation (HSCT) for leukemia. Although majority of the patients develop systemic relapse, extramedullary relapse has been also observed after HSCT. The incidence of central nervous system (CNS) relapse after allogeneic HSCT ranged from 2.9% to 11% [1-3]. Risk factors for CNS relapse identified in previous studies included CNS involvement before HSCT [2] and nonremission at HSCT [1]. Prophylactic intrathecal administration of methotrexate (MTX) was shown to decrease the incidence of CNS relapse of acute lymphoblastic leukemia (ALL) in the Seattle study [1], whereas the other 2

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studies failed to find the benefit of prophylactic intrathecal administration of MTX on CNS relapse in patients with acute leukemia [2,3]. There has been no generalized consensus on intrathecal administration of MTX, and in fact, a survey of the European Group for Blood and Marrow Transplantation (EBMT) had reported that the practice varied widely among centers [4].

We examined the incidence, risk factors, and outcome of CNS relapse after allogeneic HSCT in adult patients with acute myelogenous leukemia (AML), ALL, and chronic myelogenous leukemia (CML), and also evaluated the prophylactic effect of intrathecal administration of MTX on CNS relapse.

MATERIALS AND METHODS

Study Population

The study population consisted of 1226 patients, who underwent allogeneic HSCT for AML, ALL, and CML for the first time between January 1994 and December 2004 at 10 hospitals participating in the Kanto Study Group for Cell Therapy (KSGCT).

Transplantation Procedure

Of the 1226 patients, the sources of stem cell was bone marrow (BM) in 903, peripheral blood stem cells (PBSC) in 178, BM plus PBSC in 10, and cord blood (CB) in 134. Conventional myeloablative conditioning regimens such as total body irradiation (TBI) and cyclophosphamide (Cy), busulfan (Bu), and Cy, and their modified regimens were performed in 1168 patients. Among them, TBI of at least 10 Gy was performed in 815 patients. Reduced-intensity conditioning (RIC) regimens were conducted in 53 patients. Prophylaxis of graft-versus-host disease (GVHD) was attempted with calcineurin inhibitors (cyclosporine [CsA] or tacrolimus) with or without short-term MTX in the majority of patients.

Definition of CNS Relapse

CNS relapse was diagnosed as the presence of leukemic cells in the cerebrospinal fluid (CSF). Isolated CNS relapse was defined as CNS relapse without any other sites of relapse of leukemia.

Statistical Considerations

Overall survival (OS) was calculated using the Kaplan-Meier method. Cumulative incidence of CNS relapse was calculated using Gray's method, considering death without CNS relapse as a competing risk [5]. Cumulative incidence of isolated CNS relapse was calculated using Gray's method, treating systemic relapse and death without relapse as a competing risk [5]. The protective effect of chronic GVHD (cGVHD) on CNS relapse was evaluated among patients who developed bone marrow relapse within 100 days after HSCT. Factors associated with at least borderline significance ($P < .10$) in the univariate analyses were subjected to a multivariate analysis using backward stepwise proportional-hazard modeling. Finally, P values of $<.05$ were considered statistically significant.

RESULTS

Characteristics of the Patients

Characteristics of patients included in the study were listed in Table 1. The median age was 36 years, ranging from 15 to 69 years. The underlying diseases were AML (n = 533), ALL (n = 352), and CML (n = 341). Eighty-one patients had the history of CNS involvement before HSCT. Eight hundred and nine patients were in complete remission of acute leukemia or in chronic phase of CML at HSCT, and the remaining patients had active disease. In the following analyses, CML in the chronic phase was included in leukemia in complete remission.

CNS Relapse

Twenty-nine patients developed CNS relapse at a median of 296 days (9-1677 days) after HSCT, giving the cumulative incidence of 2.3% (Figure 1). The median age was 31 years (range: 17-47). The underlying disease was ALL in 18, AML in 9, and CML in 2. Sixteen patients had CNS involvement before HSCT and

Table 1. Characteristics of Patients

Median age (range) at transplantation	36 (15-69)
Sex	
Male	762
Female	464
Underlying disease	
AML	533
ALL	352
CML	341
Disease status	
CR	809
non-CR	416
History of CNS disease	
Yes	81
No	802
Type of conditioning	
Conventional	1168
Reduced intensity	53
TBI ≥10 Gy in conditioning	
Yes	815
No	404
Donor type	
Related	478
Unrelated	548
Stem cell source	
BM	902
PBSC	178
BM + PBSC	10
CB	134

CB indicates cord blood.

