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Incidence, Risk Factors, and Outcome of Immune-Mediated Neuropathies (IMNs) following Haploidentical Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Immune-mediated neuropathies (IMNs) following hematopoietic stem cell transplantation have been described recently, which, excluding Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, may present with atypical patterns. This retrospective, nested, case-control study reviewed data from 3858 patients who received haploidentical hematopoietic stem cell transplantation (haplo-HSCT) during the past 10 years at a single center, and 40 patients (1.04%) with IMN following haplo-HSCT were identified. Chronic graft-versus-host disease (cGVHD) ($P = .043$) and cytomegalovirus (CMV) viremia ($P = .035$) were recognized as independent risk factors for the development of IMN after haplo-HSCT. There were no significant differences in overall survival ($P = .619$), disease-free survival ($P = .609$), nonrelapse mortality ($P = .87$), or the incidence of relapse ($P = .583$) between patients with and without IMN after haplo-HSCT. However, patients with post-transplant IMN were at higher risk of developing cGVHD ($P = .012$) than patients who did not develop IMN. Twenty-four of the 40 patients with IMN (60%) attained neurologic improvement after treatments including vitamins B_1 and B_{12} and/or immunomodulatory agents. However, 19 (47.5%) patients still had persistent motor/sensory deficits despite receiving timely treatment. More studies are needed to help develop standardized diagnostic and therapeutic strategies for patients with post-transplant IMN.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment option for a variety of hematologic malignancies and nonmalignant disorders. In addition, during the past 2 decades, haploidentical hematopoietic stem cell transplantation (haplo-HSCT) has emerged as another viable source of stem cells for patients who fail to identify an HLA-identical donor, as a result of enhanced graft-versus-host disease (GVHD) prophylaxis, novel conditioning regimens, new strategies for relapse prophylaxis, and so on [1,2]. Unfortunately, the wide use of haplo-HSCT has given rise to an increasing number of complications following this procedure. Neurologic complications (NCs), which occur in 8.9% to 65% of patients and result in a 4.7% to 50% mortality rate, are one of the significant causes of transplant-related morbidity and mortality [3–10].

Of the NCs documented, the central nervous system (CNS) is much more frequently involved compared with the peripheral nervous system [3,4,9]. The toxicity of the drugs used for conditioning, GVHD prophylaxis, and the treatment of infections, opportunistic infections, thrombocytopenia, or disease relapse is a cause of CNS complications after HSCT [4,5,8]. Our previous studies have characterized various post-transplant CNS complications, including viral encephalitis, intracranial hemorrhage, epileptic seizures, and inflammatory demyelinating diseases [11–15].

Post-transplant peripheral neuropathies are relatively rare, occurring in only 0.7% to 6.1% of recipients [3,4,7,9]. Although

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diseases can arise from treatment toxicity, malignancy relapses, tumor infiltration, and direct infection, a small subset of patients may develop neuropathies despite experiencing none of the abovementioned causes [16–18]. The etiology of these diseases, which are known as immune-mediated neuropathies (IMNs), are believed to be secondary to GVHD, de novo autoimmune disease, or dysimmune reactions caused by viral infection [16,19]. Traditionally, post-transplant IMNs are classified by their courses as Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP), both of which can cause life-threatening motor deficits and have a significant impact on the quality of life of patients [20,21]. Recently, there have been new insights into IMN; diseases such as radiculoplexus neuropathies and multiple mononeuropathies were added to the list of previous classifications of IMN [17]. Indeed, peripheral neuropathies following allo-HSCT often have atypical clinical manifestations and fail to meet the strict diagnostic criteria of GBS or CIDP [17,21].

However, prior case reports or case series were inconclusive regarding the etiology, risk factors, and outcomes of IMN following allo-HSCT. Reports on IMN were especially inconclusive for haplo-HSCT because of the small sample size, although some speculative mechanisms already have been proposed. The evidence for atypical IMN (IMNs that fail to meet the diagnostic criteria of GBS or CIDP) is even more limited because most of the studies have focused on GBS or CIDP. In addition, to our knowledge, no analytical study has been conducted to characterize post-transplant IMN to date. The purpose of our study was to investigate the incidence, clinical features, risk factors, and outcomes of IMN following haplo-HSCT.

