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Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation in Children: Analysis of Prognostic Factors

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A B S T R A C T

Neurologic complications are serious complications after hematopoietic stem cell transplantation (HSCT) and significantly contribute to morbidity and mortality. The purpose of this study was to investigate the clinical features and prognosis in pediatric patients who had neurologic complications after allogeneic HSCT. We retrospectively reviewed the medical records of children and adolescents (19 years old or younger) who underwent allogeneic HSCT at our institution from 2000 to 2012. A total of 383 patients underwent 430 allogeneic transplantations. Among them, 73 episodes of neurologic complications occurred in 70 patients. The cumulative incidence of neurologic complications at day 400 was 20.0%. Almost two thirds of the episodes (63.0%, 46 of 73) occurred within 100 days after transplantation. Calcineurin inhibitor–related neurotoxicity was observed as the most common cause of neurotoxicity (47.9%, 35 of 73) and was significantly associated with earlier onset neurologic complications, seizure, and tremor. It also showed a significant association with lower probability of headache, abnormality of cranial nerve, and neurologic sequelae. In a multivariate analysis, days to neutrophil engraftment after HSCT, extensive chronic graft-versus-host disease (GVHD) and the existence of neurologic sequelae were identified as risk factors for mortality in patients who had neurologic complications (hazard ratio [HR], 1.08; 95% confidence interval [CI], 1.02 to 1.15; $P = .011$; HR, 5.98; 95% CI, 1.71 to 20.90; $P = .005$; and HR, 4.37; 95% CI, 1.12 to 17.05; $P = .034$, respectively). However, there was no significant difference in the 5-year overall survival between the patients who had neurologic complications without sequelae and the patients who did not have any neurologic complications (57.3% versus 61.8%, $P = .906$). In conclusion, we found that the major significant risk factors for mortality in pediatric recipients with neurologic complications were the existence of neurologic sequelae and extensive chronic GVHD.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a curative treatment modality for many malignancies and other life-threatening diseases. Since Thomas et al. performed the first HSCT in 1957, it is estimated that over 18,000 HSCT are performed annually worldwide [1,2].

Cytotoxicity related to conditioning regimens, the use of immunosuppressive agents to modulate the recipient's immune system, and the alloreactivity of donor cells often lead to serious complications after allogeneic HSCT. Neurologic complications, mainly in the central nervous system (CNS), are 1 of the most serious complications [3-5]. The incidence of neurologic complications ranges from 9.7% to 65% and they contribute to morbidity and mortality after HSCT [4,6-12]. Significant risk factors for neurologic complications are allogeneic HSCT, unrelated donors, and high-grade (>grade 2) acute graft-versus-host disease (GVHD) [7-13]. However, the factors affecting mortality among patients with neurologic complications have not been well identified, especially in the pediatric population. Furthermore, in the majority of previous studies assessing neurologic complications, which were referred to as *clinically significant* or *life-threatening neurologic events*, the incidence of neurologic complications might be underestimated. Nevertheless, there is no suggested classification or guideline for the evaluation of neurologic complication after HSCT.

Therefore, we investigated the incidence and clinical features of neurologic complications after allogeneic HSCT in the pediatric population. The main objective of this study was to evaluate the prognosis and risk factors for mortality in pediatric patients with neurologic complications after allogeneic HSCT.

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MATERIALS AND METHODS

Study Population

We defined an episode of neurologic complication as an event associated with new-onset neurologic symptom and corresponding abnormal findings on diagnostic tests. From January 2000 to December 2012, we investigated pediatric patients who underwent allogeneic HSCT for malignant and nonmalignant hematologic diseases at Samsung Medical Center in Seoul, South Korea. All patients were 19 years of age or younger at the time of allogeneic HSCT. Among these patients, we selected those who received at least 1 neurologic diagnostic test within 400 days after HSCT by searching the code number of diagnostic tests including brain magnetic resonance imaging, brain computed tomography, electroencephalography, nerve conduction study, and cerebrospinal fluid examination during the period. We then reviewed the medical records of these patients to identify episodes featuring new-onset neurologic complications. The patients who received neurologic diagnostic tests due to preexisting neurologic disease, head trauma, and mild or nonspecific events subsiding within 24 hours were excluded. This study was approved by the institutional review board at Samsung Medical Center, and the requirement for informed consent was waived because of the retrospective nature of the study.

