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# Neurologic Complications of the Central Nervous System after Allogeneic Stem Cell Transplantation: The Role of Transplantation-Associated Thrombotic Microangiopathy as a Potential Underreported Cause

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A B S T R A C T

Neurologic complications (NCs), especially those of the central nervous system (CNS), represent a severe complication after allogeneic stem cell transplantation (allo-HSCT) and are associated with relevant morbidity and mortality. We aimed to characterize the potential risk factors for the development of CNS-NC, with a special focus on the role of calcineurin inhibitors (CNIs) as a predisposing factor. For this purpose, we compared cyclosporin A (CsA) versus tacrolimus (TAC) with respect to their influence on the incidence and type of CNS-NC after allo-HSCT. We retrospectively analyzed the incidence, risk factors, and impact on outcomes of CNS-NC diagnosed during the post-transplantation follow-up in patients with different high-risk hematologic malignancies who underwent allo-HSCT at our institution over a 20-year period. All patients included in the analysis received CNI (CsA or TAC) as graft-versus-host disease (GVHD) prophylaxis. We evaluated a total of 739 consecutive patients who underwent transplantation between December 1999 and April 2019. During a median follow-up of 6.8 years, we observed a CNS-NC incidence of 17%. The development of CNS-NC was associated with decreased overall survival (OS) and increased transplantation-related mortality (TRM). The most frequent CNS-NCs were infections (30%) and neurologic adverse events related to the administration of CNI, TAC, or CsA as GVHD prophylaxis (42%). In the multivariable analysis, age, total body irradiation (TBI), and severe acute GVHD and chronic GVHD were significant risk factors in the development of CNS-NCs. TAC compared with CsA emerged as an independent predisposing factor for CNS-NCs. The TAC-associated risk of CNS-NCs was related mostly to the occurrence of transplantation-associated thrombotic microangiopathy (TA-TMA) with neurologic manifestations (neuro-TA-TMA), although the general TA-TMA incidence was comparable in the 2 CNI subgroups. CNS-NCs are associated

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with poor prognosis after allo-HSCT, with TAC emerging as a potential yet insufficiently characterized predisposing factor.



## INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HSCT) is a potentially curative treatment for patients with high-risk hematologic malignancies. The outcomes of allo-HSCT are influenced by transplantation-related mortality (TRM), which accounts for at least 20% of the overall mortality by 3 years after transplantation [1,2]. The introduction of less-toxic conditioning regimens and improvements in supportive care have permitted the extension of allo-HSCT to fragile elderly recipients, who are more prone to develop post-transplantation complications [3,4]. Neurologic complications (NCs), especially those of the central nervous system (CNS-NCs), are associated with relevant rates of morbidity and mortality, as described in previous different retrospective and prospective observational studies and literature meta-analyses [5–11]. Such complications are highly variable in both incidence (ranging from 3% to 44%) and severity (ranging from mild transient disorders to serious illnesses) [5–12].

Categories of CNS-NCs can be identified based on the underlying cause: infectious, metabolic, cerebrovascular, immune-mediated, and drug-related CNS-NCs. Together with infections, drug-related complications account for the majority of CNS-NCs after allo-HSCT [11,13,14]. Immunosuppressive drugs, especially the calcineurin inhibitors (CNIs) cyclosporine A (CsA) and tacrolimus (TAC), the most commonly used immunosuppressive agents in the prophylaxis of graft-versus-host disease (GVHD), play an important role in drug-related NCs. NCs are reported in 25% to 59% of allo-HSCT recipients treated with CNIs [15], second only to their renal side effects. The observed effects can involve both the CNS and peripheral nervous system and range from action tremor and headache to serious encephalopathy [15,16]. CNI therapy reportedly induces posterior reversible encephalopathy syndrome (PRES) in 6% to 9% of allo-HSCT recipients [17].

Simultaneously, transplantation-associated thrombotic microangiopathy (TA-TMA) in patients receiving CNIs has been detected at an incidence ranging from 0 to 64% [18,19], with 30% of these cases associated with neurologic alterations (neuro-TA-TMA) [20]. Previous studies have emphasized the role of CNIs in determining NC risk in the post-transplantation setting [21–23], but no direct comparisons of neurotoxicity between TAC and CsA are available. Given the fundamental role of CNIs in GVHD prophylaxis, a better understanding of potential underlying and avoidable risk factors and a comparison of the "neurologic tolerability" of CsA and TAC are crucial.