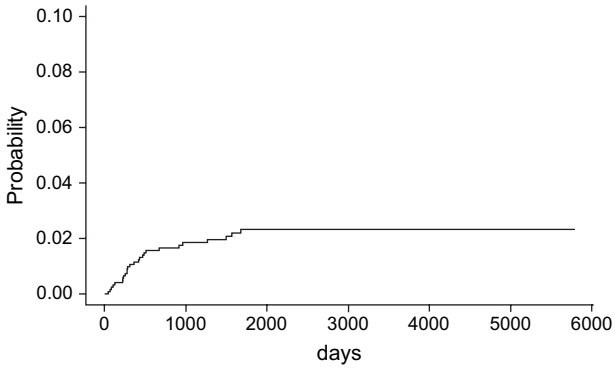

Figure 1. Cumulative incidence of CNS relapse treating death without CNS relapse as competing risk.

6 of them had active CNS disease at HSCT. OS after CNS relapse was 42% at 1 year and 18% at 3 years (Figure 2A). OS of the whole patient cohort, patients with CNS relapse, and those without CNS relapse was 59.8%, 33.2%, and 60.6%, respectively, at 3 years after transplantation.

Pretransplant factors that affected the incidence of CNS relapse after HSCT with at least borderline significance were ALL as the underlying disease, active disease at HSCT, a history of CNS leukemia, the use of TBI regimens, HSCT from an unrelated donor, and the use of prophylactic intrathecal chemotherapy after HSCT (Table 2). Among them, multivariate analysis showed that ALL as the underlying disease, active disease at HSCT, the history of CNS involvement, and the use of intrathecal chemotherapy after HSCT were independently significant (Table 2 and Figure 3). The cumulative incidences of CNS relapse in patients with and without a history of CNS involvement before HSCT were 21.3% and 1.3%, respectively (Figure 3A). Patients with ALL were at higher risk for CNS relapse even in patients in remission at HSCT without a history of CNS involvement before HSCT (ALL 2.7%, AML 0.8%, and CML 0.4%, $P = .088$, Figure 4A). Twenty-three patients who had active leukemia at HSCT had persistent disease after HSCT. Among these, only 2 patients developed CNS relapse after HSCT. However, median survival of this cohort was only 90 days after HSCT producing a 1-year survival of 14%, and thus, majority of the patients died very early, before developing CNS relapse.

Effect of Intrathecal Chemotherapy on the Incidence of CNS Relapse

The practice of intrathecal chemotherapy in allogeneic HSCT recipients varied among the 10 institutions of the KSGCT. Half of them never used prophylactic intrathecal chemotherapy before and after HSCT. The remaining half administered intrathecal prophylaxis routinely before HSCT, of which 2 institutions added intrathecal chemotherapy after

