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Supportive Care

Noninfectious Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) can be associated with neurologic complications, data on noninfectious etiologies are scanty. Therefore, we analyzed the incidence, clinical characteristics, risk factors, and influence on outcomes of noninfectious neurologic complications (NCs) in 971 consecutive patients with hematologic malignancies undergoing allo-HSCT at our center between January 2000 and December 2016. We evaluated NCs affecting the central nervous system (CNS) and peripheral nervous system (PNS). The median duration of follow-up of survivors was 71 months (range, 11 to 213 months). A total of 467 patients received a matched sibling donor (MSD) transplant, 381 received umbilical cord blood (UCB), 74 received a haploidentical transplant, and 49 received a matched unrelated donor (MUD) transplant. One hundred forty-nine (15.3%) NCs were documented at a median of 78 days after transplantation (range, 5 days before to 3722 days after). The cumulative incidence risk of developing NC was 7.5% (95% confidence interval, 6% to 8.2%) at day +90 and 13% at 5 years. The 5-year cumulative incidence of NCs was 10.8% after MSD allo-HSCT and 15.3% after alternative donor (UCB, MUD, haploidentical) allo-HSCT ($P = .004$). There were 101 (68%) CNS complications, including encephalopathy, n = 46 (31%); headache, n = 20 (13%); stroke, n = 15 (10%); seizures, n = 9 (6%), posterior reversible encephalopathy syndrome, n = 6 (4%), and myelopathy, n = 5 (3%). PNS complications (32%) included neuropathies, n = 25 (17%), and myopathies and neuromuscular junction disorders, n = 23 (17%), with 17% of the total PNS complications being immune-related. In multivariable analysis, donor type other than MSD, age ≥40 years, development of acute graft-versus-host disease (GVHD) grade II-IV (hazard ratio [HR], 3.3; $P < .00001$), and extensive chronic GVHD (HR, 3.2; $P = .0002$) were independently associated with increased risk of NCs. The 5-year overall survival (OS) was 21% in patients who developed NCs and 41% for those who did not ($P < .0001$). This difference in OS was observed in patients developing CNS NCs, but not in those developing PNS complications. In conclusion, our study reveals NCs as a frequent and heterogeneous complication that, when affecting CNS, is associated with poor prognosis following allo-HSCT.

INTRODUCTION

Neurologic complications (NCs) are commonly seen after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and are associated with relevant morbidity and mortality [1,2]. These complications are heterogeneous and not easy to classify, lumping together different entities such as infections, disease recurrence, drug-related toxicities, cerebrovascular events, and metabolic and immune-mediated disorders, among others.

NCs after allo-HSCT have been classified by the time of onset, because early NCs are usually related to conditioning regimen, bone marrow aplasia, and drug toxicities, whereas later events are often associated with the development of graft-versus-host disease (GVHD) and/or immunosuppressive therapy. The reported incidence of NCs after allo-HSCT varies widely, from 8% to 55%, across different retrospective studies according to definition of NCs, study population, follow-up, and types of allo-HSCT procedures [3-5]. Given the diverse etiologies of NCs, it is of interest to separately analyze infectious and noninfectious NCs, given the likelihood that their risk factors will differ. We previously reported the incidence of (4.9% at 5 years) and risk factors for infectious central nervous system (CNS) NCs in the allo-HSCT setting, which include

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receiving an umbilical cord blood (UCB) transplantation and disease stage beyond first complete remission [6]. Although some studies have reported the incidence of and risk factors for noninfectious NCs [1,7-9], data derived from the analysis of larger cohorts are missing.

The main objective of the present study was to analyze the incidence, characteristics, and risk factors of noninfectious and nonbaseline disease relapse-related NCs of the CNS and PNS in a large single-center cohort of consecutive allo-HSCT recipients.

METHODS

Eligibility Criteria

All consecutive adult patients with hematologic diseases undergoing allo-HSCT at the Hospital Universitario La Fe between January 2000 and December 2016 were included in this study. The hospital's Institutional Review Board approved the protocol, and written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Data Collection

We retrospectively reviewed data on patients, transplantation procedures, and NCs, including neurologic symptoms, diagnostic methods, time of onset and cause, which had been recorded in a computerized transplant database. All clinical charts from recipients with NCs were retrospectively reviewed by an expert allo-HSCT neurologist team to classify the NCs and to resolve inconsistencies and/or missing data.