PATIENTS AND METHODS

Patients

We performed a nested, case-control study based on an electronic database of 3858 patients who received haplo-HSCT at the Peking University People's Hospital between January 2008 and June 2018. All of the patients received both bone marrow and peripheral blood stem cells from HLA-mismatched related donors according to our previously described protocols [22–25]. In addition, all patients received the outpatient follow-up after discharge at the same institute. The patients who developed IMN after haplo-HSCT were included in the case group. We referred to the *International Classification of Diseases, 10th Revision* code and searched for haplo-HSCT patients who had additional diagnoses, including "nerve root and plexus disorders (G54)," "mononeuropathies of upper limb (G56)," "mononeuropathies of lower limb (G57)," "other mononeuropathies (G58)," "inflammatory polyneuropathy (G61)," or "other polyneuropathy (G62)." The search initially yielded 69 patients. Subsequently, chart reviews were performed to determine the clinical manifestations, laboratory findings (including cerebrospinal fluid [CSF]), electrodiagnostic studies such as nerve conduction studies and needle electromyography, radiologic findings, applied treatment, and outcome for each patient. Finally, 40 patients were identified with IMN following haplo-HSCT and were included in the case group (Figure 1). Individual matching was then performed by randomly selecting 3 controls from the same cohort for each identified IMN patient with the following matching criteria: time of haplo-HSCT (±90 days), sex, and follow-up time (±180 days). The study was approved by the ethics committee of Peking University People's Hospital and was in accordance with the Declaration of Helsinki.

Definition/Diagnosis of IMN

IMNs consist of a heterogeneous spectrum of peripheral nerve disorders, which are characterized by cellular infiltration, myelin loss, and/or axonal degeneration in the affected part of the nerve [26–28]. Major types of IMN include GBS, CIDP, multifocal motor neuropathy, nonsystemic vasculitic neuropathies, polyneuropathy associated with monoclonal gammopathy, and so on [26–30]. In addition to these classifications, IMNs also include brachial or lumbosacral plexopathies, multiple mononeuropathies, polyradiculopathies, or other conditions that have no alternative etiologies [16–18,21,31].

The diagnosis of IMN was directly assigned to patients with GBS and CIDP. In addition, the diagnosis of IMN was assigned to the rest of the identified patients who met the following criteria after haplo-HSCT: (1) new onset of weakness or sensory symptoms [17,31], (2) no temporal association between the neuropathy and the use of neurotoxic drugs, (3) no sign of physical compression or neoplastic infiltration of the involved peripheral nerve

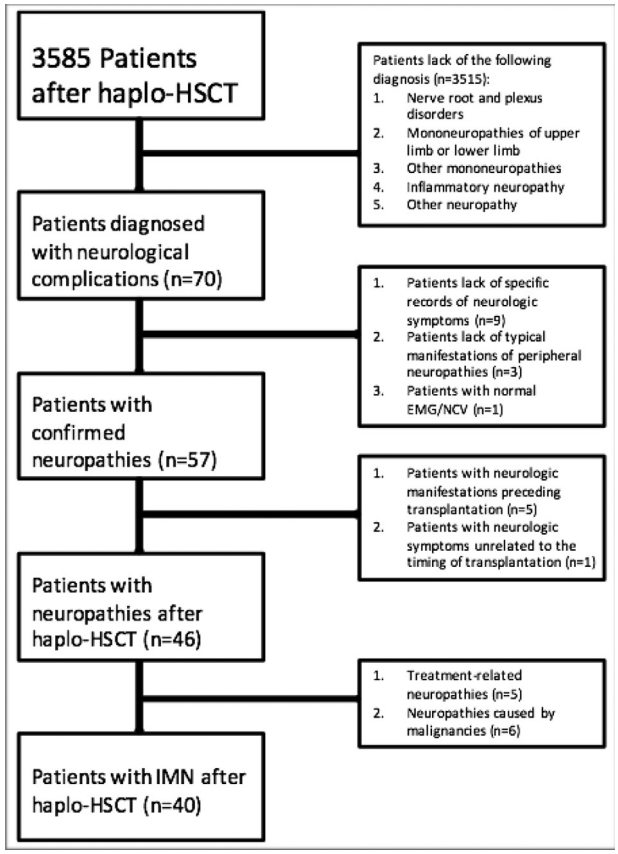

Figure 1. Flowchart of patients included in the present analysis.

[16–18,31–33], (4) no sign of infectious neuropathy or other alternative suspected etiologies for the peripheral neuropathy [16–18,31], and (5) electrodiagnostic studies showing peripheral neuropathies or CSF examination showing elevated protein with normal cells that could further confirm the diagnosis of IMN, if available [17,31,34]. Patients who did not meet these criteria, including those with peripheral neuropathy not related to the timing of haplo-HSCT or those with IMN before haplo-HSCT, were excluded from the study [17,31]. Each patient in the study was evaluated by hematologists and neurologists based on the patient's clinical manifestations, laboratory findings, electrodiagnostic studies, and radiologic findings. The final diagnosis was determined according to the opinions of both specialists.

