Risk Factor and Long-Term Outcome Analyses for Acute Limbic Encephalitis and Calcineurin Inhibitor-Induced Encephalopathy in Adults following Allogeneic Hematopoietic Cell Transplantation

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Highlights

• Older age, HLA-mismatched unrelated donors, graft-versus-host disease (GVHD) prophylaxis with calcineurin inhibitor and mycophenolate mofetil, and grade II to IV acute GVHD were identified as risk factors of post-transplant acute limbic encephalitis (PALE).

• Efficacy of addition of high-dose steroid was limited.

• MDS, HLA-mismatched unrelated donors, and grade II to IV acute GVHD were identified as risk factors of calcineurin inhibitor-induced encephalopathy (CNIE).

• The 5-year non-relapse mortality rates of PALE and CNIE were both high.

Original Manuscript

Risk factor and long-term outcome analyses for acute limbic encephalitis and calcineurin inhibitor-induced encephalopathy in adults following allogeneic hematopoietic cell transplantation

Running Head: Risk factors for acute limbic encephalitis and calcineurin inhibitor-induced encephalopathy in allogeneic HCT

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INTRODUCTION

Central nervous system (CNS) complications after allogeneic hematopoietic cell transplantation (allo-HCT) are still one of the important causes of allo-HCT-related morbidity and mortality (1, 2). Many studies reported risk factors for a composite of multiple CNS complications after allo-HCT (2-4). However, for a more precise and targeted approach, risk factor analysis for each CNS outcome is needed. Several studies have performed risk factor analyses for each CNS complication. They have included analyses for cerebrovascular disease (5), posterior reversible encephalopathy syndrome (PRES) in children (6, 7), viral encephalitis (8), and human herpesvirus-6 (HHV-6) encephalitis (9). However, further exploration on each CNS event is required to improve the management and prognosis of CNS complications after allo-HCT.

Post-transplant acute limbic encephalitis (PALE) is a rare, severe inflammatory disorder in the bilateral limbic system, including the hippocampus, and has not been examined comprehensively (10). Seeley et al. reported that although the development of PALE could be associated with the presence of HHV-6 in the cerebrospinal fluid (CSF), the study included CSF HHV-6-negative cases, too (10). Hill et al. showed that factors associated with increased risk of developing CSF HHV-6-positive PALE include the following: unrelated cord blood transplantation

(CBT), acute graft-versus-host disease (aGVHD) grades II–IV, and adult mismatch donor (11). Although HHV-6 encephalitis after allo-HCT may be defined based on the positivity of HHV-6 on the CSF (9), the diagnostic cut-off levels of CSF HHV-6 viral load discriminating HHV-6 encephalitis from HHV-6 reactivation in the CSF (i.e., HHV-6 present in CSF but not HHV-6 infectious disease) has not yet been established; furthermore, the pathogenic role of HHV-6 has not yet been fully understood. CSF HHV-6 negative cases defined by quantitative polymerase chain reaction (qPCR) can unlikely mean HHV-6 encephalitis (12). To our knowledge, only a few cases of CSF HHV-6-negative PALE were reported (10). This may be because of difficulty of awareness of PALE or wrong diagnosis as herpes simplex encephalitis. Historically, the CNS had been considered as an “immune privileged” site because it did not appear to express major histocompatibility complex (MHC) class 1 (13, 14). However, recent studies have reported that MHC class 1 protein could be expressed in hippocampal neurons (14-16); thus, the limbic system could be targeted by alloimmune reactions. This supports a speculation that alloimmune reactions, derived from HLA mismatch, may have a crucial role in the pathogenesis of CSF HHV-6-negative or HHV-6-reactivated PALE. In addition, preclinical (17, 18) and case report (19, 20) evidence on aGVHD of the CNS supports that the CNS could be targeted by alloimmune reaction including donor T cells. To our knowledge, no study

has examined the risk factors and long-term outcomes of PALE including CSF HHV-6-negative cases.

Calcineurin inhibitor-induced encephalopathy (CNIE) following allo-HCT is characterized by PRES or transplantation-associated thrombotic microangiopathy (21-24). Only two studies in children conducted risk factor analyses for PRES, mainly in non-malignant diseases including mostly hemoglobinopathies (6, 7). A few reports showed a poor prognosis of pediatric patients with CNIE after allo-HCT (6, 7, 22). However, evidence is lacking on risk factors and long-term prognosis for CNIE in adults with hematological malignancies after allo-HCT.

On the basis of these observations, we conducted a retrospective cohort study to investigate risk factors and long-term outcomes of PALE and CNIE after allo-HCT.

MATERIALS AND METHODS

Patients

We retrospectively examined consecutive patients who underwent allo-HCT at our institute between January 2005 and November 2017. In this study, opt-out consent

was selected since it was difficult to obtain written informed consent given the retrospective design of the study. This observational study was announced to the public by displaying a notice at the hospital and on its website. The protocol was carried out in accordance with the “Ethical Guidelines for Medical and Health Research Involving Human Subjects” by the Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labor and Welfare in Japan (25). The study was approved by the Human Subjects Review Committee of Osaka City University.

Transplantation Procedures

Detailed transplantation procedures employed at our institute have been described previously (26-29). Briefly, *HLA* allele typing was performed at *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1*. The conditioning regimens consisted of myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC). MAC regimens included total-body irradiation greater than fractionated 800 cGy; oral or intravenous administration of busulfan at a dose of 9 mg/kg or more and 7.2 mg/kg or more, respectively; melphalan dose at 140 mg/m^2 or more; or a thiotepa dose at 10 mg/kg or more, according to a previous report (30). Other regimens were defined as

RIC (30). Donor sources included HLA-matched or one-antigen-mismatched related bone marrow (BM) or peripheral blood (PB), HLA-matched unrelated BM/PB donor (URD), HLA-mismatched URD, haplo-identical PB donor, and umbilical cord blood (CB) donor. To prevent aGVHD, we mainly used CNIs with methotrexate (MTX) or CNIs with mycophenolate mofetil (MMF). Post-transplantation cyclophosphamide was used only for haplo-identical PB (27, 29). Supportive care included granulocyte colony-stimulating factor administration to neutrophil engraftment, and levofloxacin, fluconazole, and acyclovir prophylaxis for infections as reported previously (26).

Disease risk was categorized into low, intermediate, high, or very high risk by the refined disease risk index (DRI) (31). We defined engraftment as an absolute neutrophil count of at least 500/μl for three consecutive days. aGVHD was defined based on standard criteria (32).

Diagnosis of CNIE and PALE and Outcome Measure

As a rule, according to the allo-HCT manual of our transplantation unit, the following evaluations were performed for all patients who developed some new CNS symptoms, except for the presence of certain reasons such as clinically severe cases, along with consultation with a neurologist: brain computed tomography; brain

magnetic resonance imaging including apparent diffusion coefficient map; electroencephalography; CSF examination including bacterial, fungal, and *Mycobacterium tuberculosis* cultures; and qPCR testing for the presence of herpes simplex virus, varicella zoster virus, Epstein-Barr virus (EBV), HHV-6, and cytomegalovirus.