Transplantation Procedures

Conditioning Regimens

The conditioning regimens were administered according to institutional protocols, based on the hematopoietic stem cell source, donor type, patient age, comorbidities, and underlying disease. Conditioning regimen intensity was classified as myeloablative or reduced-intensity conditioning (RIC) following recent consensus criteria [10]. Conditioning regimens according to donor type—matched sibling donor (MSD), UCB, HLA-matched unrelated donor (MUD) considering high-resolution typing of HLA-A, -B, -C, -DRB1, and -DQB1 or haploidentical family donor—have been previously described elsewhere in detail [11-13]. Phenytoin prophylaxis (100 mg every 8 hours) was given to all patients receiving busulfan as a part of the conditioning regimen.

GVHD Prophylaxis and Therapy

GvHD prophylaxis differed according to the type of hematopoietic stem cells source. Allo-HSCT from MSD received cyclosporine combined with methotrexate with the exception of patients with aplastic anemia, who received *ex vivo* T-cell partial depletion followed by cyclosporine and prednisone. Patients undergoing allo-HSCT from an MUD received a combination of cyclosporine, methotrexate, and antithymocyte globulin (ATG), those undergoing allo-HSCT with a UCB received cyclosporine combined with either prednisone or mycophenolate mofetil (MMF), and those undergoing haploidentical allo-HSCT received either ex vivo T cell depletion without pharmacologic prophylaxis or post-transplantation cyclophosphamide (on days +3 and +4) combined with cyclosporine and MMF.

Patients developing grade II-IV acute GVHD (aGVHD) received methylprednisolone 2 mg/kg/day as initial therapy, with ATG used in steroid-refractory cases. Chronic GVHD (cGVHD) was treated with prednisone 1 mg/kg/day. Details of dosages and schedules have been reported elsewhere [12-14].

Definitions

An NC was defined as any neurologic event occurring between the start of the conditioning regimen and the last follow-up. CNS infectious NCs and/or relapse-related NCs were excluded. The onset of the neurologic event was defined as the first day of neurologic symptoms that yield to the diagnosis. NCs were divided into CNS and PNS. NCs were classified in different categories according to the final diagnosis, which was made by a combination of clinical, radiologic, laboratory, and microbiological findings and/or postmortem studies. Preexisting neurologic complications were not considered post-transplantation neurologic events, except for specific cases of clinically significant worsening myelopathy.

Cerebrovascular disorders were diagnosed by imaging studies. Diagnosis of posterior reversible encephalopathy syndrome (PRES) [15,16] was based on characteristic magnetic resonance imaging (MRI) findings and compatible clinical symptoms. The term "encephalopathy" was applied to patients with acute confusional states, with or without seizures, with uninformative imaging, microbiological, and cerebrospinal fluid (CSF) studies. In these patients, the presence of major organ failure, systemic sepsis, or drug toxicity was especially considered [9]. Patients with isolated seizures or severe headache (without other focal or encephalopathic symptoms and negative studies) were analyzed separately. Myelopathy was diagnosed in patients who developed symptoms of subacute combined degeneration of the spinal cord or acute transverse myelitis.

PNS NCs were classified as single or multiple peripheral neuropathy, myopathy, or neuromuscular junction disorders and diagnosed based on clinical features and nerve conduction studies/electromyography (EMG). Muscle biopsies and skeletal MRI were performed in selected cases when requested by the consulting neurologist (L.B.). The main etiologies of PNS complications were immune-mediated, toxicity-related, and critical illness-related. Neuralgia related to cutaneous herpes zoster reactivation, intracranial hypotension after lumbar puncture, and postural tremor were not analyzed in this study.

Endpoints and Statistical Analysis

The primary objective of the study was to analyze the characteristics and incidence of CNS and PNS NCs. Secondary endpoints included the analysis of risk factors for NCs and the impact of NCs on overall survival (OS). Clinical characteristics of patients undergoing allo-HSCT according to donor type (UCB, MUD, MSD, or haploidentical donor) were compared using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The probability of neurologic events was estimated by the cumulative incidence method (marginal probability), and the Gray test was used for comparisons [17,18]. For NC cumulative incidence analyses, relapse, graft failure, and death without NCs were considered competing events. Variables included in the analysis of risk factors were transplant type, conditioning regimen (myeloablative versus RIC), diagnosis, age, sex, cytomegalovirus (CMV) serostatus, previous transplantation, disease status at transplantation, conditioning regimen, use of ATG, GVHD prophylaxis, development of aGVHD or cGVHD, and year of transplantation. Variables with a P value $<.10$ for each endpoint were included in the multivariable analysis using the Fine and Gray method [18] for competing events and the Cox regression model [19] for time-dependent covariates (GVHD development).