Data Collection

We included patients with CNS-positive leukemia in our study. Craniospinal irradiation (cranial radiation therapy 2400 cGy, spinal radiation therapy 600 cGy) was performed from the start of consolidation chemotherapy for patients with CNS leukemia. No patients received post-transplantation intrathecal chemotherapy. We reviewed baseline clinical and demographic characteristics including age, sex, underlying disease, type of donor, source of stem cell, intensity of conditioning regimen, GVHD prophylaxis, use of high-dose total body irradiation (TBI), use of antithymocyte globulin (ATG), and the grade of acute and chronic GVHD in the identified cases of neurologic complications. To standardize the neurologic complications, we selected neurologic events at and above grade 2 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 2 CTCAE toxicity denotes moderate severity that limits self-care activities of daily living. We considered these criteria to be clinically informative because clinicians should be concerned about neurologic events and their sequelae when the severity of neurologic complications meets the CTCAE grade 2 or above. Neurologic symptoms based on depressed level of consciousness or pyramidal tract dysfunction, weakness, and sensory, behavior, and speech impairment were regarded as neurologic events. Based on previous studies on neurologic complications after allogeneic HSCT, the etiologies of the neurologic complications were classified into the following 7 groups [3,7,13,14]: (1) calcineurin inhibitor (CNI)–related neurotoxicity, which presented as posterior reversible encephalopathy syndrome (PRES) and/or toxic encephalopathy with symmetrically reduced diffusion in the periventricular and supraventricular white matter in brain magnetic resonance imaging diffusion findings without any definite etiologies; (2) infectious diseases, defined by the detection of pathogens in cerebrospinal fluid upon a culture and/or polymerase chain reaction (PCR). In case of fungal infection, we used revised definition of European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group [15,16]; (3) disease progression caused by CNS relapse of underlying disease; (4) post-transplantation lymphoproliferative disorder (PTLD); (5) metabolic disturbances; (6) vascular disorders (intracranial hemorrhage, thrombosis); and (7) others. We also assessed the existence of neurologic sequelae due to neurologic complications at 6 months after the onset of neurologic events. For convenience, we categorized the degree of disability to 5 scales using the modified Rankin Scale (mRS), which is widely used for the evaluation of stroke patients: (1) none, mRS 0 (no clinical symptoms with or without resolution of lesions on neuroimaging studies); (2) mild, mRS 1 and 2 (no significant disability and slight disability, respectively, able to manage without assistance despite symptoms); (3) moderate, mRS 3 and 4 (moderate and moderately severe disability, respectively, requiring some help and in some cases needing assistance to walk); (4) severe, mRS 5 (severe disability, requiring constant nursing care and attention, bedridden, incontinent); and (5) death, mRS 6 [17].

Conditioning Regimen and GVHD Prophylaxis

The conditioning regimens were determined by underlying disease, age, and status according to the protocols. The intensity of conditioning was determined by the patient baseline state and the state of underlying disease. We divided patients by the intensity of conditioning into a myeloablative group and a reduced-intensity group according to the protocols. High dose-TBI (≥total of 10 Gy) and busulfan (16 mg/kg for an oral dose or 12.8 mg/kg for an intravenous dose) were usually regarded as the myeloablative conditioning regimen, depending on the specific protocol. CNI alone or with other immunosuppressants (mycophenolate mofetil, steroids, and methotrexate) was/were used for GVHD prophylaxis. Cord blood recipients received cyclosporine A and methylprednisolone until December 2004, and cyclosporine A plus mycophenolate mofetil thereafter. The diagnosis of acute and chronic GVHD was based on standard clinical criteria and biopsies when available [18]. Acute GVHD with grade II or above was controlled with steroids, mainly methylprednisolone.

Statistical Analyses

Categorical variables were compared using Fisher's exact test or chi-square test. Continuous variables were compared using the Mann-Whitney *U* test. Differences in clinical features between CNI-related neurotoxicity group and non–CNI-related neurotoxicity group were compared by univariate analysis. For convenience, we defined *non–CNI-related neurotoxicity* as all causes of neurologic complications except CNI-related neurotoxicity. Multivariate logistic regression analysis was performed to evaluate the risk factors for neurologic sequelae. We selected variables which were well-known factors for neurologic complication, such as age at HSCT, use of TBI, donor type, underlying disease type, CNI-related neurotoxicity, severe acute GVHD (grade ≥ 3), and extensive chronic GVHD. Cox proportional hazards analysis was used to evaluate the independent risk factors for mortality. In model 1, we included variables with *P* values less than .10 in the univariate analysis. In model 2, we included variables that were identified as statistically significant factors in model 1 as well as the well-known risk factors for neurologic complication in the literature because these well-known risk factors for neurologic complication might effect mortality regardless of statistical significance [7-13]. Multivariate model 1 was adjusted for (1) age at HSCT, (2) days at neutrophil engraftment, (3) use of ATG, (4) donor type (matched versus mismatched), (5) extensive chronic GVHD, and (6) the existence of sequelae. Multivariate model 2 was adjusted for following variables: (1) age at HSCT, (2) days at neutrophil engraftment, (3) underlying disease type (malignant versus nonmalignant), (4) use of TBI, (5) donor type (matched related versus unrelated and haploidentical), (6) acute GVHD (grade ≥ 3 versus no or grade I and II GVHD), (7) extensive chronic GVHD, and (8) the existence of sequelae. Days to neutrophil engraftment, extensive chronic GVHD, and the existence of sequelae were included as variables in model 2 because they were identified as significant risk factors ($P < .05$) for mortality in model 1. The cumulative incidence of neurologic complications and overall survival (OS) were determined using Kaplan-Meier analysis with the log-rank method. The null hypothesis of no difference was rejected if *P* values were less than .05, or equivalently, if 95% confidence intervals of the hazard ratio excluded 1. The statistical analyses were performed using SPSS version 19 (SPSS, Chicago, IL) and GraphPad Prism version 6.04 (GraphPad Software, La Jolla, CA).