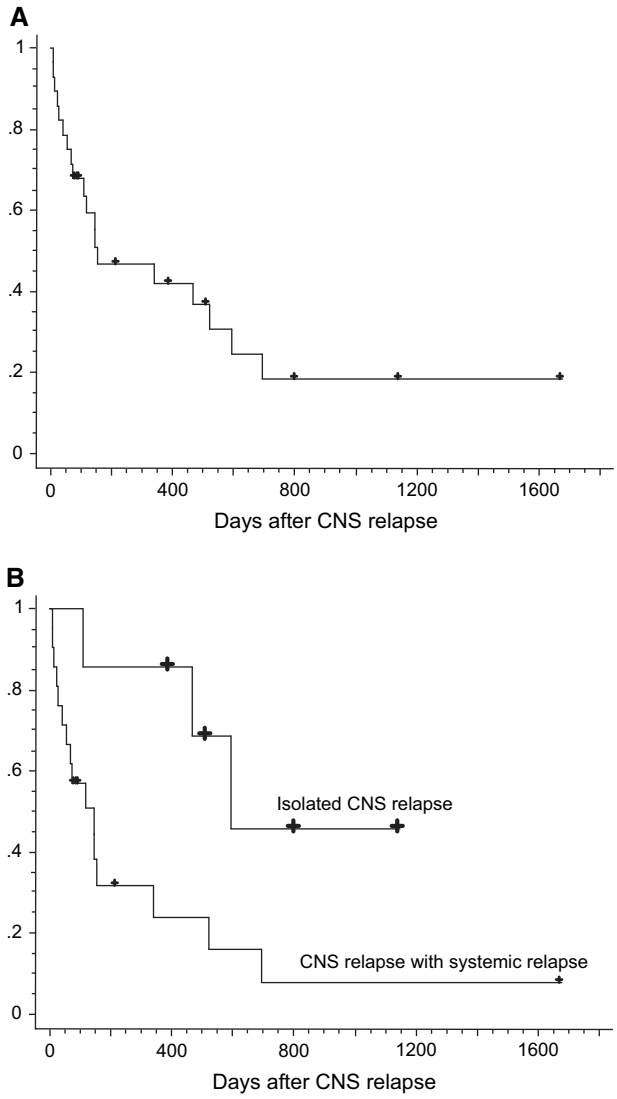

Figure 2. OS after CNS relapse (A) and that grouped according to isolated CNS relapse or CNS relapse associated with systemic relapse (B).

HSCT for high-risk patients such as those with ALL or the history of CNS involvement. In this cohort, intrathecal prophylaxis before HSCT was conducted in 701 of 887 patients and intrathecal chemotherapy after HSCT was done in 141 of 807 patients whose information about intrathecal chemotherapy was available. Antineoplastic agents used for intrathecal chemotherapy mainly consisted of MTX. The median numbers of intrathecal chemotherapy before and after HSCT were 1 (range: 1-4) and 2 (range: 1-4), respectively.

We failed to find a significant prophylactic effect of intrathecal chemotherapy for CNS relapse. The relative risk for CNS relapse was 1.52 (95% CI 0.61-3.79, $P = .37$) for intrathecal chemotherapy before HSCT and 3.92 (95% CI 1.80-8.51, $P = .00057$) for intrathecal chemotherapy after HSCT (Table 2). This adverse influence of intrathecal chemotherapy after HSCT was significant even after adjusted for the

Table 2. Impact of Pretransplant Factors on the Incidence of CNS Relapse after Transplantation

Factor		Univariate RR (95% CI)	*P* value	Multivariate RR (95% CI)	*P* value
Age		1.00 (1.00-1.00)	.15		
Sex		1.01 (0.65-1.59)	.95		
Disease	CML	1.00		1.00	
	AML	5.58 (0.70-44.5)	.10	3.60 (0.46-28.4)	.22
	ALL	17.7 (2.36-132.8)	.0052	9.55 (1.26-72.2)	.029
CR/non-CR		2.33 (1.08-5.04)	.031	2.30 (1.03-5.15)	.042
History of CNS disease		17.9 (8.30-38.6)	2.0×10^{-13}	5.62 (2.62-12.0)	9.2×10^{-6}
TBI		2.91 (1.00-8.44)	.050		
Conventional/reduced intensity		0.99 (0.47-2.07)	.97		
Related/unrelated		1.85 (1.06-3.23)	.030		
Source	BM	1.00			
	PBSC	0.24 (0.03-1.77)	.16		
	CB	0.70 (0.17-2.96)	.63		
Sex mismatch		1.06 (0.42-2.66)	.90		
HLA mismatch		0.46 (0.06-3.46)	.45		
Prophylactic IT before HSCT		1.52 (0.61-3.79)	.37		
Prophylactic IT after HSCT		3.92 (1.80-8.51)	.00057	2.57 (1.21-5.46)	.014

IT indicates intrathecal chemotherapy; CNS, central nervous system; RR, relative risk.

underlying disease, disease status at HSCT, and the history of CNS involvement before HSCT (relative risk 2.57, 95% CI 1.21-5.46, $P = .014$). Among patients without a history of CNS involvement before HSCT who were in remission at HSCT, the incidences of CNS relapse after HSCT were 3.6% and 1.6% who received and did not receive intrathecal chemotherapy after HSCT, respectively ($P = .057$, Figure 4B). In patients with a history of CNS involvement before HSCT, the incidences of CNS relapse after HSCT were 37.4% and 11.6%, respectively, who received and did not receive intrathecal chemotherapy after HSCT ($P = .018$; Figure 4C). When we limited the analysis in patients with ALL, the incidences of CNS relapse after HSCT were 6.2% and 3.7% who received and did not receive intrathecal chemotherapy after HSCT ($P = .17$), respectively, in patients without a history of CNS involvement before HSCT who were in remission at HSCT and they were 55.6% and 15.5%, respectively, in patients with a history of CNS involvement before HSCT ($P = .0081$).