In this single-center retrospective analysis, we aimed to describe the spectrum of CNS-NC that can arise after allo-HSCT and their impact on overall survival (OS). Another relevant endpoint was the identification of potential risk factors for the development of CNS-NCs, with a special focus on the role of immunosuppression.

## METHODS

### *Data Collection and Eligibility Criteria*

This retrospective study included consecutive patients undergoing allo-HSCT for different hematologic diseases between December 1999 and April 2019 at the Adult Bone Marrow Transplantation Unit of the Ulm University Hospital. The study was approved by the local Ethics Committee of the University of Ulm, and all participants provided written informed consent for the pseudo-anonymous analysis of the data.

Inclusion criteria were (1) confirmed diagnosis of a hematologic disease, malignant or nonmalignant, with an indication for allo-HSCT; (2) adult (age $\geq$18 years); (3) first allo-HSCT using a sibling donor (SIB), matched unrelated donor (MUD), or mismatched related donor (MMRD); and (4) GVHD prophylaxis with a CNI (CsA or TAC). Considering the retrospective nature of the analysis, there was no randomization between CsA and TAC. CsA was the predominant CNI used during the first 10 years of the study period, and TAC was preferentially used in the most recent period, especially following the publication of Center for International Blood and Marrow Transplant Research (CIBMTR) data suggesting potentially greater immunosuppressive power for TAC compared to CsA [24,25]. During both periods, the alternative CNI was used if required by a study protocol or by intolerance of the primary drug. All

CNS-NCs observed during the post-transplantation follow-up were documented in our local clinical database and could be collected for analysis in the present study. Patients who underwent allo-HSCT with CNIs as GVHD prophylaxis without developing CNS-NCs were considered "negative controls." Patients with CNS-NCs occurring exclusively before the start of conditioning were also included in the group of negative controls with a preexisting CNS condition. These events were evaluated as potential risk factors for the development of CNS-NCs in the post-transplantation follow-up.

### *Definitions*

The intensity of conditioning was evaluated as a potential risk factor for the development of NCs. Myeloablative conditioning (MAC), nonmyeloablative conditioning (NMA), and reduced-intensity conditioning (RIC) were defined as described previously [26,27]. Neutrophil engraftment was defined as the first of 3 consecutive days with a neutrophil count $\geq .5 \times 10^9$/L. The staging of acute GVHD (aGVHD) was performed according to 1994 Consensus Conference on Acute GVHD Grading [28], and chronic GVHD (cGVHD) was graded according to the National Institutes of Health IH Consensus Criteria [29,30]. Because of missing values, a comprehensive evaluation of the GVHD severity score was possible only for aGVHD. All patients underwent a pretransplantation evaluation of organ function. Comorbidity scores, such as the Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI) and the European Society for Blood and Marrow Transplantation (EBMT) risk score were calculated as described previously [31,32].

### *Classification of CNS Complications*

The development of neurologic symptoms during the post-transplantation follow-up triggered a standardized comprehensive workup including neurologic examination, neuroimaging (computed tomography scan and/or magnetic resonance imaging), electroencephalography, and lumbar puncture. Brain biopsies were performed only in selected patients with isolated lesions on neuroimaging and an otherwise uninformative routine workup. Six different categories of CNS-NCs were evaluated, defined as follows: (1) CNS infections presenting with typical symptoms plus characteristic neuroimaging findings and/or the identification of pathogens by PCR or culture of cerebrospinal fluid (CSF); (2) cerebrovascular events, both hemorrhagic and ischemic, defined by clinical presentation and confirmed by neuroimaging; (3) metabolic encephalopathy, defined as a change in mental status attributable to renal or liver failure, respiratory insufficiency, sepsis, or electrolyte imbalance; (4) secondary CNS malignancies, usually confirmed histologically; and (5) CNI-related complications, representing a wide spectrum of conditions including (a) CNI intolerance, defined as hallucinations, confusion, headache, and tremor with normal neuroimaging and normal CSF concomitant to the initiation of CNI assumption, but also (b) seizures, (c) PRES diagnosed based on the typical clinical and MRT findings, and (d) TA-TMA with neurologic involvement (neuro-TA-TMA).