PALE was defined as presence of acute onset of neurological symptoms mainly consisting of memory deficits, altered mental status, or seizures, and displayed hyperintensities of selective bilateral medial temporal lobe structures, particularly including the hippocampus in T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences (10, 33). In this study, PALE included cases with HHV-6-positive CSF, but not other members of the herpesvirus family according to a previous report (10). CSF HHV-6 DNA was measured by real-time qPCR (reference value, $<2\times10^2$ copy/mL). CSF HHV-6 negative PALE was defined by negative results of HHV-6 qPCR using the CSF sample. In addition, PALE did not include cases with malignant cell-positive CSF (10). Considering the retrospective assessment, treatment response to steroid and/or immunosuppressants was judged at day 90 after the start of intravenous methylprednisolone (mPSL) therapy at 1 g dosage for three consecutive days with reference to previous reports (34, 35), in similar context as follows: 1) the documented neurological status, as recorded by the attending

physician, was graded by two independent investigators according to the modified Rankin Scale (mRS) (36) and Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (37); 2) complete response was defined by the resolution of all clinical signs and symptoms and radiological findings; partial response was defined by score improvement of mRS ≥1 or CTCAE grade ≥1 and no worsening radiological and clinical findings; stable response was defined by the absence of change from baseline; and failure of therapy was defined by worsening disease. As necessary, mPSL 1 g pulse therapy was repeated weekly according to the judgment of the attending physicians. Other treatments including intravenous immunoglobulin and plasmapheresis were not used in the present study.

CNIE was defined as the presence of acute-onset neurological symptoms of PRES (e.g., headache, seizures, disorders of consciousness, and visual disturbance) with hyperintense lesions in T2-weighted or FLAIR sequences frequently presenting symmetric pattern in the parieto-occipital lobe, reflecting vasogenic edema, or neurological manifestations of thrombotic microangiopathy (TMA) during cyclosporin A or tacrolimus administration, after ruling out other possible causes (22, 38). TMA was diagnosed with reference to two previous consensus criteria (39, 40).

Statistical Analysis

Blood pressure (BP) values at onset of CNIE were compared with those at baseline using the Wilcoxon signed rank test. Landmark analysis was performed to evaluate the influence of all CNS complications on overall survival (OS), according to EBMT statistical guideline (41). To exclude the bias of early death before engraftment, 30 days after allo-HCT was set as landmark time with reference to previous reports (29, 41, 42); we compared patients divided by prior history of all CNS complications using this timepoint. The probability of OS was estimated by the Kaplan-Meier method and compared by the log-rank test. Non-relapse mortality (NRM) was calculated by Gray's method with disease relapse as a competing risk (41). We used univariable and multivariable Cox proportional hazards models with time-dependent covariates to find risk factors for all CNS complications, CNIE, and PALE and to reveal the influence of all CNS complications on OS (41). aGVHD was treated as a time-dependent covariate. We evaluated the proportional hazards assumption using Schoenfeld residuals. To evaluate the influence of missing information on CSF HHV-6 on outcome, sensitivity analysis was performed (43, 44).

All statistical tests were interpreted at a 5% significance level. All *P* values and 95% confidence intervals (CIs) were two-sided. Statistical analyses were performed using R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria) and

EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (45).

RESULTS

Patient Characteristics and All CNS Complications

A total of 485 patients between 16 and 69 years old (median, 46 years) were eligible for this study. Detailed patient characteristics at allo-HCT are shown in Table 1. The median follow-up time among the survivors was 1,836 days (range, 45–4,860 days) after allo-HCT. A total of 33 CNS complications (6.8% of the entire cohort) were identified: 11 CNIE (33%), 14 PALE (42%), three transverse myelitis (9.0%), two drug encephalopathy (6.0%), one aseptic meningitis (3.0%), one fungal brain abscess (3.0%), and one acute epidural hematoma (3.0%). The median onset day of all CNS complications was 30 days (range, 2–251 days). By landmark-time analysis, the prognosis of patients who developed any CNS complications within 30 days was significantly worse than those who did not (1-year OS, 37.5% vs. 67.2%, Log-rank $P < 0.001$). A multivariable time-dependent Cox model revealed that all CNS complications were an independent poor prognostic factor for OS (hazard ratio [HR]

2.60, 95% CI 1.72–3.94, $P < 0.001$), adjusted for age and DRI.

Risk Factors and Long-term Outcomes for PALE

Since the number of each PALE and CNIE events was not enough for employing a stable multivariable analysis within one model, we constructed several multivariable models to limit the degree of freedom of each statistical model from the viewpoint of stability (27, 46).

PALE included seven HHV6-negative CSF cases (two alive at last follow-up), five HHV6-positive CSF cases (one alive), and two unknown cases (one alive). All case presentations are described in Table 2 and Supplementary Table 1. The median onset day of PALE was 25.5 days (range, 14–122 days). In these 14 patients, in addition to foscarnet or ganciclovir, 11 received mPSL pulse therapy, two received moderate-dose mPSL therapy, and one did not receive steroid therapy. mPSL was administered by the judgment of the attending physicians, when clear CNS infections including bacteria, fungi, and tuberculosis were not found apart from HHV-6 detection. Among the 13 mPSL-treated patients, except for patient no. 3, six (46%) responded and three (23%) achieved complete remission (CR) at day 90 after mPSL administration (Supplementary Table 2). Out of five patients with CSF

HHV-6-negative PALE, three and one achieved CR and PR at day 90 after a high-dose mPSL therapy, respectively (Table 2). Concerning patient no. 3, the attending physician did not use steroids considering the possibility of HHV-6 encephalitis (CSF HHV-6 viral load, 9×10^3 copy/mL). In the multivariable Cox models, older age, HLA-mismatched URD, and grade II to IV aGVHD were significantly associated with increased risk of PALE (Table 3, Models 1–3). In addition, GVHD prophylaxis with CNI and MMF showed a significantly higher incidence of PALE than CNI and MTX (Table 3, Models 1c, 2b, and 3). The estimated 5-year NRM rate was 50% (95% CI, 21%–73%) for all patients with PALE (N = 14) (Figure 1A). The estimated 5-year OS rate was 19% (95% CI, 3.6%–44%) for all patients with PALE (Figure 1B).

In addition, considering the potential bias due to CSF HHV-6-unknown cases, although we performed sensitivity analysis by treating the unknown cases as non-PALE controls, we observed similar risk associations of the above-identified factors and PALE development (Supplementary Table 3) (44, 47). In the other sensitivity analysis treating CSF HHV-6-higher-level cases (≥50 percentile of viral load: 9×10^3 copy/mL) as control cases; we observed almost similar risk associations (Supplementary Table 3).