Nine patients developed leukoencephalopathy with a median onset of 288 days after HSCT. The incidence of leukoencephalopathy was significantly higher in patients who underwent intrathecal chemotherapy after HSCT (3.5% versus 0.5%, $P = .0076$).

Isolated CNS Relapse

Seven patients developed isolated CNS relapse at a median of 671 days (125-1677 days) after HSCT, presenting the cumulative incidence of 0.70%. Characteristics of these 7 patients were listed in Table 3. All received bone marrow as stem cell source. Prognostic factors associated with isolated CNS relapse with at least borderline significance were age, active disease at HSCT, CNS involvement before HSCT, stem cell source, the use of intrathecal chemotherapy after HSCT, and the absence of HLA mismatch. Among these, independent significant factors for isolated CNS relapse included the history of CNS involvement before HSCT, the use of PBSC or CB as stem cell source, and the absence of HLA mismatch (Table 4). The treatment of isolated CNS relapse consisted of intrathecal chemotherapy and/or cranial irradiation and CNS disease was successfully controlled in 5 of the 7 patients. Four patients developed bone marrow relapse within 1 year. However, the remaining 3 patients were alive without systemic relapse at 518, 807, and 1149 days after CNS relapse and 1283, 1478, and 2195 days after HSCT, respectively. Survival after CNS relapse was significantly better in patients who developed isolated CNS relapse than those who developed CNS relapse with systemic relapse (46% versus 8% at 3 years, $P = .023$, Figure 2B).

Effect of cGVHD on CNS Relapse

Among the 378 patients who experienced bone marrow relapse within 100 days after HSCT but were free from CNS relapse at day 100, 21 (6.1%) showed CNS relapse later on. The incidence of CNS relapse after bone marrow relapse was 7.1% in patients with cGVHD and 2.0% in those without cGVHD ($P = .14$).

Analysis Excluding CML Patients

We repeated these analyses excluding patients with CML, because the incidence of CNS relapse was extremely low, as shown in Figure 3C. The cumulative incidence of CNS relapse was 3.2%. Independently significant pretransplant factors for CNS relapse