Systemic TMA was defined by the EBMT consensus criteria until 2014 [33], and the Jodele criteria were applied thereafter [18]. These criteria supported the introduction in clinical practice of the quantitative determination of complement activation, especially via SC5b-9 both in serum and in urine, as diagnostic support in case of suspected TA-TMA, as well as the introduction of proteinuria as an early sign of renal damage. Neuro-TA-TMA was then defined as the concomitant occurrence of TA-TMA according to the established diagnostic criteria with neurologic symptoms of the CNS without evidence of other CNS disease [18,33]. The last category was (6) cGVHD of the CNS, defined as the presence of neurologic symptoms with inflammatory changes in the CSF, evidence of chronic GVHD in other target organs, and the exclusion of other potential causes [13]. Rare or infrequently reported CNS-NCs not falling into the aforementioned categories (eg, chemotherapy-induced NCs) were grouped into a general category designated "other complications."

### *Statistical Analysis*

The first part of our analysis provided a descriptive statistical overview of each variable. Median values and respective ranges were calculated. Survival rates were calculated using the Kaplan-Meier method. The median follow-up was calculated using the inverse Kaplan-Meier method by Schemper and Smith [34]. Survival curves were compared by the log-rank test, and a Cox proportional hazards model was used to assess the effect of possible prognostic factors on OS. TRM, disease-related mortality (DRM), and onset of CNS complications were treated as and competing risk endpoints, which were assessed using the Aalen-Johansen estimator for cumulative incidence, Gray's test, and cause-specific Cox proportional

hazards models. In the analysis of onset of CNS complications, only the first occurrence was considered the event of interest.

Multivariate analysis performed to evaluate potential prognostic factors for the aforementioned endpoints (OS, TRM, DRM, and onset of CNS complications) considered the following covariates: age at the time of transplantation, sex, EBMT risk score, HCT-CI score, previous auto-HSCT, preexisting CNS-NC, use of antithymocyte globulin (ATG), donor type, donor source, conditioning regimen, TBI, engraftment, occurrence of aGVHD and cGVHD, severity grade of aGVHD, and CNI prophylaxis (TAC or CsA). The underlying disease, such as acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, multiple myeloma, myeloproliferative neoplasm, and non-Hodgkin lymphoma, and disease status at the time of transplantation (complete remission, partial response, progressive disease, unknown) were considered stratum variables. Effect estimates were reported as hazard ratio (HR) with 95% confidence interval (CI).

Statistical analysis was performed with R version 3.6.3 and R packages survival 3.1-8, cmprsk 2.2-9, prodlim 2019.11.13, survminer 0.4.6, and dplyr 0.8.5.

## RESULTS

### *Patient Characteristics*

A total of 739 of 1120 (67%) consecutive patients with a diagnosis of high-risk hematologic disease underwent allo-HSCT and received GVHD prophylaxis with CNI at the adult Bone Marrow Transplantation Unit of the Department of Internal Medicine III, Ulm University Hospital between December 1999 and April 2019. Of the 739 patients 129 (17%) developed 1 or more complications involving the CNS. The median follow-up of surviving patients was 6.8 years after transplantation (range, 41 days to 19 years). Prior to transplantation, a neurologic disorder or condition was detected in 81 of the 739 patients (11%). In these 81 patients, CNS involvement of the underlying disease (n = 28; 35%), vascular events (n = 13; 16%), seizures (n = 10; 12%), infectious and/or inflammatory encephalopathy (n = 9; 11%), migraine (n = 8; 10%), metabolic encephalopathy (n = 5; 6%), and CNS neoplasm (n = 3; 4%) were the most common disorders. All patients in this analysis had undergone their first allo-HSCT. Patient, disease, and transplantation characteristics are summarized in Table 1.

Two subgroups were analyzed according to the type of CNI used as GVHD prophylaxis, CsA or TAC. The 2 groups were comparable with respect to sex, disease status at transplantation, stem cell source (peripheral blood stem cells versus bone marrow BM), comorbidity profile (EBMT risk score), and incidence of preexisting CNS conditions before allo-HSCT. However, compared to patients in the CsA group, patients in the TAC group had a higher median age and more frequently received MAC conditioning, as well as TBI and ATG (Table 1).