Risk Factors and Long-Term Outcomes for CNIE

CNIE cases included eight cyclosporin A-induced and three tacrolimus-induced cases, of which four (36%) patients were alive at the last follow-up. All case presentations are described in Supplementary Table 4. The median onset day of CNIE was 26 days (range, 2–251 days). In the multivariable Cox models, myelodysplastic syndrome (MDS) was significantly associated with increased risk of CNIE, compared with acute myeloid leukemia/acute lymphoblastic leukemia (Table 4, Models 1–3). In addition, HLA-mismatched URD was significantly associated with increased risk of CNIE, compared with HLA-matched related and unrelated donors (Table 4, Models 2 and 3). Furthermore, grade II to IV aGVHD, a post-transplant factor, showed a significantly higher incidence of CNIE (Table 4, Models 1 and 2). In addition, although each BP measure at baseline was not associated with elevated risk of CNIE, systolic BP, diastolic BP, pulse pressure, and mean arterial pressure median levels at CNIE onset were significantly higher than those at baseline in patients with CNIE (158 mmHg at onset, 108 mmHg at baseline, $P = 0.013$; 90 mmHg at onset, 66 mmHg at baseline, $P = 0.016$; 60 mmHg at onset, 44 mmHg at baseline, $P = 0.036$; and 113 mmHg at onset, 81 mmHg at baseline, $P < 0.01$, respectively). The estimated 5-year NRM rate was 63% (95% CI, 21%–83%) for all patients with

CNIE (N = 11) (Figure 1C). The estimated 5-year OS rate was 36% (95% CI, 11%–63%) for all patients with CNIE (Figure 1D).

DISCUSSION

In this study, CNS complications after allo-HCT were confirmed to be an independent risk factor for OS in agreement with previous reports (2, 4). In addition, we found that older age, HLA-mismatched URD, GVHD prophylaxis with CNI and MMF, and grade II to IV aGVHD were significantly associated with increased risk of PALE. Among patients with PALE and on high-dose mPSL therapy, 46% showed a response and 23% achieved complete remission at day 90 after initiation of mPSL therapy. Furthermore, we demonstrated that MDS, HLA-mismatched URD, and grade II to IV aGVHD were significantly associated with increased risk of CNIE after allo-HCT. Each BP component level at CNIE onset was significantly higher than that at baseline in patients with CNIE, as reported previously (48), whereas each BP component level at baseline was not significantly associated with the development of CNIE. Long-term NRM, that is, more than the median 5-year-follow-up, indicated poor prognosis of both PALE and CNIE.

It remains unclear how HHV-6 contributes to the development of PALE, what cut-off value of CSF HHV-6 viral load can discriminate HHV-6 reactivation from HHV-6 encephalitis, and what etiologies other than HHV-6 cause PALE. In this study, HLA-mismatched URD increased the risk of PALE. This supports the finding that MHC class I in limbic structures (14-16) may be targeted by alloimmune response. It is well known that activated T cells including $CD8^+$ T cells have a key role in the development of aGVHD (49). Experimental models suggested that $CD8^+$ T cells have the potential to recognize and attack MHC class 1-expressing neuronal cells (50, 51). Furthermore, in an MHC-disparate murine allo-HCT model, the hippocampus was one of the targeted lesions by donor T cells (18). In addition, in this study, as seen in reported cases of autoimmune limbic encephalitis, out of five patients with CSF HHV-6-negative PALE, three and one showed CR and PR responses to high-dose mPSL therapy, respectively (Table 2) (35, 52, 53). During the last follow-up, three out of five patients were deceased not due to NRM but relapse of primary disease. In CSF HHV-6 negative PALE cases, high-dose steroids may have the potential to improve or cure PALE. These observations suggest that alloimmune reaction derived from HLA mismatch could contribute to the development of PALE, especially in CSF HHV-6-negative or HHV-6-reactivated cases. However, the prognosis of entire PALE cases was very poor. Recent evidence suggests that in non-transplant patients with

autoimmune, especially autoantibodies-associated, limbic encephalitis, when first immunotherapies including steroids, intravenous immunoglobulin, and/or plasma exchange did not show clinical improvement, rituximab, cyclophosphamide, bortezomib, and/or tocilizumab could contribute to better outcome (34, 35, 54-56). Therefore, exploring novel treatment strategy including these for PALE is required. *In vitro* data showed that interferon-γ and tumor necrosis factor-α, both associated with aGVHD (49), upregulated MHC expression in neural stem/progenitor cells (57). Grade II to IV aGVHD might contribute to the development of PALE through MHC upregulation in limbic structures. To our knowledge, no study has reported on MMF-induced neurotoxicity. Ogata et al. reported that the group with CNI and MMF showed a clearly higher cumulative incidence of HHV-6 encephalitis than that with CNI and MTX (9). GVHD prophylaxis with CNI and MMF might contribute to the emergence of HHV-6 in the CSF. We were unable to find the reason why older age increased the risk of PALE. Further study is warranted to confirm these findings.

Although with little evidence, causes of PALE may possibly include EBV or autoantibodies apart from HHV-6 (58-60). Further mechanistic studies are needed to elucidate the etiology and pathophysiology of PALE development.

A study in pediatric recipients including approximately 40% of non-malignancies showed that CB transplantation increased the risk of PRES in the multivariable

analysis (7). Another study in children with hemoglobinopathies reported that sickle cell disease, post-allo-HCT hypertension, and grade II to IV aGVHD were associated with increased risk of PRES (6). Only one study in adults showed several associated factors including the polymorphisms in *CYP3A5* and *ABCB1* genes for the composite outcome consisting of CNI-induced peripheral neuropathy and CNIE (61). To our knowledge, no pretransplant risk factor analysis for CNIE alone has been reported in adults. Although the exact mechanism on CNIE has not been completely elucidated, in addition to the direct injuring effect of CNIs to oligodendrocytes and neurons (62), endothelial dysfunction by multiple CNI-mediated factors including direct injury by CNIs (63, 64), impaired nitric oxide and endothelin-1 homeostasis (65, 66), and decreased prostacyclin production (67, 68) appears to have a crucial role in the development of CNIE. Considering autoimmune disorders associated with PRES development (38), we can explain that alloimmune reactions during aGVHD may cause endothelial damage due to excessive cytokine release (24, 49). In addition, the finding that MDS was a risk factor of CNIE may be partly explained by the fact that a subset of MDS may be predisposed to vascular endothelial damage (e.g., vasculitis) (69, 70). However, we did not identify why HLA-mismatched URD might be associated with CNIE risk. Considering CB transplantation, predominantly comprised of HLA-mismatched donor-recipient pairs, reported as a risk factor of PRES (7),

further study is needed to examine the association of HLA mismatch on CNIE development for a more personalized allo-HCT management.

The interpretation of the results may be limited by the retrospective nature of this study, single-center setting, and small number of outcome events. However, all study participants had been treated homogeneously according to our institution's manual on allo-HCT procedure, leading to a reduced bias. In addition, we did not demonstrate the significance of CBT on the development of PALE as previously reported (11); however, this could be affected by the difference in the study population and/or an inadequate sample size. Further, larger sample size study is necessary to confirm this.