RESULTS

Case Identification and Baseline Characteristics

Between January 2000 and December 2012, a total of 383 pediatric patients underwent 430 cases of allogeneic HSCT. Neurologic diagnostic tests were performed in 92 patients (96 episodes) within 400 days after allogeneic HSCT. Patients with pre-existing cerebral disorders (n = 12), nonspecific or mild neurologic symptoms (n = 7), and head trauma (n = 3) were excluded. Finally, we identified 70 patients (73 episodes) as the neurologic complications group (Figure 1). The median age at allogeneic HSCT was 10.1 years (range, .7 to 19.0 years) and the ratio of males to females was 1.9:1 (46:24). The median follow-up after allogeneic HSCT was 26 months (range, 1 to 143 months). Table 1 summarizes the baseline characteristics of the study patients.

Clinical Features of Neurologic Complications

The cumulative incidences of neurologic complications at days 30, 100, 200, and 400 were 5.9%, 12.3%, 15.9%, and 20.0%, respectively (Supplemental Figure 1). Almost two thirds of the episodes (63.0%, 46 of 73) of neurologic complications occurred within 100 days after allogeneic HSCT (Figure 2). The etiologies of neurologic complications are listed in

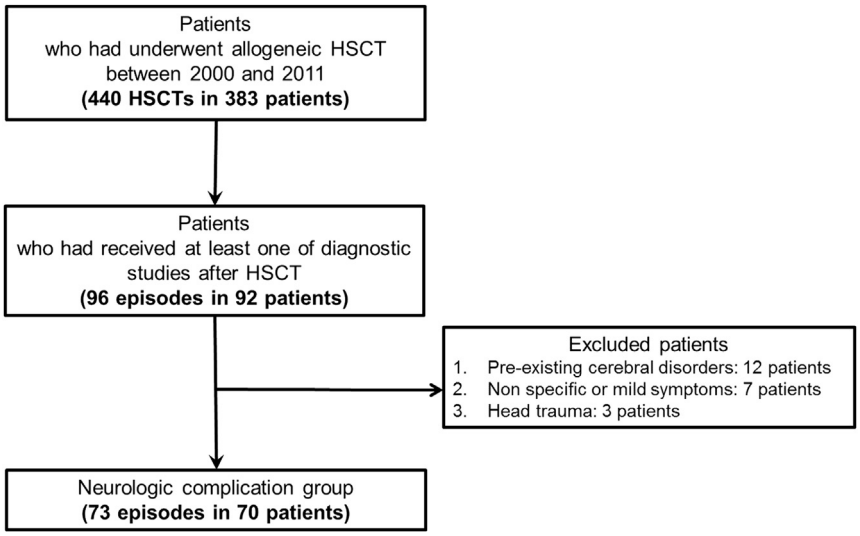

Figure 1. Flow chart of case selection.

Table 2. CNI-related neurotoxicity was the most frequent etiology (47.9%, 35 of 73), followed by infectious disease (11.0%, 8 of 73), CNS relapse of underlying disease (8.2%, 6 of 73), PTLD (6.8%, 5 of 73), metabolic disturbances (4.1%, 3 of 73), vascular disorders (2.7%, 2 of 73), and others (19.2%, 14 of 73). Among the 14 other episodes, 9 episodes (12.3%, 9 of 73) were of unknown causes, 4 (5.5%, 4 of 73) were related to chemotherapy, and 1 (1.3%, 1 of 73) was related to radiotherapy. CNI-related neurotoxicity represented 58.7% of all etiologies (27 of 46) occurring within 100 days after HSCT and 29.6% of etiologies (8 of 27) occurring after day 100.

Seizure (50.7%, 37 of 73) was the most frequent neurologic symptom, followed by abnormality of cranial nerve (such as ophthalmoplegia, visual fields defect, or facial palsy; 11.0%, 8 of 73), headache (8.2%, 6 of 73), abnormality of peripheral nervous system (such as motor weakness or sensory deficit; 6.8%, 5 of 73) and tremor (6.8%, 5 of 73), altered levels of consciousness (5.5%, 4 of 73), and others (11.0%, 8 of 73). Seizure was also the most frequent symptom (71.4%, 25 of 35) in episodes with an etiology caused by CNI-related neurotoxicity.

We evaluated the neurologic sequelae at 6 months after the onset of neurologic complications. Thirty-one neurologic episodes (42.5%, 31 of 73) had remaining neurologic sequelae. Among these episodes with sequelae, 11 episodes (15.1%, 11 of 73) remained mild, 6 episodes (8.2%, 6 of 73) remained moderate, 4 episodes (5.5% 4 of 73) remained severe sequelae, and 10 patients (13.7%, 10 of 73 in episodes; 14.3%, 10 of 70 in patients) died because of neurologic complication.

Two patients died before the assessment of sequelae, and their causes of death were not associated with neurologic complications. One patient died because of engraftment failure and the other patient died from coronary artery stenosis related to GVHD. We grouped these cases into unknown group (Supplemental Table 2).