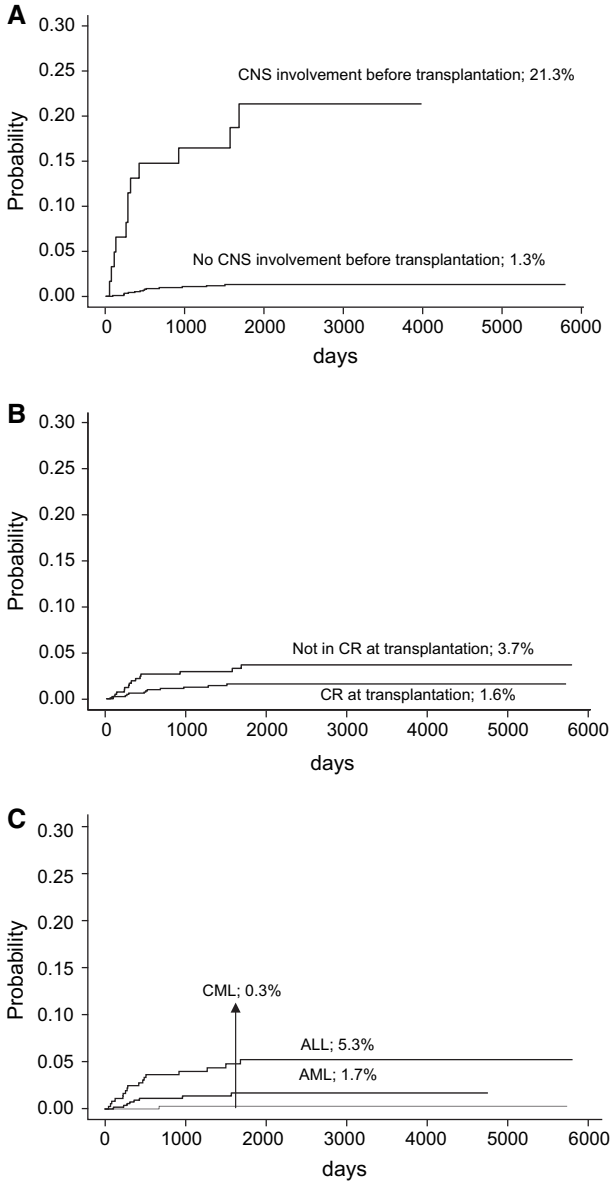

Figure 3. Cumulative incidence of CNS relapse grouped according to the history of CNS involvement before transplantation (A), disease status at transplantation (B), and underlying disease (C).

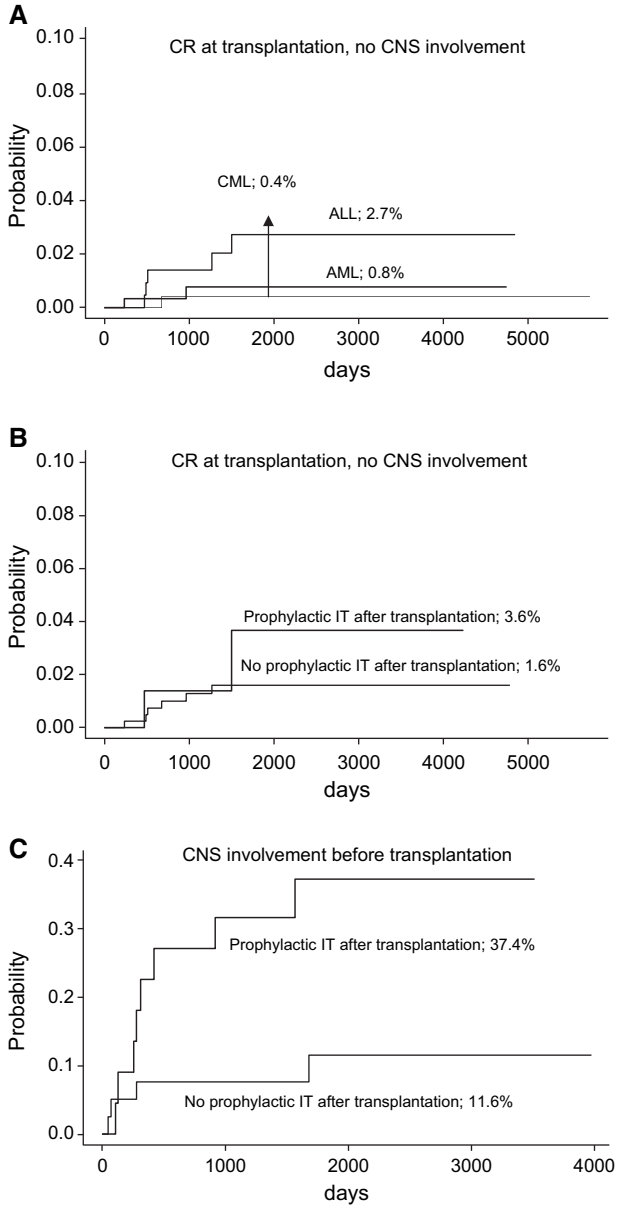

Figure 4. Cumulative incidence of CNS relapse in patients in remission at transplantation without a history of CNS involvement before transplantation grouped according to the underlying disease (A) and the use of prophylactic intrathecal chemotherapy (IT) after transplantation (B). Cumulative incidence of CNS relapse in patient with CNS involvement before transplantation grouped according to the use of prophylactic IT after transplantation (C).

were the same as the analyses including CML patients; ALL compared to AML as the underlying disease (RR 2.68, 95% CI 1.18-6.11, $P = .019$), active disease at HSCT (RR 2.49, 95% CI 1.08-5.73, $P = .032$), the history of CNS involvement (RR 5.64, 95% CI 2.60-12.3, $P = .000012$), and the use of intrathecal chemotherapy after HSCT (RR 2.69, 95% CI 1.25-5.81, $P = .012$). The cumulative incidence of isolated CNS relapse was 0.9%. Independently significant pretransplant factors for CNS relapse included ALL compared to AML as the underlying disease, the history of CNS involvement, the use of PBSC as stem cell source, the absence of HLA mismatch, and the use of intrathecal chemotherapy after HSCT.