In conclusion, these results provide evidence that HLA-mismatched URD and aGVHD may independently contribute to the development of PALE possibly partly through HLA-mismatch-derived alloimmune responses. In addition, other than aGVHD, we identified MDS and HLA-mismatched URD as novel predictors of CNIE after allo-HCT. Future validation studies including focus on GVHD prophylaxis and donor source selection are warranted to improve the management and long-term prognosis of PALE and CNIE.

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Authors' Contributions

NT, HK, MH, and HN contributed to the concept and design of the study. HO, AH, and MNa contributed to the acquisition of the data. NT and HK analyzed the data, interpreted the results, and wrote the manuscript. HO, KY, YM, MK, TT, SK, SN, MNi, AH, MNa, YN, TN, MH, and HN interpreted the results and reviewed critically and revised the manuscript. All authors read and approved the final version.

Figure Legends

Figure 1. Cumulative incidence curves of non-relapse mortality (NRM) and relapse and overall survival curve in patients with PALE (n = 14) and CNIE (n = 11), and patients without CNSC (n = 452). (A, B) Patients with PALE. (C, D) Patients with CNIE. (E, F) Patients without CNSC. Estimated 5-year NRM and relapse rates were 29% (95% CI, 25%–34%) and 29% (95% CI, 25%–33%) for patients without CNSC (n = 452), respectively (Figure 1E). The estimated 5-year OS rate was 46% (95% CI, 41%–50%) for patients without CNSC (n = 452) (Figure 1F).

PALE, post-transplant acute limbic encephalitis; CNIE, calcineurin inhibitor-induced encephalopathy; CNSC, central nervous system complications.

Figure

Figure 1

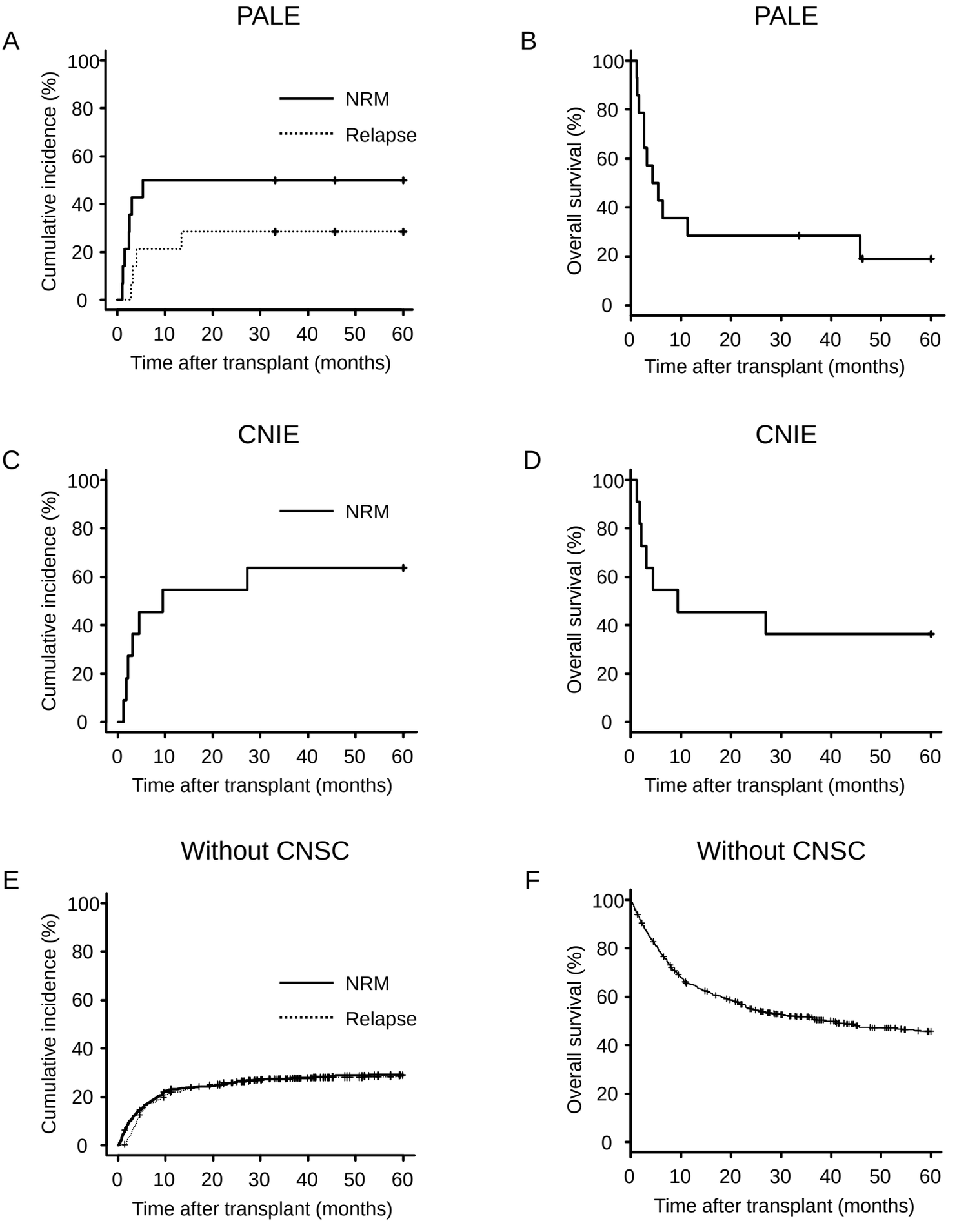

Table 1. Baseline characteristics of study patients who underwent allogeneic hematopoietic cell transplantation

Characteristics	Total	PALE (+)	CNIE (+)
Number of patients, n	485	14	11
Male, n (%)	274 (56.5)	11 (78.6)	6 (54.5)
Median age at transplantation (range), years	46 (16–69)	56.5 (32–66)	43 (18–55)
Primary diseases, n (%)			
Acute leukemia (AML/ALL)	292 (60.0)	8 (57.1)	3 (27.3)
Myelodysplastic syndrome	59 (12.1)	1 (7.1)	5 (45.5)
Malignant lymphoma	93 (19.1)	5 (35.7)	2 (18.2)
Others*	41 (8.5)	0 (0.0)	1 (9.1)
Disease Risk Index, n (%)			
Low	21 (4.3)	0 (0.0)	0 (0.0)
Intermediate	209 (43.0)	8 (57.1)	5 (45.5)
High	178 (36.7)	3 (21.4)	4 (36.4)
Very high	49 (10.1)	3 (21.4)	1 (9.1)
Unknown	28 (5.8)	0 (0.0)	1 (9.1)
Number of allo-HCT, n (%)			
First	394 (81.2)	13 (92.9)	9 (81.8)
Second	76 (15.7)	1 (7.1)	1 (9.1)
Third	15 (3.1)	0 (0.0)	1 (9.1)
Donor, n (%)			
HLA-matched or -one allele-mismatched sibling PB or BM and HLA-matched URD	191 (39.4)	2 (14.3)	0 (0.0)
HLA-mismatched URD	36 (7.4)	3 (21.4)	2 (18.2)
Umbilical cord blood	110 (22.7)	4 (28.6)	5 (45.5)
Haplo-identical PB	118 (24.3)	5 (35.7)	2 (18.2)
Allele unknown URD	30 (6.2)	0 (0.0)	2 (18.2)
Conditioning regimen, n (%)			
Total-body irradiation-based MAC	113 (23.3)	0 (0.0)	4 (36.4)
Busulfan, melphalan, or thiotepa-based MAC	177 (36.5)	5 (35.7)	4 (36.4)
Reduced-intensity conditioning	195 (40.2)	9 (64.3)	3 (27.3)