OS was calculated from the date of transplantation until death or the last follow-up. Time-to-event analyses were performed using Kaplan-Meier estimates [20] and, for comparison, log-rank tests [21]. If NCs were found to have an impact on OS in the univariate analysis, a semi-landmark plot was constructed to illustrate the effect. Statistical analysis was performed using R version 2.12.2 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Patient, Transplantation, and Graft Characteristics

Nine hundred seventy-one consecutive allo-HSCT recipients who allografted at our institution were included in this study. Patient, disease, and transplantation characteristics according to the development of NCs are summarized in Table 1. In our series, allo-HSCT was performed using an MSD in 467 patients (48%), UCB in 381 patients (39%) with UCB, 49 (5%) from an MUD, and 74 (8%) from a haploidentical donor. The median patient age was 41 years, and most patients had acute leukemia (63%). A myeloablative conditioning regimen was used in most cases (63%). The median follow-up of surviving patients was 71 months (range, 11 to 213 months). There were differences in median follow-up according to donor source, being longer with UCB (87 months) and MSDs (67 months) and shorter with MUDs (23 months) and haploidentical donors (24 months) ($P < .0001$).

Incidence, Types, and Timing of Neurologic Complications

A total of 149 episodes of NCs were documented in 132 patients. Sixty-three cases (42%) were detected after MSD allo-HSCT, 72 (49%) after UCB allo-HSCT, 9 (6%) after MUD allo-HSCT, and 5 (3%) after haploidentical donor allo-HSCT. CNS NCs (68%; n = 101) were more common than PNS NCs (32%; n = 48). The most frequent NC was encephalopathy (31%; n = 46), followed by myopathy (13%; n = 23) and peripheral neuropathy (13%; n = 25) (Table 2). The median time from transplantation to the onset of NCs was 78 days (range, 5 days before to 3722 days after) overall, 65 days for CNS NCs, and 101 days for PNS NCs ($P = .02$).

The cumulative incidence risk of developing at least 1 episode of NC was 6% at day +30, 11% at 1 year, and 13% at 5 years. The 5-year cumulative incidence according to donor source was 11% with an MSD, 17% with UCB, 16% with an MUD, and

Table 1
Patient, Transplantation, and Disease Characteristics According to the Development of NCs

Characteristic	All Patients	Patients with NCs	Patients without NCs	*P* Value
Number of patients	971	132	839	
Age, yr, median (range)	41 (17-70)	46 (17-66)	41 (17-71)	.57
Donor source, n (%)				.019
MSD	467 (48)	53 (40)	414 (49)	
MUD	49 (5)	8 (6)	41 (5)	
UCB	381 (39)	66 (50)	315 (38)	
Haploidentical	74 (8)	5 (4)	69 (8)	
Sex, n (%)				.80
Male	579 (60)	82 (62)	497 (59)	
Female	392 (40)	50 (38)	342 (41)	
Diagnosis, n (%)				.70
AML/MDS	472 (49)	61 (46)	411 (49)	
ALL	207 (21)	24 (18)	184 (22)	
CML	43 (4)	8 (6)	35 (4)	
CLPD	170 (17)	28 (21)	141 (17)	
AA	46 (5)	6 (5)	40 (5)	
Other	33 (3)	5 (4)	28 (3)	
Disease status, n (%)				.55
Early	466 (48)	42 (32)	236 (28)	
Intermediate	208 (21)	32 (24)	195 (51)	
Advanced	293 (30)	58 (44)	408 (49)	
Prior HSCT, n (%)	225 (23)	34 (26)	191 (23)	.44
CMV serostatus pretransplantation, n (%)				.39
Positive	732 (76)	106 (80)	626 (74)	
Negative	238 (25)	26 (20)	212 (25)	
Conditioning regimen, n (%)				.04
Myeloablative	616 (63)	73 (55)	543 (65)	
Reduced intensity	355 (37)	59 (45)	296 (35)	
Donor/recipient sex mismatch, n (%)				1
Female to male	257 (27)	35 (27)	222 (27)	
GVHD prophylaxis, n (%)				.02
CyA + prednisone	356 (37)	46 (35)	310 (37)	
CyA + MMF	114 (12)	28 (21)	86 (10)	
CyA + MTX	415 (43)	52 (39)	363 (43)	
Ex vivo T cell depletion	29 (3)	2 (2)	27 (3)	
CFM post + CyA + MMF	45 (5)	3 (2)	42 (5)	
Others	12 (1)	1 (1)	11 (1)	