We analyzed the sequelae according to etiology. Among the total of 35 CNI-related neurotoxicity episodes, 26 episodes (74.3%, 26 of 35) did not have any sequelae and 8 episodes (22.9%, 8 of 35) did. In the episodes of infectious disease, 4 episodes did not have any sequelae and the other 4 episodes resulted in death. The reasons for death included 2 cases of invasive fungal diseases (1 proven and 1 possible fungal infection by definition) and 2 cases of meningoencephalitis by virus infection (1 cytomegalovirus and 1 varicella-zoster virus).

We also analyzed sequelae according to symptom. Among the total of 37 seizure episodes, 22 episodes presented with seizure (59.5%, 22 of 37) and did not have any sequelae (among them, 19 episodes presented with only 1 single seizure episode), whereas the other 15 episodes (40.5%, 15 of 37) had sequelae. In the episodes presenting with tremor, among a total of 5 tremor episodes, 4 episodes subsided within 6 months and 1 episode had persisting mild sequelae (Supplemental Table 2).

Statistical Analyses of Clinical Features and Outcomes

CNI-related neurotoxicity versus non–CNI-related neurotoxicity

There were no significant differences in the baseline characteristics, including the age, sex, underlying disease, type of donor, source of stem cell, intensity of conditioning regimen, and severity of GVHD between the 2 groups (Table 1). Seizures occurred more frequently in the CNI-related neurotoxicity group than in non–CNI-related neurotoxicity group (67.5% versus 32.4%, $P = .001$), and neurologic sequelae were less frequent in CNI-related neurotoxicity group than in non–CNI-related neurotoxicity group (25.8% versus 74.2%, $P = .002$). All cases with abnormality of cranial nerve (n = 8) occurred in the non–CNI-related neurotoxicity group ($P = .005$), whereas all cases of tremor (n = 5) occurred in the CNI-related neurotoxicity group ($P = .022$). The median onset of neurologic complications was earlier in CNI-related neurotoxicity group (day 44; range, 3 to 377) than in the non–CNI-related neurotoxicity group (day 105; range, −7 to 384) ($P = .009$) (Table 3). We also explored whether certain symptoms or the onset or existence of neurologic sequelae were associated with other specific etiologies; however, no definitive associations were apparent, except for CNI-related neurotoxicity.

Risk factors for neurologic sequelae

In univariate analysis, CNI-related neurotoxicity was associated with fewer episodes of neurologic sequelae than non–CNI-related neurotoxicity (hazard ratio [HR], .19; 95%

Table 1
Patient Characteristics

Characteristic	All	CNI	Non-CNI	*P* Value
No. of neurologic episodes (%)	73	35 (47.9)	38 (52.1)	
No. of patients (%)*	70			
Male sex	48 (65.8)	21 (60.0)	27 (71.1)	.30
Age at diagnosis, median (range), yr	8.6 (0-17.7)	6.5 (0-12.6)	9.8 (0-17.7)	.10
Age at HSCT, median (range), yr	10.2 (.7-19.0)	8.3 (1.1-17.9)	10.9 (.7-19.0)	.10
Underlying disease				.40
ALL	19 (26.0)	7 (20.0)	12 (31.6)	
AML	21 (28.8)	8 (22.9)	13 (34.2)	
SAA	11 (15.1)	6 (17.1)	5 (13.2)	
Others (malignant)†	11 (15.1)	7 (20.0)	4 (10.5)	
Others (nonmalignant)‡	11 (15.1)	7 (20.0)	4 (10.5)	
No. of HSCT				1.00
1	59 (80.8)	28 (80.0)	31 (81.6)	
≥2	14 (19.2)	7 (20.0)	7 (18.4)	
Source of stem cells				.50
BM	19 (26.0)	12 (34.3)	7 (18.4)	
PB	20 (27.4)	9 (25.7)	11 (28.5)	
CB	31 (42.5)	13 (37.1)	18 (47.4)	
Combined§	3 (4.1)	1 (2.9)	2 (5.3)	
Type of donor				.90
Matched related	9 (12.3)	4 (11.4)	5 (13.2)	
Matched unrelated	35 (47.9)	18 (51.4)	17 (44.7)	
Mismatched unrelated	25 (34.2)	11 (31.4)	14 (36.8)	
Haploidentical	4 (5.5)	2 (5.7)	2 (5.3)	
Myeloablative conditioning regimen	69 (94.5)	33 (94.3)	36 (94.7)	1.00
Use of TBI	31 (42.5)	15 (42.9)	16 (42.1)	1.00
Use of ATG	43 (58.9)	21 (60.0)	22 (57.9)	1.00
Use of fludarabine	30 (41.1)	13 (37.1)	17 (44.7)	.60
Use of busulfan	32 (43.8)	14 (40.0)	18 (47.4)	.60
GVHD prophylaxis				.30
CsA only	9 (12.3)	4 (11.4)	5 (13.2)	
CsA + MTX	25 (34.2)	14 (40.0)	11 (28.9)	
CsA + MMF	25 (34.2)	9 (25.7)	16 (42.1)	
CsA + steroid	10 (13.7)	7 (20.0)	3 (7.9)	
Others‖	4 (5.5)	1 (2.9)	3 (7.9)	
Days to neutrophil engraftment, median (range)¶	16 (9-47)	15 (9-47)	16 (9-33)	
Grade of acute GVHD				.80
None	13 (17.8)	5 (14.3)	8 (21.1)	
1-2	39 (53.4)	19 (54.3)	20 (52.6)	
≥3	21 (28.8)	11 (31.4)	10 (26.3)	
Extent of chronic GVHD				.60
None	22 (30.1)	8 (22.7)	14 (36.8)	
Limited	14 (19.2)	7 (20.0)	7 (18.4)	
Extensive	28 (38.4)	15 (42.9)	13 (34.2)	
Not applicable	9 (12.3)	5 (14.3)	4 (10.5)	

ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; SAA, severe aplastic anemia; BM, bone marrow; PB, peripheral blood; CB, cord blood; CsA, cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil.
Data presented are n (%), unless otherwise indicated.

* There were 3 patients who had both CNI-related and non–CNI-related episodes. One patient had CNI and unknown etiology and 2 patients had both CNI and infectious etiology.

† Includes 1 case of hemophagocytic lymphohistiocytosis, 2 cases of juvenile myelomonocytic leukemia, 2 cases of lymphoma, 2 cases of chronic myeloid leukemia, and 4 cases of neuroblastoma.

‡ Includes 1 case of congenital dyserythropoietic anemia, 2 cases of Fanconi anemia, 2 cases of osteopetrosis, 3 cases of pure red cell aplasia, and 3 cases of primary immunodeficiencies.

§ Includes 1 BM + PB and 2 PB + CB.

‖ Includes 1 tacrolimus, 1 tacrolimus + MMF, and 2 tacrolimus + MTX.

¶ Two cases of engraftment failure were not included in this result.

confidence interval [CI], .07 to .53; $P = .001$). In the multivariate analysis, we adjusted for age at HSCT, use of TBI, donor type, underlying disease type, severe acute GVHD (grade ≥ 3), and extensive chronic GVHD, as well as CNI-related neurotoxicity. CNI-related neurotoxicity was still identified as the only significant factor that was associated with fewer episodes of neurologic sequelae (HR, .23; 95% CI, .07 to .75; $P = .015$) (Supplemental Table 1).

Risk factors for mortality

Including cases with all causes of death, the age at allogeneic HSCT, days to neutrophil engraftment after allogeneic HSCT, extent of chronic GVHD, and the existence of neurologic sequelae were regarded as variables ($P < .10$) to evaluate in the multivariate analysis. Days to neutrophil engraftment after HSCT and the existence of neurologic sequelae had a significant hazard effect on mortality (HR, 1.06; 95% CI, 1.01 to 1.12; $P = .019$; and HR, 3.04; 95% CI, 1.33 to 6.96; $P = .008$, respectively). In the mortality group, the median time to neutrophil engraftment was 16 (range, 9 to 47) days, whereas it was 13.5 days in the survival group (range, 9 to 21). We reanalyzed those data after excluding 11 patients who died because of disease progression. Age at HSCT, days to neutrophil engraftment, use of ATG, donor type (matched versus mismatched), extensive chronic GVHD, and the existence of sequelae were regarded as variables ($P < .10$)

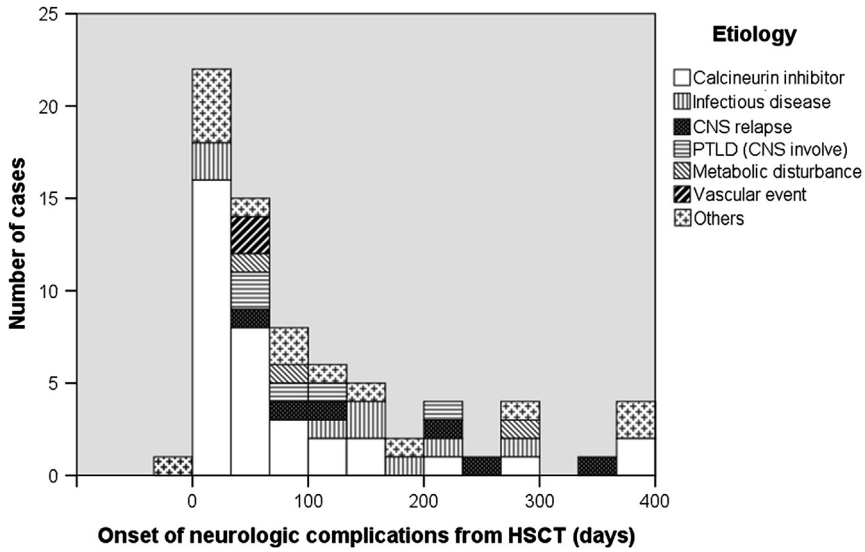

Figure 2. Onset of neurologic complications after allogeneic HSCT according to etiologies.

for multivariate analysis (Supplemental Table 3). In multivariate model 1, days to neutrophil engraftment after HSCT, extensive chronic GVHD, and neurologic sequelae were significant risk factors for mortality (HR, 1.07; 95% CI, 1.01 to 1.14; $P = .022$; HR, 7.03; 95% CI, 2.05 to 24.15; $P = .002$; and HR, 5.02; 95% CI, 1.30 to 19.34; $P = .019$, respectively). In multivariate model 2, days to neutrophil engraftment after HSCT, extensive chronic GVHD, and neurologic sequelae were also identified as significant risk factors for mortality (HR, 1.08; 95% CI, 1.02 to 1.15; $P = .011$; HR, 5.98; 95% CI, 1.71 to 20.90; $P = .005$; and HR, 4.37; 95% CI, 1.12 to 17.05; $P = .034$, respectively) (Table 4).