### *Neurologic Complications after Allo-HSCT: Type and Incidence*

A total of 152 CNS-NCs were documented in 129 patients (median, 1 episode per patient; range, 1 to 3). The complications were divided into 2 categories: CNI-associated CNS-NCs, such as CNI intolerance, seizures, PRES, and TA-TMA, and non-CNI-associated CNS-NCs, encompassing CNS infections, metabolic encephalopathy, both ischemic and hemorrhagic cerebrovascular events, secondary CNS neoplasm, and CNS cGVHD. Among the 152 episodes, CNI-associated CNS-NCs were most frequently observed (n = 64; 42%), followed by infections (n = 46; 30%) and vascular complications (n = 20; 13%). Overall, the median time from transplantation to the onset of CNS-NCs was 133 days (range, 1 to 4907 days). CNI-associated CNS-NCs were detected earlier compared to non-CNI-related CNS-NCs (median, 104 days [range, 1 to 849 days] versus 155 days [range, 1 to 4907 days]). Among the non-CNI-associated CNS-NCs, CNS infections were by far the most common (46 of 88; 52%). The most frequently detected pathogens were viruses (HHV-6, HSV-1 and -2, VZV), *Toxoplasma gondii*, and fungi such as *Aspergillus* and *Mucorales*. Metabolic encephalopathy was diagnosed in only 9 cases (6% of all episodes). The frequencies of NCs due to secondary neoplastic diseases of the CNS (n = 3; 2% of all episodes) or CNS cGVHD (n = 3; 2% of all episodes) was even lower (Figure 1). Among the 152 CNI-associated complications, CNI intolerance was detected in 22 cases, accounting for 14% of all episodes and for 34% of all CNS-NCs considered CNI-related. Most frequently, such clinical alterations developed as a consequence of elevated CNI blood levels. Seizures were observed in 11 of the 152 cases (7%); PRES, in 6 cases (4%). A relatively high proportion of patients developed TA-TMA with concomitant neurologic involvement; the 25 episodes represented 16% of the post-transplantation neurologic events and 39% of the CNI-associated complications.

**Table 1**
Patient, Disease, and Transplantation Characteristics

| Characteristic | All Patients | CsA Prophylaxis Group | TAC Prophylaxis Group | *P* Value |
|---|---|---|---|---|
| Patients, n (%) | 739 | 417 (56) | 322 (44) | |
| Age, yr, median (range) | 52 (18-75) | 51 (41-57) | 56 (45-63) | **<.001** |
| Sex, n (%) | | | | |
| Female | 281 (38) | 161 (39) | 120 (37) | .8 |
| Male | 458 (62) | 256 (61) | 202 (63) | |
| Diagnosis, n (%) | | | | |
| AML | 234 (31) | 138 (33) | 96 (30) | **.004** |
| ALL | 87 (12) | 52 (12) | 35 (11) | |
| MDS | 93 (13) | 37 (8.9) | 56 (17.5) | |
| MPN | 95 (13) | 49 (12) | 46 (14) | |
| MM | 84 (12) | 59 (14) | 25 (7.8) | |
| NHL | 121 (16) | 69 (17) | 51 (16) | |
| Other | 25 (3) | 13 (3.1) | 13 (3.7) | |
| Disease status at allo-HSCT, n (%) | | | | |
| CR/PR | 598 (81) | 343 (83) | 255 (79) | .2 |
| PD | 136 (19) | 69 (17) | 67 (21) | |
| Unknown | 5 | 5 | 0 | |
| EBMT risk score, median (range) | 3 (0-5) | 4 (3-5) | 3 (0-5) | .5 |
| Previous auto-HSCT, n (%) | 131 (18) | 85 (20) | 46 (14) | **.04** |
| Preexisting CNS condition, n (%) | 81 (11) | 42 (10) | 39 (12) | .4 |
| Donor type, n (%) | | | | |
| Sibling | 239 (32) | 153 (36.5) | 86 (27) | **<.001** |
| MUD | 485 (66) | 262 (63) | 223 (69) | |
| Haploidentical | 15 (2) | 2 (.5) | 13 (4) | |
| Donor source, n (%) | | | | |
| BM | 24 (3) | 400 (96) | 315 (98) | .2 |
| PBSCs | 715 (97) | 17 (4) | 7 (2) | |
| Conditioning regimen, n (%) | | | | |
| MAC | 404 (55) | 198 (47) | 206 (64) | **<.001** |
| RIC/NMA | 335 (45) | 219 (53) | 116 (36) | |
| TBI, n (%) | | | | |
| None | 468 (63) | 235 (56) | 233 (72) | **<.001** |
| Low-intermediate (2-8 Gy) | 124 (17) | 82 (20) | 42 (13) | |
| High (12 Gy) | 147 (20) | 100 (24) | 47 (15) | |
| ATG, n (%) | 435 (59) | 230 (55) | 205 (64) | **.024** |

P values were calculated using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Bold type indicates statistical significance.
AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma; CR, complete remission; PR, partial remission; PD, progressive disease; PBSCs, peripheral blood stem cells.