AML indicates acute myelogenous leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; CLPD, chronic lymphoproliferative disorder; AA, aplastic anemia; CyA, cyclosporine A; MTX, methotrexate; CFM, cyclophosphamide

6% with a haploidentical donor ($P = .014$). The distribution of NCs according to post-transplantation period is shown in Table 3.

Table 2
Distribution of Noninfectious NCs

NC	n (%)
Total	149 (100)
CNS	101 (68)
Stroke	15 (10)
PRES	6 (4)
Encephalopathy	46 (31)
Isolated seizures	9 (6)
Headache	20 (13)
Myelopathy	5 (3)
PNS	48 (32)
Neuropathy	25 (17)
Myopathies and neuromuscular junction disorders	23 (17)

CNS Involvement

CNS NCs were documented in 101 cases (68% of all NCs) at median of 65 days after stem cell infusion (range, 5 days before to 2982 days after). The cumulative incidence of CNS complications was 5% at +30 days, 8% at 1 year, and 9% at 5 years. There were no differences in the cumulative incidence of CNS NCs according to stem cell source.

Stroke. Stroke occurred in 15 patients, with a median time to event of 55 days (range, 1 to 478 days). The cumulative incidence of developing stroke was 1.8% at 5 years.

Except for 1 case, all events were hemorrhagic, including subdural (n = 6), lobar (n = 6), cerebellar (n = 1), and subarachnoid (n = 1) hemorrhages. The median platelet count at the time of the hemorrhagic event was 16×10^9/L (range, 10 to 41×10^9/L). Clinical onset consisted of impaired consciousness in 8 patients, including 2 with associated headache, and the other patients presented with seizures (n = 1), headache (n = 2), confusional syndrome (n = 2), or hemiparesis (n = 2).

Table 3
NCs According to Post-Transplantation Period

NC	Days 0-30, n (%)	Days 31-100, n (%)	Days 101-365, n (%)	1 yr+, n (%)
Events, n (%)	69 (100)	26 (100)	30 (100)	24 (100)
Stroke	6 (9)	2 (8)	4 (13)	3 (13)
PRES	5 (7)	0	0	1 (4)
Encephalopathy	25 (36)	7 (26)	7 (23)	7 (29)
Isolated seizures	4 (6)	1 (4)	3 (10)	1 (4)
Headache	17 (25)	0	1 (3)	2 (8)
Myelopathy	1 (1)	2 (8)	0	2 (8)
Neuropathy	6 (54)	6 (43)	8 (53)	5 (63)
Myopathy and neuromuscular junction disorders	5 (45)	8 (57)	7 (47)	3 (37)

The only patient with ischemic stroke had an acute middle cerebral artery stroke. Stroke was the primary cause of death in 10 patients (71%) at a median of 3 days from diagnosis (range, 0 to 17 days), despite surgical evacuation of the hematoma in 5 of these patients.

PRES. There were 6 episodes of PRES (3% of all NCs), including 4 after UCB allo-HSCT, 1 after MSD allo-HSCT, and 1 after MUD allo-HSCT. The median time to event was 24 days (range, 12 to 656 days). The 5-year cumulative incidence of PRES was .7%.

Symptoms included tonic-clonic seizures in all cases, with cortical visual disturbances in 2 cases, cerebellar ataxia in 1 patient, and variable degrees of confusional states. All patients presented with the typical symmetrical white matter lesions localized mainly in the occipital lobes on MRI [22]. Precipitating factors included cyclosporine use (n = 5), severe hypertension (n = 4), renal failure (n = 1), and sepsis with multiple organ dysfunction (n = 1) in the only patient who was not receiving treatment with a calcineurin inhibitor (CNI). None of the patients had active GVHD at the diagnosis of PRES. In patients treated with a CNI, this treatment was discontinued and MMF was started. All patients recovered completely except for 1 patient who developed a lobar and subarachnoid hemorrhage requiring surgical craniotomy. Except for this case, and another patient who died from GVHD, the remaining patients recovered fully and were still alive at the last follow-up.