Ten patients died from direct neurologic complications within 6 months of developing the neurologic episode (Supplemental Table 2). Among those, 2 patients died of CNS relapse. Of the remaining 8 patients, 4 patients with extensive chronic GVHD died of direct CNS causes, including CMV encephalitis, CNS aspergillosis, brain abscess, and disseminated PTLD involving the CNS. Three patients without extensive chronic GVHD died of varicella-zoster virus encephalitis (n = 1) and disseminated PTLD with CNS involvement (n = 2).

When we looked at the mortality data for all patients beyond 6 months (data not shown), 25 patients with neurologic complication died. Twelve patients with extensive chronic GVHD died (48%). Among them, 6 (50%) died of GVHD itself and 3 (25%) died of CNS infection. In patients who died with neurologic sequelae (n = 15), 5 patients (33.3%) died of severe acute or extensive chronic GVHD and 4 patients (26.7%) died of CNS infection. Out of 25 patients, 11 patients had newly developed neurologic symptoms, including intractable seizure (n = 6), decreased level of consciousness (n = 2), ophthalmoplegia (n = 1), decreased visual activity (n = 1), and ascending paralysis (n = 1) within 4 weeks before death.

Table 2
Etiology of Neurologic Complications

Etiology	No. of episodes, n (%)	Median onset, (range), d
CNI-related neurotoxicity	35 (47.9)	44 (3-377)
Infectious disease	8 (11.0)	146.5 (10-286)
Virus*	4	129 (10-154)
Bacteria	0	
Fungus†	2	243.5 (201-286)
Unidentified origin‡	2	101 (19-183)
CNS relapse	6 (8.2)	172 (66-347)
PTLD (CNS involvement)	5 (6.8)	155 (54-209)
Metabolic disturbance	3 (4.1)	79 (35-268)
Vascular event§	2 (2.7)	53 (47-59)
Others‖	14 (19.2)	87.5 (−7 to 384)
Total	73	62 (−7 to 384)

* Includes 1 cases of *Human herpesvirus* type 6 meningitis, 1 case of varicella-zoster virus encephalitis, and 2 cases of cytomegalovirus diseases (encephalitis, ventriculitis).

† Includes 1 proven case of invasive Aspergillosis disease, and 1 possible case of invasive fungal disease.

‡ Includes 1 case of cavernous sinusitis and 1 case of meningitis, in which the pathogens were not proven.

§ Includes 1 case of subdural hemorrhage and 1 case of intracranial hemorrhage with subdural hemorrhage.

‖ Includes 1 case of radiotherapy-related neurotoxicity, 4 cases of chemotherapy-related neurotoxicity, and 9 unknown cases.

Overall survival

The 5-year OS rate was significantly lower in neurologic complications group than in group without neurologic complications (44.6% in the neurologic complications group versus 61.8% in group without neurologic complications, $P = .013$) (Figure 3A). Among the neurologic complications group, the 5-year OS rate showed almost a 2-fold difference depending on the existence of neurologic sequelae (29.7% in sequelae group versus 56.9% in the without-sequelae group, $P = .007$) (Figure 3B). After the exclusion of 11 of deaths due to disease progression, the 5-year OS rate showed a similar difference between 2 groups (37.1% in sequelae group versus 73.2% in without-sequelae group, $P = .015$) (Supplemental Figure 2). There were no significant differences in the 5-year OS rate between the group with neurologic complications without sequelae and the group without any neurologic complications (57.3% versus 61.8%, $P = .906$) (Figure 3C), and between the CNI-related neurotoxicity and non–CNI-related neurotoxicity groups (61.6% versus 33.3%, $P = .087$).

DISCUSSION

The main finding of this study is the identification of risk factors for mortality in pediatric recipients with neurologic

Table 3
Clinical Differences of Neurologic Complications between the CNI-Related Neurotoxicity Group and the Non–CNI-Related Neurotoxicity Group

	CNI (n = 35)	Non-CNI (n = 38)	*P* Value
Symptom			
Seizure	25 (71.4)	12 (31.6)	.001
Headache	0	6 (100)	.026
Altered level of consciousness	2 (50.0)	2 (50.0)	1.00
CN abnormality	0	8 (100)	.005
PN abnormality	0	5 (100)	.055
Tremor	5 (100)	0	.022
Others*	3 (37.5)	5 (62.5)	.712
Median onset after HSCT, (range), d	44 (3-377)	105 (−7 to 384)	.009
Within 100 d	27 (58.7)	19 (41.3)	.028
After 100 d	8 (29.6)	19 (70.4)	
Association of fever	16 (57.1)	12 (42.9)	.238
Sequelae	8 (25.8)	23 (74.2)	.002

CN indicates cranial nerve; PN, peripheral nerve.
* Includes 1 case of dysarthria with paresthesia, 1 case of amnesia, 1 case of chorea, 1 case of vertigo, 1 case of delirium, 1 case of anxiety with irritability, and 2 cases of ataxia.