Conditioning Regimen and GVHD Prophylactic Therapy

All 3858 haplo-HSCT recipients received a modified busulfan/cyclophosphamide + antithymocyte immunoglobulin regimen for myeloablative conditioning before transplantation [25,35,36]. According to the protocols developed by our institution, hydroxyurea (40 mg/kg) was administered twice on day −10, and intravenous cytarabine (4 g/m^2) was administered on day −10 and day −9. Busulfan was administered intravenously (3.2 mg/kg/d) from day −8 to day −6, cyclophosphamide (1.8 g/m^2) was given intravenously over 1 hour on day −5 and day −4, and oral semustine (250 mg/m^2) was given once on day −3. Intravenous antithymocyte immunoglobulin (2.5 mg/kg/d; Sang Stat, Lyon, France) was administered from day −5 to day −2 [25,35,36].

All patients from the case group and the control group received a cyclosporine A (CsA) + mycophenolate mofetil + short-term methotrexate (MTX) regimen as GVHD prophylaxis. CsA (1.25 mg/kg) was started on day −1 and the CsA dose was adjusted according to the serum levels during the first 3 months after haplo-HSCT. CsA was then tapered down beginning on day +90 and finally discontinued on day +180. The GVHD prophylactic therapy also included MTX (15 mg/m^2) on day +1, MTX (10 mg/m^2) on day +3 and day +6, and mycophenolate mofetil (0.5 g, twice daily) given from day −10 to day +30 [25,35,36].

Statistical Analysis

Continuous variables were compared using a Student *t* test. Categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test. The potential risk factors for the development of IMN were first investigated using a univariate analysis, and factors with *P* values <.05 were

included in the Cox proportional hazards regression analysis. Overall survival (OS) and disease-free survival (DFS) were estimated using Kaplan-Meier analysis, and the differences were evaluated using the log-rank test. The cumulative incidences of acute GVHD (aGVHD), chronic GVHD (cGVHD), relapse, and nonrelapse mortality (NRM) were calculated using the cumulative incidence estimator, taking the competing risks into account. The competing risk outcomes were compared between groups using Gray's test. All P values were 2-sided, and $P < .05$ was considered statistically significant. The analyses were performed using SPSS (IBM, Armonk, NY) version 20.0 software or the R software (R Foundation for Statistical Computing, Vienna, Austria) version 3.5.1.

RESULTS

Patients' Characteristics

Of the 3858 patients who received haplo-HSCT at our institution between January 1, 2008, and June 30, 2018, 40 patients with IMN following the transplantation and 120 corresponding controls (patients receiving haplo-HSCT who did not develop IMN) were enrolled in our study. The detailed description of the characteristics of the 160 patients is provided in Table 1.

Incidence, Onset, and Type

Of the 3858 haplo-HSCT patients, the incidence of post-transplant IMN was 1.04%. The median time between the haplo-HSCT and the onset of neurologic complaints that were caused by IMN was 78 days (range, 17 to 508 days). Among the 40 cases of IMN, 55% appeared within 100 days after transplantation.

Regarding the patterns of the 40 cases of IMN, there were 10 cases of GBS (including 2 cases of Miller-Fisher syndrome) and 30 cases of unclassified peripheral neuropathies that failed to meet the diagnostic criteria for GBS or CIDP. No cases of CIDP were identified. The main clinical manifestations of IMN were weakness (n = 23, 57.5%), altered sensation (n = 23, 57.5%), hyporeflexia (n = 10, 25%), and pain (n = 4, 10%). None of the 40 patients with IMN experienced autonomic symptoms. Among the 28 patients with IMN for whom results from an electrodiagnostic study were available, 10 (35.7%) mainly presented demyelinating features (a slow nerve conduction velocity, dispersion of evoked compound action potentials, conduction block or marked prolongation of distal latencies), 8 (28.6%) presented predominantly axonal features (a reduced amplitude of evoked compound action potentials with relative preservation of the nerve conduction velocity), and the remaining patients (35.7%) simultaneously presented both demyelinating and axonal features. The radiologic results (brain magnetic resonance imaging [MRI] and/or spinal cord MRI) were accessible for 34 patients with IMN. None of these patients had imaging features indicating infection, tumor