Encephalopathy. Encephalopathy occurred in 46 cases (24% of all NCs). The median time to onset of encephalopathy was 29 days after allo-HSCT (range, 5 days before to 2982 days after). The cumulative incidence of encephalopathy was 5% at 5 years.

Thirteen patients (28%) had drug-related encephalopathy, associated with cyclosporine (n = 4), morphine (n = 6), voriconazole (n = 2), or acyclovir (n = 1). In all these cases, symptoms cleared after discontinuation of the causative drug. Major organ (mainly liver) failure was seen in 10 patients (22%), all but 1 of whom died. Five patients (11%) developed encephalopathy during the course of systemic sepsis without CNS involvement. Multifactorial encephalopathy associated with toxicity or metabolic disorders was diagnosed in 13 cases (28%). No precipitating factor was identified in 5 patients. Twenty-four of these patients (52%) died from concomitant complications at a median of 12 days (range, 0 to 24 days) from the diagnosis of encephalopathy.

Isolated Seizures. Nine patients developed isolated seizures, 6 after UCB allo-HSCT and 3 after MSD allo-HSCT, at a median of 55 days (range, 1 to 1932 days). The cumulative incidence of isolated seizures was .8% at 5 years. Epileptic seizures included complex partial seizures (n = 3), tonic-clonic generalized seizures (n = 5), and myoclonic seizures (n = 1). Precipitating factors were abnormally high serum levels of cyclosporine (n = 5) and fever (n = 2). The etiology was unknown in 2 patients.

Headache. Severe headache occurred in 20 patients, leading the physician to request complementary tests to discard a secondary headache. Ten occurred after MSD allo-HSCT, 6 after UCB allo-HSCT, 2 after haploidentical donor allo-HSCT, and 2 after MUD allo-HSCT. The median time to onset of headache was 10 days from transplantation (range, 1 to 1602 days). The 5-year cumulative incidence risk was 2%. Abnormally high serum levels of cyclosporine were detected in 5 patients (25%), including 3 with high blood pressure and 1 with impaired renal function.

Myelopathy. Five patients developed myelopathy, 2 patients after MSD allo-HSCT and 3 after UCB allo-HSCT. The 5-year cumulative incidence was .7%, and the median time from transplantation to myelopathy was 83 days (range, 15 to 626 days).

Two patients had myelopathic symptoms related to treatments administered before the transplantation procedure (postradiation therapy thoracic myelopathy and cauda equina syndrome after intrathecal chemotherapy) that worsened after the conditioning regimen. One patient had acute postinfectious longitudinally extensive myelitis following disseminated adenovirus infection, which rapidly led to respiratory failure and death. Two patients had mild paraparesis with pyramidal signs and sensory cordonal ataxia due to combined spinal degeneration of unknown cause (abnormal somatosensory evoked potentials with normal nerve conduction, MRI spinal imaging, and metabolic studies). Three patients (60%) died within the first 60 days after diagnosis owing to concomitant complications.

PNS Involvement

We found 48 NCs involving PNS, which accounted for 32% of all NCs at a median of 101 days after transplantation (range, 5 days before to 3722 days after). The cumulative incidence risk of PNS complications was 1.5% at 30 days, 3.4% at 1 year, and 4.2% at 5 years. PNS complications are classified according to etiology in Table 4.

Peripheral Neuropathy. Peripheral neuropathy was diagnosed in 25 patients, including 12 (48%) UCB allo-HSCT recipients, 11 (44%) MSD allo-HSCT recipients, 1 (4%) MUD allo-HSCT recipient, and 1 (4%) haploidentical donor allo-HSCT recipient. The median time to onset of peripheral neuropathy

Table 4
Classification of PNS NCs According to Etiology (N = 48)

NC	n (%)
Toxicity	26 (54)
Polyneuropathy	11 (23)
Glucocorticoid-induced myopathy	15 (31)
Immune-mediated	8 (17)
Acute neuropathy - Guillain Barré Syndrome	4 (8) 2
Neuromyotonia	1 (2)
Myositis	2 (4)
Myasthenia gravis	1 (2)
Critical illness-related	14 (29)
Neuropathy	9 (19)
Myopathy	5 (10)

was 167 days (range, 5 to 3722 days). The 5-year cumulative incidence of peripheral neuropathy was 2.5%.