DISCUSSION

The cumulative incidences of CNS relapse and isolated CNS relapse were 2.3% and 0.70% in this cohort, respectively, which were almost comparable with those in previous studies (Table 5) [1-3]. The history of CNS leukemia before HSCT was identified as the strongest predictive factor for CNS relapse after HSCT in our study as previously reported [1,2].

We could not show a beneficial effect of prophylactic intrathecal chemotherapy on the incidence of

Table 3. Characteristics of Patients Who Developed Isolated CNS Relapse after Transplantation

Patient No.	1	2	3	4	5	6	7
Age	23	31	24	35	26	41	18
Sex	M	M	M	M	F	M	M
Disease	CML	CML	ALL	AML	ALL	ALL	ALL
Disease status	CP2	BC	RL2	RL1	RL2	CR1	RL2
History of CNS disease	Yes	Yes	Yes	Yes	Yes	No	No
Stem cell source	BM	BM	BM	BM	BM	BM	BM
Donor type	R	R	U	R	R	R	U
HLA mismatch	No	Yes	No	No	No	No	Yes
Conditioning regimem	Bu+Cy	CA+Cy+TBI	ETP+Cy+TBI	CA+Cy+TBI	ETP+Cy+TBI	Cy+TBI	CA+Cy+TBI
Days to an isolated CNS relapse	671	134	125	1565	276	1265	1677
CNS treatment	IT+RT	IT+RT	IT	IT+DLI	RT	IT+RT	IT
Systemic relapse	No	No	Yes	Yes	Yes	Yes	No
Days from HSCT to systemic relapse	164	1680	444	1572			
Day from CNS relapse to systemic relapse	39	115	168	307			
Outcome	Alive	Alive	Dead	Dead	Dead	Alive	Alive
Follow-up duration (days)	1478	1283	236	2031	870	1661	2195

IT indicates intrathecal chemotherapy; RT, radiation; DLI, donor lymphocyte infusion; BU, busulfan; CY, cyclophosphamide; CA, cytarabine; ETP, etoposide; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation.

CNS relapse after HSCT. The incidence of CNS relapse was rather higher in patients who received intrathecal chemotherapy after HSCT. This was probably biased by the fact that significantly higher proportion of patients received intrathecal chemotherapy after HSCT among patients with CNS involvement before HSCT than those without CNS leukemia (47.4% versys 13.4%, $P < .0001$). However, intrathecal chemotherapy after HSCT significantly adversely affected the incidence of CNS relapse even after adjusted for the underlying disease, disease status at HSCT, and the history of CNS involvement before HSCT. Also, a benefit of intrathecal chemotherapy after HSCT was not shown in patients with ALL, in contrast with the previous reports [1,6]. This discrepancy might have resulted from the difference in the intensity of the intrathecal chemotherapy. Intrathecal chemotherapies were administered 6 times after HSCT in the Seattle group, whereas the medium number of intrathecal chemotherapy in the current study was only 2 (range: 1-4). Therefore, the intensity of intrathecal chemotherapy might be important to sufficiently prevent CNS relapse after HSCT. However, they observed the development of leukoencephalopathy in 7 of the 415 patients and we also observed leukoencephalopathy significantly more frequently in patients who received intrathecal chemotherapy after HSCT than those who did not. Therefore, such an intensive intrathecal chemotherapy should be avoided for patients at low risk for CNS relapse. We had a concern that the use of intrathecal chemotherapy after HSCT might delay immune recovery and thereby

Table 4. Impact of Pretransplant Factors on the Incidence of Isolated CNS Relapse after Transplantation