Table 1
Demographic Characteristics of Patients after Haplo-HSCT

Characteristic	Patients with IMN (n = 40)	Control (n = 120)	*P* Value
Age, mean (SD), y	27.28 (11.66)	26.68 (13.85)	.808
Sex			
Male	27 (67.5)	81 (67.5)	
Female	13 (32.5)	39 (32.5)	
Underlying disease			.798
AML	18 (45.0)	47 (39.2)	
ALL	14 (35.0)	45 (37.5)	
Others	8 (20.0)	28 (23.3)	
ABO compatibility			.645
ABO match	24 (60.0)	67 (55.8)	
ABO mismatch	16 (40.0)	53 (44.2)	
Donor-patient sex matched			.583
Sex identical	20 (50.0)	66 (55.0)	
Sex mismatch	20 (50.0)	54 (45.0)	
Donor-patient relationship			.673
Parent-child	24 (60.0)	66 (55.0)	
Sibling-sibling	9 (22.5)	33 (27.5)	
Child-parent	7 (17.5)	18 (15.0)	
Others	0 (0)	3 (2.5)	
Engraftment time			
WBC	13.60 (3.64)	13.56 (3.24)	.795
PLT	26.28 (20.25)	16.60 (7.13)	.000
aGVHD	28 (70.0)	67 (55.8)	.114
cGVHD	11 (27.5)	11 (9.2)	.004
Graft source	BM + PBSCs	BM + PBSCs	
Conditioning regimen	Modified BU/CY + ATG	Modified BU/CY + ATG	
GVHD prophylaxis	CsA + ATG + MMF	CsA + ATG + MMF	
Antecedent infection			
Bacterial	12 (30.0)	43 (35.8)	.480
Fungus	3 (7.5)	15 (12.5)	.378
CMV	38 (95.0)	93 (77.5)	.013
EBV	4 (10.0)	18 (15.0)	.426

Values are presented as number (%) unless otherwise indicated.
AML indicates acute myelocytic leukemia; ALL, acute lymphoblastic leukemia; PLT, platelet; BM, bone marrow; PBSC, peripheral blood stem cell; BU, busulfan; CY, cyclophosphamide; ATG, antithymocyte immunoglobulin; MMF, mycophenolate mofetil; EBV, Epstein-Barr virus.

infiltration, or hemorrhage at the time of the IMN diagnosis, but 3 patients with IMN showed evidence of possibly concomitant CNS demyelinating diseases. Nineteen of the 40 patients with IMN underwent CSF testing. The CSF protein level was increased in 16 patients (84.2%), and the mean (SD) CSF protein level was 0.80 (0.58) g/L (range, 0.14 to 2.58 g/L). The mean WBC count was 1.17 cells/μL (range, 0-7 cells/μL); no malignant cells were detected in any of the CSF samples. Five patients with IMN had transiently positive CSF viral PCR results, but a definite temporal association between the positive viral PCR results and the onset or progression of neurologic complaints was not observed. In addition, the transient appearance of positive CSF viral PCR results did not correlate with any significant increase in the CSF WBC count. Normally, positive CSF viral PCR results with increased CSF WBC count implied that the neuropathies were caused by direct infection.

Risk Factors

The potential risk factors for IMN were analyzed using univariate analysis, as shown in Table 2. We found that cGVHD ($P = .024$) and cytomegalovirus (CMV) viremia ($P = .024$) were significantly associated with the development of IMN. Both of these factors were thereafter analyzed in a multivariate Cox proportional hazards model. Finally, both CMV viremia (hazard ratio, 4.643; 95% confidence interval [CI], 1.114 to 19.347; $P = .035$) and cGVHD (hazard ratio, 2.063; 95% CI, 1.025 to 4.154; $P = .043$) were identified as independent risk factors for IMN following haplo-HSCT (Table 2).

Outcomes

aGVHD and cGVHD

When calculating the cumulative incidences of aGVHD or cGVHD, death without GVHD, relapse, and secondary transplant were considered competing risks. Among the 160 patients included in our study, 95 (59.38%) developed aGVHD. The cumulative incidences of aGVHD were 69.2% (95% CI, 66.9% to 71.6%) and 56.5% (95% CI, 55.7% to 57.3%) for the cases and the controls, respectively. There were no significant differences in the possibilities of developing aGVHD between patients from the case group and those from the control group ($P = .24$) (Figure 2). Eleven (27.5%) of the 40 patients with IMN developed cGVHD, which led to a 1-year cumulative incidence of 26.8% (95% CI, 24.4% to 29.2%). The incidence of the development of cGVHD after haplo-HSCT in the case group was significantly higher than that in the control group ($P = .012$).

OS and DFS

The probabilities of OS were 85.6% (95% CI, 71.9% to 99.2%) and 91.1% (95% CI, 85.4% to 96.8%) in the case and control groups, respectively. Overall, 4 patients died in the case group. The mean survival times were 2241.3 days (95% CI, 1950.2 to 2532.5) and 2439.3 days (95% CI, 2303.4 to 2575.1) in the case and control groups, respectively ($P = .619$). The probabilities of DFS were 80.9% (95% CI, 66.6% to 95.2%) and 84.5% (95% CI, 76.5% to 92.5%) for patients with and without IMN, respectively. The median relapse-free survival time was 2126.0 days (95% CI, 1810.8 to 2441.1) in the case group and 2298.0 days (95% CI, 2120.5 to 2475.4) in the control group ($P = .609$).