Four patients had an acute immune-mediated neuropathy. Two patients developed Guillain-Barré syndrome at days +50 and +346 after UCB allo-HSCT, 1 of them as a probable postinfectious neuropathy after CMV reactivation. They presented with CSF albumin-cytologic dissociation, and their electrophysiological study data met the criteria for demyelinating polyradiculoneuropathy. They were treated with intravenous immunoglobulin and fully recovered. We registered a third case of acute sensory-motor polyneuropathy (PNP) in a patient at 6 months after MSD allo-HSCT. This patient did not improve after treatment with i.v. immunoglobulins. The fourth patient developed a multifocal sensory neuropathy 8 years after MSD allo-HSCT. The origin was considered immune, related to his chronic GVHD, once MRI, CSF studies, and electrophysiological studies ruled out other causes. This patient improved clinically after treatment with i.v. immunoglobulins. Another patient was diagnosed at 10 years after MSD allo-HSCT with neuromyotonia with cramp-fasciculation syndrome in the context of extensive chronic GVHD. This patient improved after rituximab was added to his immunosuppressive treatment.

Three patients developed severe subacute sensory ataxic neuropathy, 2 of them in concert with bilateral optic neuropathy. After extensive studies, the origin was considered toxic in 2 of the 3 (tacrolimus in 1, cyclosporine and isoniazide in the other), and outcomes were poor despite withdrawal of the offending drugs. In the third patient, who had no optic nerve involvement, the etiology was not evident. Eight patients developed mild sensory motor axonal PNP, 6 of them after the conditioning regimen, and 3 patients suffered from moderate to severe critical illness sensory-motor axonal PNP. Unilateral or bilateral mononeuropathies of peroneal nerves were detected in 6 patients, associated with critical illness and severe weight loss.

Two patients died because of progression of the neuropathy and other 12 patients died from concomitant complications, at a median time from diagnosis of 43 days (2-1180).

Myopathies and Neuromuscular Junction Disorders. Myopathy was diagnosed in 23 patients. The median time to diagnosis was of 95 days after allo-HSCT (range, 5 days before to 1464 days after). The 5 year cumulative incidence of myopathy was 2.4%. Fifteen patients (65%) presented with glucocorticoid-induced myopathy; 7 of these patients underwent a complete study with EMG, and 1 patient underwent muscle biopsy, which revealed atrophy of muscle fibers in the absence of inflammatory infiltrate and necrosis. All 15 patients were receiving steroid treatment with a minimum dose of 20 mg/day. Five patients (22%) had critical illness myopathy.

Two patients (9%) developed myositis at days +90 and +100 after MSD allo-HSCT. Both of them had chronic extensive GVHD, and deltoid muscle biopsy revealed dermatomyositis-like histological abnormalities. One of these patients also developed cramp-fasciculation syndrome with neuromyotonic discharges on EMG. Another patient developed myasthenia gravis with anti-acetylcholine receptor antibodies in the setting of cGVHD at 2 years after MSD allo-HSCT.

Analysis of Risk Factors for Neurologic Events

Multivariable analyses identified the use of an alternative donor (ie, UCB, MUD, or haploidentical) (hazard ratio [HR], 1.7; 95% confidence interval [CI], 1.12 to 2.3; $P = .009$), age >40 years (HR, 1.6; 95% CI, 1.1 to 2.7; $P = .009$), acute GVHD grade II-IV (HR, 3.3; 95% CI, 2.2 to 5; $P < .00001$), and extensive chronic GVHD (HR, 3.2; 95% CI, 1.7 to 5.9; $P = .0002$) as risk factors for developing NCs.

The 5 year cumulative incidence of NCs was 10.8% (95% CI, 8% to 14%) in MSD allo-HSCT recipients and 15.3% (95% CI, 12% to 18.5%) in alternative donor allo-HSCT recipients ($P = .004$) (Figure 1). The 5 year cumulative incidence of NCs was 10.5% (95% CI, 8% to 13.2%) in patients age <40 years and 15.8% (95% CI, 13% to 19%) in older patients ($P = .02$) (Figure 2).