Table 4
Multivariate Analysis for Mortality in Patients with Neurologic Complications

Variable	Model 1			Model 2		
	HR	95% CI	*P*	HR	95% CI	*P*
Excludes 11 patients who died due to disease progression (n = 59)						
Age at HSCT	1.03	.92-1.16	.586	1.02	.91-1.15	.712
Days to neutrophil engraftment after HSCT	1.07	1.01-1.14	.022	1.08	1.02-1.15	.011
Underlying disease						
Malignant versus nonmalignant				.73	.17-3.08	.664
Conditioning regimen						
TBI versus non-TBI				.94	.24-3.70	.944
ATG versus non-ATG	1.85	.45-7.61	.393			
Donor type						
Matched related versus others*				.0†	0-.	.979
Matched versus mismatched	.74	.19-2.92	.666			
Severe acute GVHD (grade ≥ 3)				.94	.27-3.33	.929
Extensive chronic GVHD	7.03	2.05-24.15	.002	5.98	1.71-20.90	.005
Sequelae	5.02	1.30-19.34	.019	4.37	1.12-17.05	.034

Multivariate model 1 was adjusted for age at HSCT, days to neutrophil engraftment, use of ATG, donor type (matched versus mismatched), extensive chronic GVHD, and the existence of sequelae; multivariate model 2 was adjusted for age at HSCT, days to neutrophil engraftment, use of TBI, donor type (matched related versus unrelated and haploidentical), extensive chronic GVHD, and the existence of sequelae.
* Includes matched unrelated, mismatched unrelated, and haploidentical donors.
† There were 9 matched related donors included in our study. Among them, 3 CNS relapse cases were excluded in mortality analysis and the remaining 6 cases all lived.

complications. Moreover, we found that the neurologic complications caused by CNI-related neurotoxicity have certain distinct clinical features.

The cumulative incidence of neurologic complications at 1 year was 20.0% (95% CI, 15.7% to 24.23%). In the literature, the incidence of neurologic complications was reported with a range from 9.7% to 65%. This wide range may be due to the heterogeneity of study populations and extensive variation in definitions of neurologic complications [4,6-14]. If the severity was confined to clinically significant neurologic complications (CTCAE grade 3 and above, or possibly assumed), the incidence ranges from 9.7% to 23% at around 6 to 12 months after HSCT [4,6,7,9,12]. Considering the extended setting of this study (CTCAE grade 2 and above), the incidence might be underestimated but comparable. Almost two thirds of neurologic complications (63.0%, 46 of 73) occurred within 100 days after allogeneic HSCT. CNI-related neurotoxicity was the most common etiology (Figure 2). Faraci et al. reported a similar pattern of onset and frequency of the etiologies in 37 children with severe CNS complications (CTCAE grade 3 or 4) after HSCT regardless of the type of HSCT [9]. We found similar results in a larger and more homogenous study population.

CNI-related neurotoxicity has been reported to be 1 of the most frequent neurologic complications after allogeneic HSCT [3,6,9,12]. It has been suggested that CNI-induced endothelial damage causes subcortical edema in the posterior circulation by hyperperfusion injury and by the lack of autoregulation [19,20]. In our study, CNI-related neurotoxicity was significantly associated with seizure and tremor that occurred as earlier onset events. It also showed a significant association with lower probability of headache, abnormalities in cranial nerves, and neurologic sequelae (Tables 1 and 3). However, it did not influence OS. In our study, having neurologic sequelae was identified as significant risk factor for mortality in patients with neurologic complications (Tables 3 and 4).

Because CNI-related neurotoxicity was associated with a lower probability of neurologic sequelae, we examined whether this was related to decreased mortality. However, there was no statistically significant difference in a 5-year OS rate between CNI-related neurotoxicity group and non–CNI-related neurotoxicity group (61.6% versus 33.3%, $P = .087$). Koh et al. and Iguchi et al. also reported that there was no significant difference in the long-term survival between CNI and non-CNI groups [8,12]. In contrast, Siegal at el. reported inferior 1-year survival in patients with PRES, which was mainly caused by CNI. Although our analysis did not detect any statistically significant difference, OS of the CNI-related neurotoxicity group appears to be nearly twice that of the non–CNI-related neurotoxicity group. To clarify the association between CNI and prognosis, further well-designed cohort studies are needed.

Neurologic complications after HSCT increase mortality. Siegal et al. retrospectively analyzed CNS complications occurring within 100 days after allogeneic HSCT in 302 adult recipients and reported a 1-year survival of 28% and 72% in patients with and without CNS complications, respectively ($P < .001$) [6]. Koh et al. reported a lower 5-year OS rate in pediatric recipients with CNS complications compared with their counterparts (52.1% versus 64.9%, $P = .014$) [12]. In cases of neurologic sequelae, we could not find any studies that analyzed the association between neurologic sequelae and mortality, except 1 descriptive study of late sequelae [21].