Relapse and NRM

Using a competing risk model, the cumulative incidences of NRM at 1 year and 2 years after haplo-HSCT in patients with IMN were 5.29% (95% CI, 4.14% to 6.44%) and 9.35% (95% CI, 7.69% to 11.0%), respectively. Three patients in the case group died without relapse. Among these patients, 1 died of complications from GBS, and the other 2 deaths were caused by unrelated pulmonary infections. For the control group, the incidences of NRM at 1 year and 2 years after haplo-HSCT were 6.46% (95% CI, 6.03% to 6.89%) and 7.86% (95% CI, 7.37% to 8.35%), respectively. No significant difference in the NRM incidence was observed between the case group and the control group ($P = .87$). The cumulative incidences of relapse for all of the 160 enrolled patients were 4.28% (95% CI, 4.01% to 4.55%) and 6.56% (95% CI, 6.21% to 6.93%) at 1 year and 2 years after

Table 2
Risk Factors for IMN following Haplo-HSCT Identified by Univariate Analysis and Multivariate Analysis

Risk Factor	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age (>18 vs ≤18)	0.931	0.473-1.834	.837			
Underlying disease						
AML						
ALL	0.906	0.451-1.822	.782			
Others	0.785	0.341-1.806	.570			
ABO compatibility (match vs mismatch)	0.809	0.430-1.524	.512			
Donor-patient sex (match vs mismatch)	1.258	0.677-2.339	.468			
Donor-patient relationship						
Parent-child						
Sibling-sibling	0.803	0.373-1.727	.574			
Child-parent	1.802	0.466-2.512	.854			
Others	0.000	0.000-0.000	.977			
aGVHD	1.720	0.874-3.384	.116			
cGVHD	2.230	1.114-4.466	.024*	2.063	1.025-4.154	.043*
Bacterial infection	0.838	0.426-1.647	.607			
Fungal infection	0.600	0.185-1.945	.394			
CMV viremia	5.165	1.245-21.421	.024*	4.643	1.114-19.347	.035*
EBV viremia	0.674	0.240-1.895	.455			

Univariate statistics: Log rank test. Multivariate statistics: Cox regression.
HR indicates hazard ratio.
* $P < .05$ in the analysis.

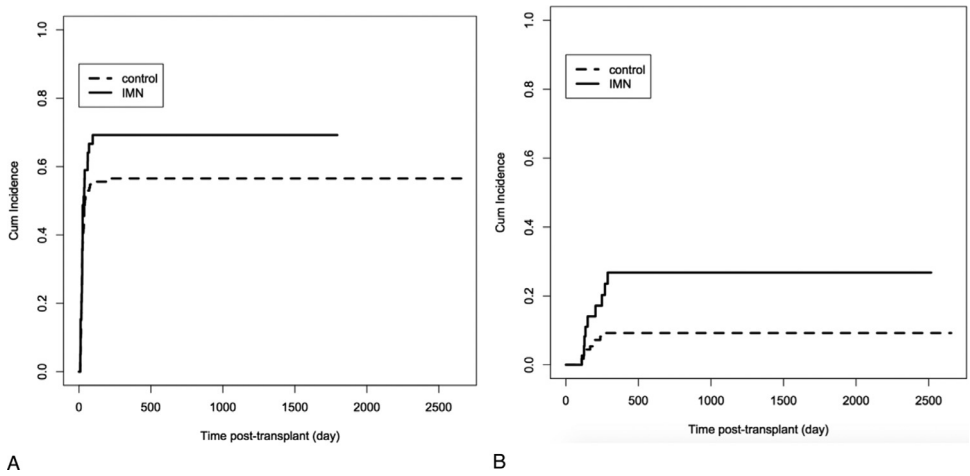

Figure 2. The incidence of aGVHD (A) or cGVHD (B) based on the occurrence of IMN after haplo-HSCT. aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; haplo-HSCT, haploidentical hematopoietic stem cell transplantation.

haplo-HSCT, respectively. In the case group, 3 patients (2 with GBS and 1 with polyneuropathy) experienced malignant relapses, and 1 patient died as a result of the relapse. Regarding the temporal association between malignancy relapses and the IMN, 2 of the 3 relapses occurred within 2 months after the onset of neuropathies, whereas the other patient who experienced relapse presented with skin involvement approximately 50 days before the appearance of neurologic manifestations. No difference in the relapse rate was observed between the case and the control groups ($P = .583$) (Figure 3).