Regarding risk factors for encephalopathy, multivariable analysis identified the use of a fludarabine-containing conditioning regimen (HR, 2.9; 95% CI, 1.2 to 3.8; $P < .004$) and age >40 years (HR, 2; 95% CI, 1.1 to 4; $P = .04$) were independently associated with a higher risk of developing this complication. No significant risk factors were associated with the remaining types of NCs.

Survival. A semi-landmark analysis revealed a 5-year OS of 21% for patients who developed NCs and 41% for those without NCs ($P < .0001$; Figure 3). This statistically significant difference in OS was due to a lower OS in recipients with CNS NCs ($P = .001$), whereas patients who developed PNS NCs had similar OS (32%) as those without NCs ($P = .40$).

The 5-year OS according to the type of NC were stroke, 7%; isolated seizures, 17%; headache, 39%; encephalopathy, 14%; myelopathy, 33%; PRES, 67%; myopathy, 34%; and peripheral neuropathy, 39% ($P < .012$).

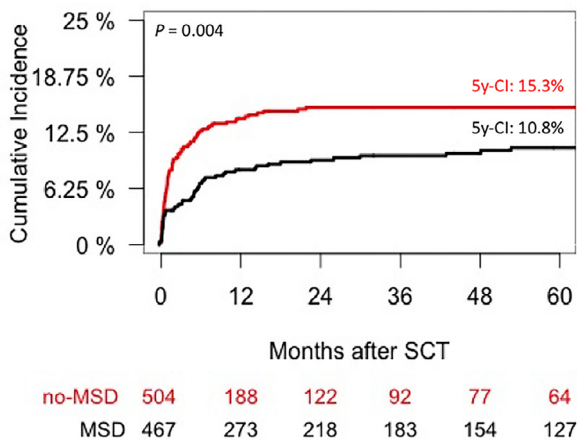

Figure 1. Cumulative incidence of NCs according to the type of transplantation: MSD allo-HSCT or alternative donor (no-MSD) allo-HSCT.

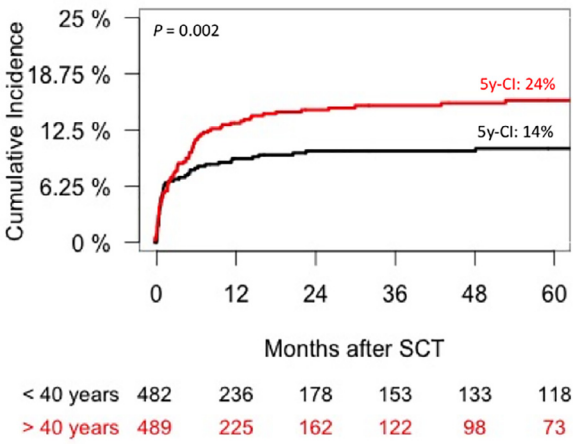

Figure 2. Cumulative incidence of NCs according to recipient age.

DISCUSSION

This study shows that NCs are relatively common in patients undergoing allo-HSCT. NCs were more frequent in recipients of allo-HSCT from an alternative donor, patients age >40 years, and patients who developed GVHD. CNS NCs, but not PNS NCs, were associated with poor OS.

The rate of NCs in our study (7.5% at 3 months and 13% at 5 years after allo-HSCT) is within the wide range reported previously [4,7,8,23,24]; however, comparisons across studies are difficult owing to the heterogeneity of patient and transplantation characteristics, definitions of neurologic events, and duration of follow-up. In this study, we only considered primary NCs occurring after allo-HSCT, excluding NCs due to CNS infection, as reported previously [6], and NCs due to relapse of the baseline disease. We did not consider preexisting NCs, except for 2 patients who experienced dramatic worsening of a previous myelopathy. Since a previous history of headache was not available for some patients, we cannot rule out a possible estimation of this specific event.