GVHD prophylaxis			
CNI with MTX	261 (53.8)	2 (14.3)	9 (81.8)
CNI with MMF	68 (14.0)	4 (28.6)	0 (0.0)
Others†	156 (32.2)	8 (57.1)	2 (18.2)
Blood pressure components before allo-HCT, mmHg (range)			
Systolic blood pressure	112 (80–164)	115 (84–156)	108 (98–154)
Diastolic blood pressure	67 (40–102)	70 (46–84)	66 (54–76)
Pulse pressure	45 (18–93)	45 (30–76)	44 (26–82)
Mean arterial pressure	82 (59–119)	86 (59–105)	81 (72–99)
Acute GVHD prior to diagnosis of CNSC			
Grade II to IV, n (%)	245 (50.5)	9 (64.3)	9 (81.8)

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; BM, bone marrow; CNI, calcineurin inhibitor; CNIE, calcineurin inhibitor-induced encephalopathy; CNSC, central nervous system complications; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; PALE, post-transplant acute limbic encephalitis; PB, peripheral blood; URD, unrelated PB or BM donor.

* Others included adult T-cell leukemia/lymphoma, chronic myelogenous leukemia, aplastic anemia, chronic active Epstein-Barr virus infection, myelofibrosis, chronic neutrophilic leukemia.

† Others included calcineurin inhibitor alone and post-transplantation cyclophosphamide.

Table 2. Patients' characteristics at onset and outcomes in patients with post-transplant acute limbic encephalitis (PALE) (N = 14)

Pt no.	Age (y)/ sex	Disease	Donor	Conditioning regimen	GVHD prophyla-xis	LE onset (days)	Symptoms	aGVHD grade (days, organ) prior to PALE onset	HHV-6 DNA in CSF/PB (copy/mL)	Antiviral therapy	mPSL pulse therapy	Day 90 treatment response*	Outcome/ follow-up (cause of death)
1	59/M	AML	Haplo	RIC	CNI/MMF /PTCY	94	Depressed level of conscious-ness/ amnesia/ confusion	None	$7\times10^4/2\times10^2$	FCN+ GCV	Yes	PD	Death, 130 d (relapse)
2	59/M	AML	Haplo	RIC	CNI/MMF /PTCY	22	Confusion/ amnesia	G3 (11, skin 2/gut 3)	3×10^4/NA	FCN+ GCV	Yes	PR	Alive, 2.8 y
3	45/M	AML	HLA-mis matched URD	Busulfan-based MAC	CNI/MMF	26	Depressed level of conscious-ness	G4 (14, skin 3/ gut 3/liver 4)	9×10^3/NA	FCN	None	NE	Death, 77 d (acute GVHD)
4	60/F	AML	uCB	RIC	CNI/MMF	24	Depressed level of conscious-ness/ amnesia	G4 (9, gut 3/liver4)	2×10^3/NA	FCN+ GCV	Yes	PD	Death, 48 d (acute GVHD)

5	57/M	ATL	HLA-mismatched URD	Busulfan-based MAC	CNI alone	25	Amnesia/ depressed level of conscious-ness	G2 (12, skin 3)	9×10^2/NA	GCV	Yes†	PR	Death, 3.8 y (relapse)
6	32/F	ALL	Haplo	RIC	CNI/MMF /PTCY	34	Amnesia/ tremors	G3 (13, skin 2/gut 4)	Neg/Neg	FCN	Yes	PR	Death, 191 d (relapse)
7	49/M	MDS	rPB	Busulfan-based MAC	CNI/MTX	23	Amnesia	None	Neg/Neg	FCN	Yes	CR	Alive, 3.8 y
8	34/M	AML	HLA-mismatched URD	Busulfan-based MAC	CNI/MTX	30	Amnesia	G2 (13, skin 3)	Neg/NA	GCV	Yes	CR	Alive, 10.6 y
9	56/M	AML	Haplo	Busulfan-based MAC	CNI/MMF /PTCY	34	Amnesia/ confusion	None	Neg/NA	GCV	Yes	CR	Death, 342 d (relapse)
10	55/M	ATL	uCB	RIC	CNI/MMF	21	Amnesia/ confusion/ depressed level of conscious-ness	G3 (13, skin 3/ gut 3/liver 1)	Neg/NA	FCN	Yes	PD	Death, 94 d (relapse)

11	66/M	ML	uCB	Melphalan-based MAC	CNI/MMF	27	Depressed level of conscious-ness/ amnesia	G3 (2, gut 3)	NA/Neg	FCN	Yes	PD	Death, 78 d (hepatic SOS)
12	61/F	ML	rPB	RIC	CNI alone	122	Depressed level of conscious-ness	None	NA/NA	GCV	Yes	PD	Death, 163 d (relapse)
13	61/M	ATL	uCB	RIC	CNI alone	17	Depressed level of conscious-ness	None	NA/NA	None	Yes†	PD	Death, 36 d (relapse)
14	50/M	AML	Haplo	RIC	CNI/MMF /PTCY	14	Depressed level of conscious-ness	G4 (4, skin 1/gut3/ liver 4)	NA/NA	GCV	Yes	PD	Death, 34 d (acute GVHD)

Abbreviations: CNI, calcineurin inhibitor; CR, complete remission; FCN, foscarnet; GCV, ganciclovir; GVHD, graft-versus-host disease; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; NE, not evaluable; Neg, negative; PB, peripheral blood; PTCY, post-transplant cyclophosphamide; RIC, reduced-intensity conditioning; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy; uCB, umbilical cord blood; URD, unrelated PB or BM donor.

* Treatment response to mPSL was judged at day 90 after the start of mPSL therapy except for Pt. No.3 not receiving mPSL.

† Two received moderate-dose mPSL (1 mg/kg/body). The others received mPSL pulse therapy at 1 g dosage for three consecutive days.