We also found increased mortality in patients with neurologic complications compared with patients without neurologic complications. Among the former, patients with sequelae showed significantly higher mortality than patients without sequelae (Figure 3B). In multivariate analysis, we confirmed that the existence of neurologic sequelae and extensive chronic GVHD were major significant risk factors for mortality in patients with neurologic complications after allogeneic HSCT. Days to neutrophil engraftment also appeared to be a risk factor with an HR of 1.08 (95% CI, 1.02 to 1.15; $P = .011$).

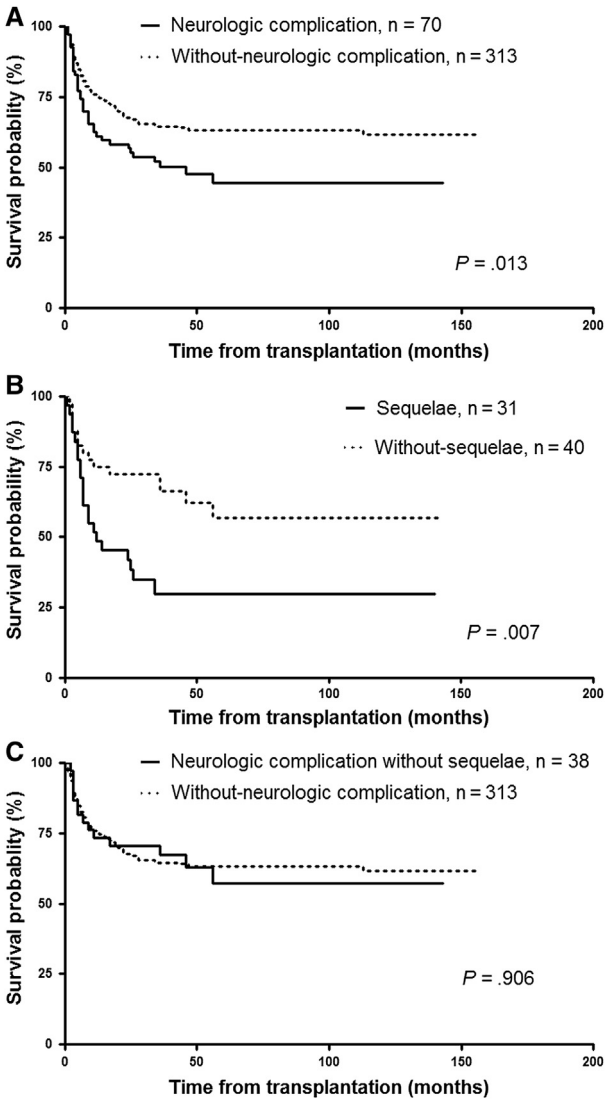

Figure 3. (A) Overall survival between neurologic complications group and the group without neurologic complications. (B) Overall survival between the sequelae group and the group without sequelae in patients with neurologic complications. (C) Overall survival between the group with neurologic complications without sequelae and the group without any neurologic complications.

There were 2 interesting results concerning mortality. First, as we mentioned earlier, the survival rate in the CNI-related neurotoxicity group was higher than that of the non–CNI-related neurotoxicity group. Second, there was no significant difference in the survival rate between patients who had neurologic complications without sequelae and those without neurologic complications. This indicates that if neurologic complication did not persist 6 months after onset, there was no significant effect on mortality.

Of note, in addition to severe GVHD, CNS pathologies, particularly CNS infection and CNS involving PTLD, appear to be important risks for mortality. As a possible explanation, severe immunosuppression to control GVHD might have contributed to the development of these CNS pathologies. Therefore, it appears that GVHD and CNS pathologies are inter-related for increased mortality.

This study had limitations. First, it was a retrospective study and mainly included data about brain-imaging studies. To minimize this measurement bias, we also included data for nerve conduction study. However, this might be insufficient to represent all the peripheral nervous system episodes when compared with CNS episodes. Furthermore, the grade of adverse events might be related to the severity of sequelae. However, because of insufficient data in the medical records, we could not analyze the association. Finally, the number of episodes with CNI-associated neurotoxicity could have been overestimated. Currently, there is no clear definition or guideline on CNI-related neurotoxicity. We identified CNI-associated neurotoxicity cases as a diagnosis of exclusion in symptomatic recipient with abnormal brain-imaging findings, such as PRES or toxic encephalopathy. However, we did not routinely perform pre-HSCT brain imaging studies in all recipients. Brain white matter abnormalities could have already existed in asymptomatic patients before HSCT.

Nevertheless, this study has several strengths. First, this is the first study to analyze the neurologic sequelae and the risk factors for mortality in pediatric recipients of allogeneic HSCT with neurologic complications. Second, we tried to use standardized and authorized measurement tools to allow for easier comparison with further studies. Third, we identified the clinical features of CNI-associated neurotoxicity in a large pediatric population.

In conclusion, neurologic complication commonly occurs in pediatric HSCT recipients. Major significant risk factors for mortality in pediatric recipients with neurologic complication were the existence of neurologic sequelae and extensive chronic GVHD.

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SUPPLEMENTARY DATA

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