Despite the limitations inherent to the study's retrospective nature, this single-center study included a large series of patients who received a relatively homogeneous conditioning regimen, supportive care, and management of clinical complications, including NCs. One aim of this study was to evaluate NCs according to donor source. We found an increased rate of NCs after transplantation from an alternative donor (UCB, MUD, or haploidentical) compared with an MSD. There is scant published data on the impact of donor source on the incidence of NCs, and all available studies also included infectious complications [9,23-25], which have been classically more frequent after allo-HSCT with an alternative donor [26,27]. It is very likely that the higher incidence of NCs in this setting is associated with the higher rates of morbidity, transplant-related mortality (MRT), and GVHD that characterizes HSCT from alternative donors, with the consequent increase in the use of potentially neurotoxic drugs. In line with this interpretation, we found an association between grade II-IV aGVHD and extensive cGVHD and NCs. Apart from the increased use of potentially neurotoxic drugs as noted above, GVHD can be involved in immunologic-based complications affecting PNS, as reported elsewhere [22].

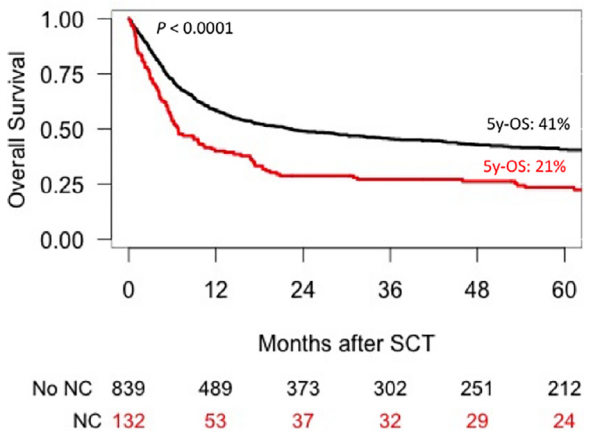

Figure 3. OS in patients with NCs and without NCs.

Regarding the frequency of the different complications, we detected a higher incidence of PNS NCs (32% of all NCs) than in other studies [7,8], likely due to the delayed onset of PNS events and the longer duration of follow-up in our study.

Encephalopathy has previously been reported as an important cause of NCs [1] and was the most common NC (31%) seen in the present study. We did not observe any severe neurotoxicity directly attributed to fludarabine [28], but we found that the use of a fludarabine-based conditioning regimen and older age were associated with an increased risk of encephalopathy. This finding is especially relevant because fludarabine has replaced cyclophosphamide in many conditioning regimens [29] and is a recognized factor associated with neurotoxicity [30,31]. In fact, there is evidence supporting the hypothesis that fludarabine neurotoxicity is due to an abnormal synaptic function determined by cross-talk with adenosine A1 receptors within nervous tissues [32]. Because fludarabine-containing regimens are considered standard of care for allo-HSCT, neurotoxicity is an uncommon but possible adverse event [28,31], particularly in older patients.

In our patients, a number of CNS complications were attributed, at least in part, to cyclosporine A, such as headache, seizures, encephalopathy, and PRES. Contrary to other studies [23], we did not detect a negative effect of PRES on OS. Earlier recognition of this and prompt replacement of the suspicious drugs for GVHD prophylaxis could have been helpful in PRES management. Because most of our patients (>90%) received cyclosporine as GVHD prophylaxis, the use of CNI as a risk factor for NCs could not be analyzed.

An interesting finding is the high rate of immune-mediated PNS complications (17% of all PNS events), which have been previously reported in the literature as isolated cases [34-36]. We found 2 cases of Guillain-Barré syndrome that responded to i.v. immunoglobulin treatment. We also diagnosed 2 patients with myositis out of 22 patients developing myopathy, mostly steroid-induced myopathy. Because treatment strategies are the opposite (tapering steroids versus adding more immunosuppressive treatment), in a given patient with limb girdle muscle weakness, a clinical evaluation by a neurologist should be performed together with nerve conduction studies/EMG. Skeletal MRI and muscle biopsy are helpful in selected cases. Regarding myasthenia gravis, this uncommon NC has been documented in the literature as isolated case reports [37] in patients with other manifestations of chronic GVHD, like our patient. More controversial are the CNS manifestations of chronic GVHD [33,38]. We did not find any case of GVHD affecting CNS, but because our current understanding of this complication is incomplete, patients could have been underdiagnosed.

In agreement with previous reports [3,8,23], patients who developed NCs after SCT had a high mortality rate. However,

only those NCs affecting the CNS had a negative impact on survival.

In conclusion, NCs are a significant and diverse clinical problem after allo-HSCT. Deeper knowledge of the clinical presentation, timing, and risk factors of different NCs can guide clinical practice by implementing preventing strategies and paying close attention to these patients for early recognition and intervention.

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