Table 3. Risk factors for the development of post-transplant acute limbic encephalitis (PALE) by univariable and multivariable Cox models (n = 485)

Factors	Hazard ratio (95% CI)	*P* value
Univariable analysis		
Age at transplantation	1.70 (1.07–2.73)	0.026
Gender		
Male	1.00 (reference)	
Female	0.47 (0.19–1.16)	0.10
Primary diseases		
Acute leukemia (AML/ALL)	1.00 (reference)	
Myelodysplastic syndrome	0.60 (0.08–4.81)	0.63
Malignant lymphoma	2.00 (0.65–6.09)	0.23
Donor		
HLA-matched or -one allele-mismatched sibling PB or BM and HLA-matched URD	1.00 (reference)	
HLA-mismatched URD	8.16 (1.36–48.8)	0.022
Umbilical cord blood	3.72 (0.68–20.3)	0.13
Haplo-identical PB	4.21 (0.82–21.7)	0.086
Conditioning regimen		
Reduced-intensity conditioning	1.00 (reference)	
Myeloablative conditioning	0.34 (0.12–1.00)	0.049
GVHD prophylaxis		
CNI with MTX	1.00 (reference)	
CNI with MMF	8.31 (1.52–45.4)	0.015
Acute GVHD prior to development of PALE		
No	1.00 (reference)	
Grade II to IV	6.19 (1.89–20.3)	0.003
Multivariable analysis		
Model 1a		
Age at transplantation	1.69 (1.04–2.75)	0.034
Donor		
HLA-matched or -one allele-mismatched sibling PB or BM and HLA-matched URD	1.00 (reference)	
HLA-mismatched URD	7.52 (1.26–45.0)	0.027
Umbilical cord blood	3.51 (0.64–19.2)	0.15
Haplo-identical PB	4.16 (0.81–21.5)	0.09

Model 1b		
Age at transplantation	1.66 (1.04–2.66)	0.034
Conditioning regimen		
Reduced-intensity conditioning	1.00 (reference)	
Myeloablative conditioning	0.37 (0.13–1.08)	0.068
Model 1c		
Age at transplantation	1.59 (0.98–2.57)	0.059
GVHD prophylaxis		
CNI with MTX	1.00 (reference)	
CNI with MMF	6.87 (1.25–37.7)	0.027
Model 1d		
Age at transplantation	1.71 (1.07–2.75)	0.025
Acute GVHD prior to development of PALE		
No	1.00 (reference)	
Grade II to IV	6.21 (1.90–20.2)	0.003
Model 2a		
Donor		
HLA-matched or -one allele-mismatched sibling PB or BM and HLA-matched URD	1.00 (reference)	
HLA-mismatched URD	7.99 (1.33–47.8)	0.023
Umbilical cord blood	3.49 (0.64–19.1)	0.15
Haplo-identical PB	2.16 (0.36–12.8)	0.40
Conditioning regimen		
Reduced-intensity conditioning	1.00 (reference)	
Myeloablative conditioning	0.34 (0.10–1.16)	0.084
Model 2b		
Donor		
HLA-matched or -one allele-mismatched sibling PB or BM and HLA-matched URD	1.00 (reference)	
HLA-mismatched URD	16.7 (2.56–109)	0.003
Umbilical cord blood	3.08 (0.52–18.1)	0.21
Haplo-identical PB	0.51 (0.005–53.3)	0.78
GVHD prophylaxis		
CNI with MTX	1.00 (reference)	
CNI with MMF	9.81 (1.62–59.4)	0.013

Model 2c		
Donor		
HLA-matched or -one allele-mismatched sibling PB or BM and HLA-matched URD	1.00 (reference)	
HLA-mismatched URD	5.74 (0.95–34.8)	0.058
Umbilical cord blood	3.30 (0.60–18.1)	0.17
Haplo-identical PB	3.61 (0.70–18.7)	0.13
Acute GVHD prior to development of PALE		
No	1.00 (reference)	
Grade II to IV	5.08 (1.54–16.7)	0.008
Model 3		
Conditioning regimen		
Reduced-intensity conditioning	1.00 (reference)	
Myeloablative conditioning	0.58 (0.18–1.95)	0.38
GVHD prophylaxis		
CNI with MTX	1.00 (reference)	
CNI with MMF	6.43 (1.11–37.3)	0.038
Acute GVHD prior to development of PALE		
No	1.00 (reference)	
Grade II to IV	5.90 (1.81–19.2)	0.003

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; BM, bone marrow; CNI, calcineurin inhibitor; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; PALE, Post-transplant acute limbic encephalitis; PB, peripheral blood; URD, unrelated PB or BM donor.

Table 4. Risk factors for the development of calcineurin inhibitor-induced encephalopathy (CNIE) after allogeneic hematopoietic cell transplantation by univariable and multivariable Cox models (n = 485)

Factors	Hazard ratio (95% CI)	*P* value
Univariable analysis		
Age at transplantation	0.78 (0.51–1.21)	0.27
Gender		
Male	1.00 (reference)	
Female	1.03 (0.44–2.37)	0.95
Primary diseases		
Acute leukemia (AML/ALL)	1.00 (reference)	
Myelodysplastic syndrome	8.22 (1.96–34.4)	0.04
Malignant lymphoma	2.24 (0.37–13.4)	0.47
Donor		
HLA-matched or -one allele-mismatched sibling PB or BM and HLA-matched URD	1.00 (reference)	
HLA-mismatched URD	14.2 (2.75–73.1)	0.002
Umbilical cord blood	1.89 (0.27–13.4)	0.53
Haplo-identical PB	1.76 (0.25–12.5)	0.57
Conditioning regimen		
Total-body irradiation-based MAC	1.00 (reference)	
Busulfan, melphalan, or thiotepa-based MAC	0.66 (0.17–2.65)	0.56
Reduced-intensity conditioning	0.49 (0.11–2.17)	0.34
Blood pressure components before allo-HCT, mmHg (per standard deviation) (range)		
Systolic blood pressure	1.03 (0.57–1.88)	0.91
Diastolic blood pressure	0.81 (0.44–1.51)	0.51
Pulse pressure	1.26 (0.72–2.19)	0.42
Mean arterial pressure	0.89 (0.48–1.64)	0.70
Acute GVHD prior to development of CNIE		
No	1.00 (reference)	
Grade II to IV	35.4 (4.00–313)	0.001

Multivariable analysis		
Model 1		
Primary diseases		
Acute leukemia	1.00 (reference)	
Myelodysplastic syndrome	9.00 (2.15–37.7)	0.003
Malignant lymphoma	1.92 (0.32–11.5)	0.48
Acute GVHD prior to development of CNIE	37.7 (4.07–348)	0.001
Model 2		
Donor		
HLA-matched or -one allele-mismatched sibling PB or BM and HLA-matched URD	1.00 (reference)	
HLA-mismatched URD	9.13 (1.76–47.5)	0.004
Umbilical cord blood	1.46 (0.20–10.4)	0.71
Haplo-identical PB	1.25 (0.17–9.28)	0.83
Acute GVHD prior to development of CNIE	33.5 (3.03–370)	0.004
Model 3		
Primary diseases		
Acute leukemia/malignant lymphoma	1.00 (reference)	
Myelodysplastic syndrome	6.49 (1.88–22.5)	0.003
Donor		
HLA-matched or -one allele-mismatched sibling PB or BM and HLA-matched URD	1.00 (reference)	
HLA-mismatched URD	15.7 (2.99–82.4)	0.001
Umbilical cord blood/haplo-identical PB	1.89 (0.34–10.3)	0.47

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; BM, bone marrow; CNI, calcineurin inhibitor; CNIE, calcineurin inhibitor-induced encephalopathy; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; PB, peripheral blood; URD, unrelated PB or BM donor.