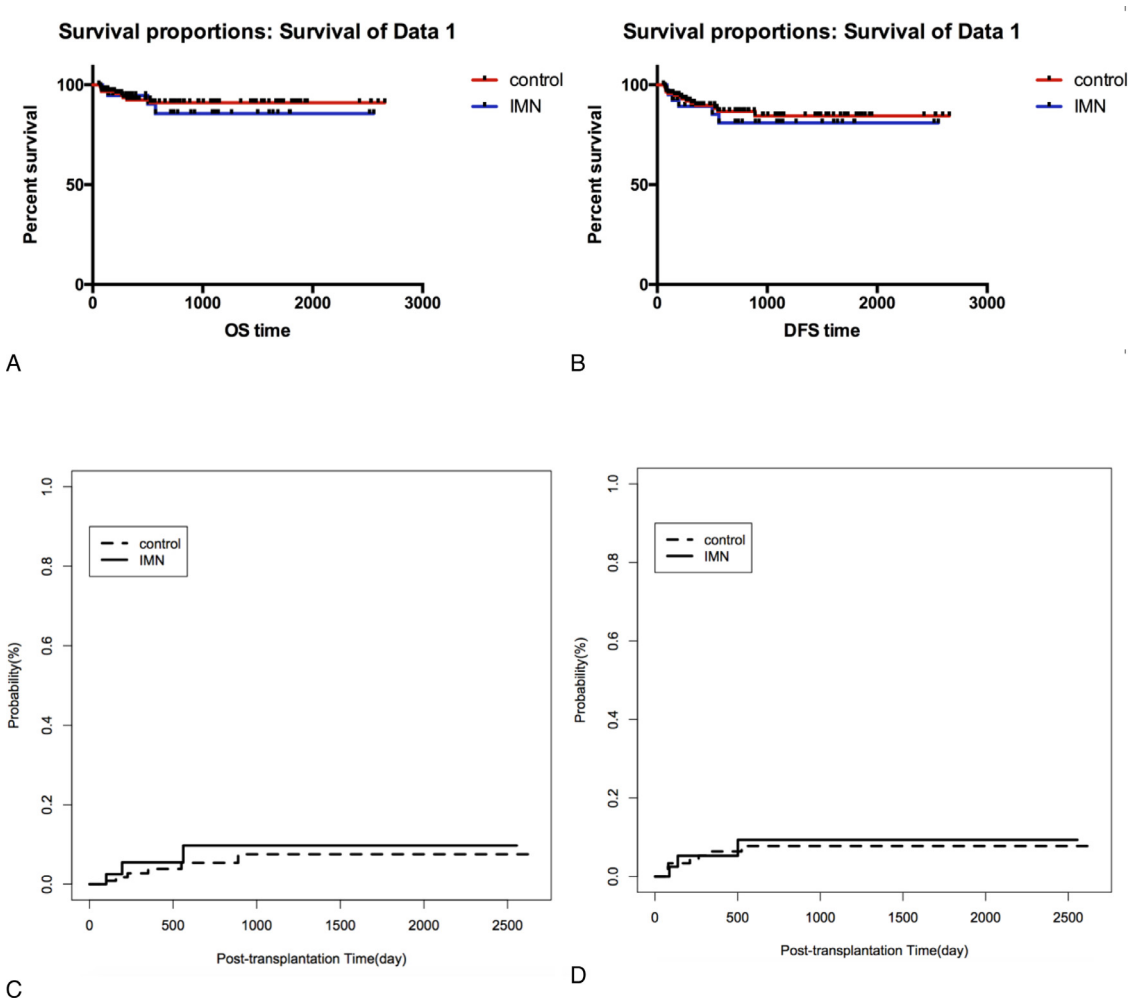

Figure 3. Clinical outcomes based on the occurrence of IMN after haplo-HSCT. OS (A) and DFS (B), the incidence of NRM (C), and the incidence of relapse (D). NRM, nonrelapse mortality; haplo-HSCT, haploidentical hematopoietic stem cell transplantation.

Treatments and Outcomes

In our study, 2 groups of agents were used, including neurotrophic treatments (vitamins B_1 and B_{12}) and immunomodulatory agents (intravenous immunoglobulin [IVIG], plasma exchange, and steroids), to treat post-transplant IMN. Supportive therapies (intubation) were given whenever necessary. Different therapeutic strategies for IMN were administered to patients with GBS and IMN patients without GBS (non-GBS patients). For the 10 patients with GBS, the first-line therapy included IVIG (20 g/d for 5 consecutive days) or plasma exchange, together with subsidiary vitamins B_1 and B_{12}. Second-line therapy included steroids, which were given empirically. Third-line therapy could have included rituximab, although we did not use this agent in the current study. Regarding the treatment outcomes of the neurologic manifestations, 7 patients achieved partial remission, 2 patients did not achieve remission (including 1 death caused by GBS), and the relevant record was unavailable for 1 patient.