Factor		Univariate RR (95% CI)	*P*-Value	Multivariate RR (95% CI)	*P*-Value
Age		0.99 (0.98-1.00)	.055		
Sex		1.05 (0.47-2.34)	.90		
Disease	CML	1.00			
	AML	0.73 (0.04-11.9)	.82		
	ALL	5.31 (0.61-45.9)	.13		
CR/non-CR		4.98 (0.97-25.7)	.055		
History of CNS disease		48.3 (9.37-249.4)	3.6×10^{-6}	48.1 (9.40-245.9)	3.3×10^{-6}
TBI		3.21 (0.38-26.8)	.28		
Conventional/reduced intensity		1.08 (0.26-4.49)	.92		
Related/unrelated		1.45 (0.65-3.24)	.37		
Source	BM	1.00		1.00	
	PBSC	N.A.	<.0001	N.A.	<.0001
	CB	N.A.	<.0001	N.A.	<.0001
Sex mismatch		1.58 (0.26-9.41)	.62		
HLA mismatch		N.A.	<.0001	N.A.	<.0001
Prophylactic IT before HSCT		1.09 (0.21-5.61) 0.92			
Prophylactic IT after HSCT		7.11 (1.62-31.2) 0.0094			

N.A. indicates not assessable because no events were observed in the group; IT, intrathecal chemotherapy; RR, relative risk.

Table 5. Cumulative Incidence of CNS Relapse after HSCT in Prior Studies and Our Study

	n	Underlying Disease (AML/ALL/CML)	History of CNS Leukemia (%)	CR at Transplant (%)	Allogeneic Transplant (%)	Incidence of CNS Relapse (%)	Reference
1	415	217/198/0	23.4	47.7	100	2 in AML, 13 in ALL	1
2	92	0/92/0	22.8	100	71.7	11	2
3	487	366/121*/0	3.5	100	67.6	2.9	3
4	1226	533/352/341	9.2	65.8	100	2.3	Present report

*Including 5 patients with acute unclassified leukemia.

increase the risk of systemic relapse, but the incidence of systemic relapse was not significantly different between those who received intrathecal chemotherapy and those who did not (relative risk 1.11, 95% CI 0.79-1.55, $P = .56$). The use of total body irradiation (TBI) in the conditioning regimen has been considered to prevent CNS relapse, because irradiation is effective for so called sanctuary sites of chemotherapy. However, the incidence of CNS relapse was also rather higher in patients who received the TBI regimen. This may be again because of the fact that significantly higher proportion of patients received the TBI regimen among patients with CNS involvement before HSCT than those without CNS leukemia (81.5% versus 57.9%, $P < .0001$).

As for stem cell source, isolated CNS relapse was observed exclusively after BMT. A possible explanation for this may be the year effect, because allogeneic PBSCT and CBT started after 2000 in Japan. However, the year of HSCT of patients who developed isolated CNS relapse evenly ranged between 1997 and 2002. Another possible explanation is the presence of graft-versus-CNS relapse effect enhanced by increased incidence of cGVHD after allogeneic PBSCT and the presence of HLA-mismatch in CBT. The significantly higher incidence of CNS relapse after autologous HSCT than that after allogeneic HSCT suggested the existence of such an immunologicprotection against CNS relapse [2]. Isolated extramedullary relapse was also reported to be observed earlier in autologous HSCT than in allogeneic HSCT [7]. Furthermore, successful treatment of CNS relapse with reduced-intensity transplantation may suggest the presence of graft-versus-leukemia CNS leukemia effect [8], although the other reports doubted such effect against for CNS lesions [9-12]. The observed tendency toward a lower CNS relapse incidence after bone marrow relapse in patients with cGVHD than those without cGVHD in the current study might support this speculation, although we have no immunologic evidence.

The prognosis of patients who developed relapse after allogeneic HSCT has been reported to be extremely poor [13,14]. Also, survival after isolated CNS relapse was reported to be no better than that after bone marrow relapse in pediatric patients with AML and adult patients with ALL [15,16]. However, in the current study, 3 of the 7 patients who developed isolated CNS relapse were alive for more than a year without leukemia, resulting in the significantly better survival than those who developed CNS relapse after or simultaneously with systemic relapse. We could not identify the reason for this discrepancy, but the age and underlying disease of the study population differed between our study and the previous report. We consider that an intensive treatment against CNS leukemia is warranted for adult patients with isolated CNS relapse.

In conclusion, we confirmed that ALL as the underlying disease, active disease at HSCT, and the history of CNS involvement before HSCT were significant predictors for CNS relapse after HSCT. We failed to show a significant prophylactic effect of intrathecal chemotherapy to prevent CNS relapse and such a prophylactic treatment should be avoided for patients at low risk for CNS relapse. The prognosis for isolated CNS relapse was surprisingly good.

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