Twenty of the 25 cases of Neuro-TA-TMA (80%) occurred in patients receiving TAC as GVHD prophylaxis (Figure 1). Indeed, the 1-year cumulative incidence of Neuro-TA-TMA was significantly higher in the TAC group compared to the CsA group (6.26% [95% CI, 3.6% to 8.92%] versus 1.44% [95% CI, .29% to 2.59% for CsA]; $P < .001$). This significantly higher incidence of Neuro-TA-TMA as the underlying cause of CNS-NCs in the TAC group was an unexpected finding.

To better understand these findings, we performed a descriptive analysis to analyze the overall incidence of TA-TMA in our entire cohort of transplant recipients, independent of the development of neurologic manifestations. Owing to changes in the diagnostic criteria for TA-TMA in 2014, including proteinuria and complement

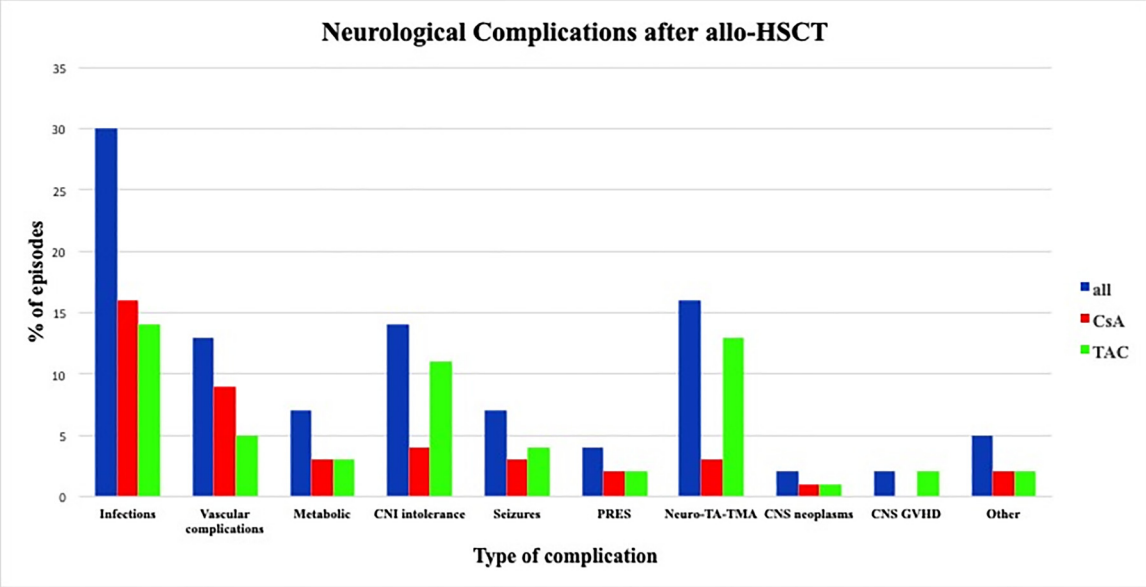


**Figure 1.** Characterization and incidence of neurologic complications after allo-HSCT. Blue bars indicate episodes occurring in the entire study population, red indicates episodes occurring in patients undergoing GVHD prophylaxis with CsA, and green indicates episodes occurring in patients undergoing GVHD prophylaxis with TAC

activation, aimed at potentially allowing the detection of oligosymptomatic cases of TA-TMA, we chose to comprehensively assess TA-TMA frequency by splitting the observational interval into 2 separate periods, before and after this change [18,33]. During the first period, 1999 to 2014, the 1-year cumulative incidence of TA-TMA in our cohort of consecutive transplantation recipients (first allo-HSCT only) receiving CNI as GVHD prophylaxis was 3.06% (95% CI, 1.54% to 4.59%). In this period, we observed a significantly higher 1-year cumulative incidence of TA-TMA in the TAC group compared to the CsA group (6.61% [95% CI, 2.43% to 10.19%] versus 1.69% [95% CI, .03% to 3.04%]; $P < .001$). When applying the new and more sensitive diagnostic criteria from Jodele et al. [18] starting in 2015, the 1-year cumulative incidence of TA-TMA overall increased to 13% (95% CI, 8.83% to 17.3%), with no significant difference between the 2 CNI groups (8.07% [95% CI, 1.29% to 14.9%] for CsA versus 14.71% [95% CI, 9.59% to 19.8%] for TAC; $P = .246$).