For the 30 non-GBS patients, vitamins B_1 and B_{12} were administered as the first-line therapy, and 6 patients (20%) achieved neurologic improvements without further treatments. Immunomodulatory agents (IVIG, plasma exchange, and steroids) were used as the second-line therapy, when the neurologic manifestations were unable to be controlled by vitamins B_1 and B_{12} alone. Third-line therapy could have included rituximab, although we never used this agent. Among the 15 non-GBS patients receiving immunomodulatory agents, steroids and/or IVIG were administered empirically. Four patients achieved complete remission, 7 patients achieved partial remission, and 2 patients did not achieve remission. In summary, of the 40 patients with IMN, neurologic manifestations were improved in 24 (60%) patients after treatment. Only 1 patient with IMN died (2.5%) in our study, but the incidence of motor/sensory deficits was at least 47.5% (19 of 40 patients). No clear evidence of neurologic relapses was observed in our study. The detailed description of the treatment outcomes is shown in Table 3.

DISCUSSION

Traditionally, the phenotypes of post-transplant IMN were believed to be GBS and CIDP, which had been reported for 30 years [20,37,38]. In our study, the frequency of GBS following haplo-HSCT was 0.26%, which was in accordance with the previously reported incidences of 0.12% to 0.2% [16,17]. However, in 2014, Karam et al. [17] extended the traditional definition of IMN and described several atypical subtypes of IMN such as multiple mononeuropathy, which means that we might have underestimated the incidence of post-transplant IMN. However, many of the IMN cases that were enrolled in the study by Karam et al. received auto-HSCT rather than allo-HSCT or haplo-HSCT. After carefully reviewing the charts of 3858 haplo-HSCT patients from our institution, we identified 40 patients with IMN. To our knowledge, this is the first time that the incidence of IMN following haplo-HSCT has been reported.

In contrast to GBS and CIDP, which have typical manifestations and strict diagnostic criteria, the atypical subtypes of IMN were diagnosed by exclusion after carefully ruling out all alternative etiologies, such as the toxicity of the conditioning regimen or GVHD prophylaxis, infection, and malignancy [16–18,20,21,32]. Nerve conduction studies and electromyography are important for confirming the diagnosis of IMN. However, 30% of our patients with IMN were unwilling or unable to undergo the electrodiagnostic testing. In these cases, radiologic studies such as MRI could be performed to help exclude CNS diseases and to attribute the patients' complaints to peripheral nervous system diseases. Although nerve biopsies can provide the most direct and accurate evidence of IMN, none of our patients with IMN received this invasive procedure after a risk-benefit analysis was performed. More than 50% of the patients experienced the onset of IMN within 100 days after haplo-HSCT, but there was 1 case of GBS occurring 508 days after transplantation. Although we could not simply regard this GBS onset as a transplantation complication, several late-onset nervous system immune-mediated diseases have been reported [18].

The pathogenetic mechanisms of post-transplant IMN have not been completely elucidated, but several possible mechanisms have been proposed, such as (1) molecular mimicry of infectious antigens (such as CMV and *Campylobacter jejuni*), (2) immunologic dysregulation, (3) GVHD, (4) paraneoplastic syndrome, and (5) drugs [16–18,39–41]. In our study, 95% of patients with IMN exhibited preceding CMV viremia before the onset of neurologic manifestations, and CMV viremia was identified as one of the independent risk factors associated with the occurrence of IMN after haplo-HSCT, supporting the role of infection in causing IMN. However, Fujisaki et al. [40] claimed that the post-transplant development of GBS in patients with CMV infections might result from a peripheral expansion of mature lymphocytes that was associated with a rapid immune reconstruction in response to CMV infection, instead of the cross-reacting mechanism. Transplant patients are incapable of producing antibodies to defend against viral infections as effectively as nontransplant populations. In line with this hypothesis, only 2 of our patients with IMN displayed positive anti-GM1 antibodies that cross-reacted with ganglioside-like epitopes between infective pathogens and the components of peripheral nerves. We also identified 12 patients with positive bacterial cultures before the development of IMN, but *C. jejuni* was not detected.

Table 3
Treatments and Outcomes of IMN following Haplo-HSCT

Pattern of Post-Transplant IMN (n)	Treatment of Neuropathies (n)	Treatment Outcomes* (n)
GBS (10)	IVIG/plasma exchange ± steroids (10)	Partial remission (7) Non-remission (2) Lack of records (1)
Non-GBS (30)	Vitamins B_1 and B_{12} alone (15)	Complete remission (6) Lack of records (9)
	Vitamins B_1 and B_{12} + immunomodulatory agents (15)	Complete remission (3) Partial remission (8) Nonremission (2) Lack of records (2)

* Treatment outcome: nonremission; partial remission (with persistent motor/sensory deficits); complete remission (without any sequela of motor/sensory deficits); nonremission (no response to treatment of neuropathies).