References

1. Schmidt-Hieber M, Engelhard D, Ullmann A, Ljungman P, Maertens J, Martino R, et al. Central nervous system disorders after hematopoietic stem cell transplantation: a prospective study of the Infectious Diseases Working Party of EBMT. J Neurol. 2020;267(2):430-9.
2. Sakellari I, Gavriilaki E, Papagiannopoulos S, Gavriilaki M, Batsis I, Mallouri D, et al. Neurological adverse events post allogeneic hematopoietic cell transplantation: major determinants of morbidity and mortality. J Neurol. 2019;266(8):1960-72.
3. Mannina D, Berneking L, Both A, Timm W, Urbanowicz T, Wolschke C, et al. Major central nervous system complications after allogeneic stem cell transplantation: A large retrospective study on 888 consecutive adult patients. Eur J Haematol. 2020;105(6):722-30.
4. Dowling MR, Li S, Dey BR, McAfee SL, Hock HR, Spitzer TR, et al. Neurologic complications after allogeneic hematopoietic stem cell transplantation: risk factors and impact. Bone Marrow Transplant. 2018;53(2):199-206.
5. Lin T-A, Gau J-P, Liu Y-C, Ko P-S, Wang H-Y, Chien S-H, et al. Cerebrovascular disease after allogeneic hematopoietic stem cell transplantation: incidence, risk, and clinical outcome. International Journal of Hematology. 2019;109(5):584-92.
6. Gaziev J, Marziali S, Paciaroni K, Isgrò A, Di Giuliano F, Rossi G, et al. Posterior Reversible Encephalopathy Syndrome after Hematopoietic Cell Transplantation in Children with Hemoglobinopathies. Biol Blood Marrow Transplant. 2017;23(9):1531-40.
7. Zama D, Masetti R, Cordelli DM, Vendemini F, Giordano L, Milito G, et al. Risk factor analysis of posterior reversible encephalopathy syndrome after allogeneic hematopoietic SCT in children. Bone Marrow Transplant. 2014;49(12):1538-40.
8. Zhang XH, Zhang JM, Han W, Chen H, Chen YH, Wang FR, et al. Viral encephalitis after haplo-identical hematopoietic stem cell transplantation: Causative viral spectrum, characteristics, and risk factors. Eur J Haematol. 2017;98(5):450-8.
9. Ogata M, Oshima K, Ikebe T, Takano K, Kanamori H, Kondo T, et al. Clinical characteristics and outcome of human herpesvirus-6 encephalitis after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2017;52(11):1563-70.
10. Seeley WW, Marty FM, Holmes TM, Upchurch K, Soiffer RJ, Antin JH, et al. Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. Neurology. 2007;69(2):156-65.
11. Hill JA, Koo S, Guzman Suarez BB, Ho VT, Cutler C, Koreth J, et al. Cord-blood hematopoietic stem cell transplant confers an increased risk for human herpesvirus-6-associated acute limbic encephalitis: a cohort analysis. Biol Blood Marrow Transplant. 2012;18(11):1638-48.
12. Hill JA. Human herpesvirus 6 in transplant recipients: an update on diagnostic and treatment strategies. Curr Opin Infect Dis. 2019;32(6):584-90.

13. Engelhardt B, Vajkoczy P, Weller RO. The movers and shapers in immune privilege of the CNS. Nat Immunol. 2017;18(2):123-31.
14. Goddard CA, Butts DA, Shatz CJ. Regulation of CNS synapses by neuronal MHC class I. Proc Natl Acad Sci U S A. 2007;104(16):6828-33.
15. Cebrián C, Zucca FA, Mauri P, Steinbeck JA, Studer L, Scherzer CR, et al. MHC-I expression renders catecholaminergic neurons susceptible to T-cell-mediated degeneration. Nat Commun. 2014;5:3633.
16. Tooyama I, Kimura H, Akiyama H, McGeer PL. Reactive microglia express class I and class II major histocompatibility complex antigens in Alzheimer's disease. Brain Res. 1990;523(2):273-80.
17. Kaliyaperumal S, Watkins B, Sharma P, Furlan S, Ramakrishnan S, Giver C, et al. CD8-predominant T-cell CNS infiltration accompanies GVHD in primates and is improved with immunoprophylaxis. Blood. 2014;123(12):1967-9.
18. Hartrampf S, Dudakov JA, Johnson LK, Smith OM, Tsai J, Singer NV, et al. The central nervous system is a target of acute graft versus host disease in mice. Blood. 2013;121(10):1906-10.
19. Ruggiu M, Cuccuini W, Mokhtari K, Meignin V, Peffault de Latour R, Robin M, et al. Case report. Medicine. 2017;96(42):e8303.
20. Saad AG, Alyea EP, 3rd, Wen PY, Degirolami U, Kesari S. Graft-versus-host disease of the CNS after allogeneic bone marrow transplantation. J Clin Oncol. 2009;27(30):e147-9.
21. Khosla J, Yeh AC, Spitzer TR, Dey BR. Hematopoietic stem cell transplant-associated thrombotic microangiopathy: current paradigm and novel therapies. Bone Marrow Transplant. 2018;53(2):129-37.
22. Straathof K, Anoop P, Allwood Z, Silva J, Nikolajeva O, Chiesa R, et al. Long-term outcome following cyclosporine-related neurotoxicity in paediatric allogeneic haematopoietic stem cell transplantation. Bone Marrow Transplant. 2017;52(1):159-62.
23. Maffini E, Festuccia M, Brunello L, Boccadoro M, Giaccone L, Bruno B. Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2017;23(3):388-97.
24. Laskin BL, Goebel J, Davies SM, Jodele S. Small vessels, big trouble in the kidneys and beyond: hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Blood. 2011;118(6):1452-62.
25. Ethical Guidelines for Medical and Health Research Involving Human Subjects [Available from: https://www.lifescience.mext.go.jp/files/pdf/n2181_01.pdf.]
26. Okamura H, Nakamae M, Koh S, Nanno S, Nakashima Y, Koh H, et al. Interactive web application for plotting personalized prognosis prediction curves in allogeneic hematopoietic cell transplantation using machine learning. Transplantation. 2020, in press.
27. Ido K, Koh H, Hirose A, Okamura H, Koh S, Nanno S, et al. Donor KIR2DS1-Mediated Decreased Relapse and Improved Survival Depending on Remission Status at HLA-Haploidentical Transplantation with Post-Transplantation Cyclophosphamide. Biol Blood Marrow Transplant.

2020;26(4):723-33.