Consistent with our results of identifying cGVHD as an independent risk factor for IMN after haplo-HSCT, previous studies have described several cases of GBS, CIDP, and other demyelinating polyneuropathies occurring as one of the manifestations of GVHD, particularly cGVHD [19,21,42,43]. Saad et al. [44] also performed a brain biopsy, indicating that the nervous system potentially represents an isolated target organ of GVHD. In our study, 12 patients with IMN exhibited the emergences of neurologic symptoms while concomitant systemic GVHD manifestations still existed. In addition, more than 70% of the patients with IMN had a history of GVHD compared with less than 60% of the patients in control group, all of whom indicated that GVHD might be relevant to some of the cases of IMN. Regarding the underlying mechanisms, IMN and cGVHD appear to be caused by a common immunologic mechanism, the activation of T cells, macrophages, and the generation antibodies that result in tissue destruction in GVHD and peripheral nerve demyelination in IMN such as CIDP. However, GVHD is not a mandatory criterion for diagnosing post-transplant IMN. HSCT might still perturb the immune system and decrease the tolerance of the immune system in the absence of GVHD, causing the development of self-reactive T cells or B cells and an aberrant immune response [18,45].

Karam et al. [17] implied that a possible paraneoplastic etiology might play a role in the occurrence of IMN because the authors observed a close relationship between the timing of malignancy relapses and the onset of neurologic symptoms. The authors identified 3 early relapse patients among 6 patients with IMN following allo-HSCT, whereas in our study, only 2 of the 40 patients with IMN experienced relapses within 50 days from the onset of neurologic symptoms. We did not observe a significant difference in the incidence of relapse between patients with or without IMN using a competing risk model. Therefore, more careful evaluation of cancer relapses might be necessary for the patients with IMN, but the association between IMN and hematologic malignancies requires further investigation. Previous studies also revealed that certain drugs, such as high-dose methotrexate, high-dose (Cytosine arabinoside) Ara-C, and bortezomib, could potentiate or precipitate NC, such as GBS, and may also cause IMN [32,46]. However, none of these associations were identified in our study.

For nontransplant IMN, each subtype of IMN has its own standard therapeutic strategy. Commonly used treatments for IMN include 3 groups of agents: immunomodulatory agents (IVIG, plasma exchange, and steroids), immunosuppressive agents (eg, azathioprine, methotrexate), and monoclonal antibodies (eg, rituximab) [27]. Although a standard therapeutic strategy for post-transplant IMN is currently unavailable, the same categories of agents were applied to treat IMN in previous studies [16–18,21,47,48]. Because immunosuppressive agents and monoclonal antibodies were mainly used in refractory cases, in our practice, only neurotrophic treatments (vitamins B_1 and B_{12}) and immunomodulatory agents (IVIG, plasma exchange, and steroids) were administered in our study.

Only IVIG and plasma exchange have been proven to be effective treatments for GBS, whereas both oral and intravenous steroids were not shown to be beneficial [27,49]. Therefore, we used dichotomous therapeutic strategies for patients with GBS (including Miller-Fisher syndrome) and non-GBS patients, respectively. Notably, 6 patients with IMN enrolled in our study achieved complete neurologic improvements with vitamin supplementation alone, and no neurologic relapses were observed after treatment. Both of these findings were consistent with the results from previous studies arguing that IMN tended to be monophasic diseases that improve spontaneously [17]. Although post-transplant IMN rarely caused mortality directly (2.5%) and at least 60% of patients had positive neurologic responses after treatment, we still noticed a rather high incidence (47.5%) of persistent motor/sensory deficits, indicating that IMN might substantially impair patients' quality of life. However, negative impacts of IMN on OS, DFS, or NRM were not observed. Although previous studies revealed that NC negatively influenced patient outcomes, most deaths were actually caused by CNS complications rather than peripheral neuropathies following HSCT.

The retrospective nature of our study and the lack of standard diagnostic criteria are the main limitations of our study. Currently, the diagnosis of IMN requires the exclusion of other common causes of neuropathies. A nerve biopsy is the only examination that is able to confirm the immune-mediated mechanisms. Our study, however, failed to enroll a single patient with IMN for whom a result from a nerve biopsy was available. In addition, the use of *International Classification of Diseases, 10th Revision* codes to generate the preliminary list of potential patients with IMN rather than reviewing the records of all of our 3858 haplo-HSCT patients might have underestimated the incidence of IMN. Finally, the lack of a standardized therapeutic strategy and scoring system to quantify neurologic improvements might have affected our evaluation of treatment outcomes. Similarly, our follow-up methods were relatively subjective, which might have generated some bias.

In conclusion, CMV viremia and cGVHD are independent risk factors associated with IMN, the rare complication of halo-HSCT. Patients with IMN following halo-HSCT are at a higher risk of developing cGVHD. Prompt interventions might help improve the neurologic outcomes of patients with post-transplant IMN. However, approximately half of the patients with IMN still presented with persistent motor/sensory deficits after timely treatments. In the future, multicenter prospective studies are needed to help develop standardized diagnostic and therapeutic strategies for patients with post-transplant IMN (Figure 1).

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