28. Nishimoto M, Koh H, Tokuwame A, Makuuchi Y, Kuno M, Takakuwa T, et al. Drug interactions and safety profiles with concomitant use of caspofungin and calcineurin inhibitors in allogeneic haematopoietic cell transplantation. Br J Clin Pharmacol. 2017;83(9):2000-7.
29. Nanno S, Koh H, Nakashima Y, Katayama T, Okamura H, Koh S, et al. Diagnostic value of serum ferritin and the risk factors and cytokine profiles of hemophagocytic syndrome following allogeneic hematopoietic cell transplantation. Leuk Lymphoma. 2017;58(7):1664-72.
30. Giralt S, Ballen K, Rizzo D, Bacigalupo A, Horowitz M, Pasquini M, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2009;15(3):367-9.
31. Armand P, Kim HT, Logan BR, Wang Z, Alyea EP, Kalaycio ME, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood. 2014;123(23):3664-71.
32. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-8.
33. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. The Lancet Neurology. 2016;15(4):391-404.
34. Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 2014;83(2):142-50.
35. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12(2):157-65.
36. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19(5):604-7.
37. Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Accessed on January, 2021.]
38. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. J Neurol. 2017;264(8):1608-16.
39. Ruutu T, Barosi G, Benjamin RJ, Clark RE, George JN, Gratwohl A, et al. Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an International Working Group. Haematologica. 2007;92(1):95-100.
40. Ho VT, Cutler C, Carter S, Martin P, Adams R, Horowitz M, et al. Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2005;11(8):571-5.
41. Iacobelli S, Committee ES. Suggestions on the use of statistical methodologies in studies of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2013;48 Suppl 1:S1-37.

42. Storer BE. Statistical considerations in studies of late effects in HCT. Biol Blood Marrow Transplant. 2009;15(1 Suppl):25-8.
43. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.
44. Greenland S. Basic methods for sensitivity analysis of biases. Int J Epidemiol. 1996;25(6):1107-16.
45. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452-8.
46. Katz MH. Multivariable analysis: A practical guide for clinicians and public health researchers. Cambridge, UK: Cambridge University Press; 2011, 3rd edn. p.93-117.
47. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bmj. 2007;335(7624):806-8.
48. Hammerstrom AE, Howell J, Gulbis A, Rondon G, Champlin RE, Popat U. Tacrolimus-associated posterior reversible encephalopathy syndrome in hematopoietic allogeneic stem cell transplantation. Am J Hematol. 2013;88(4):301-5.
49. Zeiser R, Blazar BR. Acute Graft-versus-Host Disease - Biologic Process, Prevention, and Therapy. N Engl J Med. 2017;377(22):2167-79.
50. Ehling P, Melzer N, Budde T, Meuth SG. CD8(+) T Cell-Mediated Neuronal Dysfunction and Degeneration in Limbic Encephalitis. Front Neurol. 2015;6:163.
51. Scheikl T, Pignolet B, Dalard C, Desbois S, Raison D, Yamazaki M, et al. Cutting edge: neuronal recognition by CD8 T cells elicits central diabetes insipidus. J Immunol. 2012;188(10):4731-5.
52. Yeshokumar AK, Gordon-Lipkin E, Arenivas A, Cohen J, Venkatesan A, Saylor D, et al. Neurobehavioral outcomes in autoimmune encephalitis. J Neuroimmunol. 2017;312:8-14.
53. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. Ann N Y Acad Sci. 2015;1338(1):94-114.
54. Suppiej A, Nosadini M, Zuliani L, Pelizza MF, Toldo I, Bertossi C, et al. Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review. Brain Dev. 2016;38(7):613-22.
55. Scheibe F, Prüss H, Mengel AM, Kohler S, Nümann A, Köhnlein M, et al. Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis. Neurology. 2017;88(4):366-70.
56. Lee WJ, Lee ST, Moon J, Sunwoo JS, Byun JI, Lim JA, et al. Tocilizumab in Autoimmune Encephalitis Refractory to Rituximab: An Institutional Cohort Study. Neurotherapeutics. 2016;13(4):824-32.
57. Johansson S, Price J, Modo M. Effect of inflammatory cytokines on major histocompatibility complex expression and differentiation of human neural stem/progenitor cells. Stem Cells. 2008;26(9):2444-54.
58. Kremer S, Matern JF, Bilger K, Lioure B, Fornecker Y, Stoll-Keller F, et al. EBV limbic encephalitis after allogenic hematopoietic stem cell transplantation. J Neuroradiol. 2010;37(3):189-91.

59. Rathore GS, Leung KS, Muscal E. Autoimmune Encephalitis Following Bone Marrow Transplantation. Pediatr Neurol. 2015;53(3):253-6.
60. Toda J, Maeda T, Akuta K, Kusakabe S, Ueda T, Fujita J, et al. Limbic encephalitis with antibodies to N-methyl-D-aspartate (NMDA)-type glutamate receptor after allogeneic transplantation. Int J Hematol. 2020;112(2):254-7.
61. Yanagimachi M, Naruto T, Tanoshima R, Kato H, Yokosuka T, Kajiwara R, et al. Influence of CYP3A5 and ABCB1 gene polymorphisms on calcineurin inhibitor-related neurotoxicity after hematopoietic stem cell transplantation. Clin Transplant. 2010;24(6):855-61.
62. McDonald JW, Goldberg MP, Gwag BJ, Chi SI, Choi DW. Cyclosporine induces neuronal apoptosis and selective oligodendrocyte death in cortical cultures. Ann Neurol. 1996;40(5):750-8.
63. Kochi S, Takanaga H, Matsuo H, Ohtani H, Naito M, Tsuruo T, et al. Induction of apoptosis in mouse brain capillary endothelial cells by cyclosporin A and tacrolimus. Life Sci. 2000;66(23):2255-60.
64. Zoja C, Furci L, Ghilardi F, Zilio P, Benigni A, Remuzzi G. Cyclosporin-induced endothelial cell injury. Lab Invest. 1986;55(4):455-62.
65. Ramzy D, Wallen J, Badiwala MV, Tumiati LC, Tepperman E, Ross HJ, et al. Endothelin-1 antagonism and nitric oxide augmentation prevents cyclosporine-induced vasomotor impairment. J Heart Lung Transplant. 2011;30(1):77-85.
66. Ramzy D, Rao V, Tumiati LC, Xu N, Miriuka S, Delgado D, et al. Role of endothelin-1 and nitric oxide bioavailability in transplant-related vascular injury: comparative effects of rapamycin and cyclosporine. Circulation. 2006;114(1 Suppl):I214-9.
67. Brown Z, Neild GH, Lewis GP. Inhibition of prostacyclin formation by cyclosporin is not due to reduced availability of arachidonic acid in membrane phospholipids of cultured human endothelial cells. Biochem Pharmacol. 1990;39(6):1136-8.
68. Brown Z, Neild GH. Cyclosporine inhibits prostacyclin production by cultured human endothelial cells. Transplant Proc. 1987;19(1 Pt 2):1178-80.
69. Wang C, Yang Y, Gao S, Chen J, Yu J, Zhang H, et al. Immune dysregulation in myelodysplastic syndrome: Clinical features, pathogenesis and therapeutic strategies. Crit Rev Oncol Hematol. 2018;122:123-32.
70. Grignano E, Jachiet V, Fenaux P, Ades L, Fain O, Mekinian A. Autoimmune manifestations associated with myelodysplastic syndromes. Ann Hematol. 2018;97(11):2015-23.