### *Impact of Neurologic Complications on OS*

In univariate analysis, the development of CNS-NCs had an adverse impact on outcomes (HR, 4.62; $P < .001$). This was true for all categories of CNS-NCs except CNI intolerance.

In the multivariable analysis, the development of CNS-NCs was seen to exert a negative impact on OS by significantly increasing the TRM (HR, 5.37; $P < .001$). Other factors negatively affecting OS were male sex (HR, 1.34; $P = .007$), higher HCT-CI (1-point increase: HR, 1.19; $P < .001$), higher EBMT risk score (1-point increase: HR, 1.13; $P = .052$), preexisting CNS condition (HR, 1.48; $P = .016$), previous auto-HSCT (HR, 2.15; $P < .001$), aGVHD (grade III-IV versus none: HR, 3.18 [$P < .001$]; grade I-II versus none: HR, 1.11 [$P = .4$]), cGVHD (HR, 1.33; $P = .020$), and bone marrow as the stem cell source (HR, 1.76; $P = .044$). The use of ATG and use of TAC (instead of CsA) emerged as protective factors for OS (HR, .76; $P = .034$) (Table 2). In the multivariable analysis, TAC showed a positive impact on TRM (HR, .76; $P = .024$).

### *Risk Factors for the Development of NCs after Allo-HSCT*

Our multivariable analysis identified relevant factors that could potentially predispose to the development CNS-NCs after allo-HSCT, including advanced age, use of TBI at any dose in the conditioning regimen, severe aGVHD (grade III-IV), and cGVHD of any severity. Furthermore, the use of TAC for GVHD prophylaxis significantly increased the risk of CNS-NCs compared to the use of CsA (HR, 1.81; $P = .007$) (Table 3).

## DISCUSSION

In this large single-center study, we retrospectively analyzed more than 700 patients over a 20-year period for the development of neurologic adverse effects. The most relevant findings of our analysis can be summarized as (1) CNS-NCs are common (incidence, 17%) and negatively impact

**Table 2**
Multivariable Analysis of Factors Influencing OS after Allo-HSCT

| Variable | HR | 95% CI | *P* Value |
|---|---|---|---|
| Age at allo-HSCT | 1 | .99-1.01 | .8 |
| Sex | | | |
| Female | - | - | |
| Male | 1.34 | 1.08-1.67 | **.007** |
| EBMT risk score | 1.13 | 1.00-1.28 | **.052** |
| HCT-CI score | 1.19 | 1.09-1.28 | <**.001** |
| Previous auto-HSCT | 2.15 | 1.40-3.28 | <**.001** |
| Preexisting CNS condition | 1.48 | 1.08-2.03 | **.016** |
| Donor type | | | |
| Sibling | - | - | |
| MUD | 1.12 | .87-1.45 | .4 |
| Haploidentical | .89 | .40-1.97 | .8 |
| Donor source | | | |
| PBSCs | - | - | |
| BM | 1.76 | 1.01-3.07 | **.044** |
| Conditioning regimen | | | |
| MAC | - | - | |
| RIC/NMA | .99 | .77-1.28 | >.9 |
| TBI | | | |
| None | - | - | |
| Low-intermediate (2-8 Gy) | 1.07 | .77-1.50 | .7 |
| High (12 Gy) | .98 | .66-1.46 | >.9 |
| ATG | .76 | .58-.98 | **.034** |
| GVHD prophylaxis | | | |
| CsA | - | - | |
| TAC | .76 | .60-.96 | **.024** |
| Engraftment | .11 | .07-.18 | <**.001** |
| aGVHD | | | |
| None | - | - | |
| Grade I-II1-2 | 1.11 | .89-1.40 | .4 |
| Grade III-IV | 3.18 | 2.29-4.42 | <**.001** |
| cGVHD (any grade) | 1.33 | 1.05-1.68 | <**.001** |
| CNS complications after allo-HSCT | 5.37 | 4.09-7.04 | <**.001** |

*P* values were calculated using the Cox proportional hazards model. Bold type indicates statistical significance.

OS; (2) Neuro-TA-TMA is a frequent potential cause of CNS-NCs after allo-HSCT; (3) TAC is a major risk factor for CNS-NCs, along with age, TBI, and severe a GVHD and cGVHD; (4) the TAC-associated increase in CNS-NC risk is related mostly to Neuro-TA-TMA; and (5) the use of TAC as GVHD prophylaxis still improves OS by reducing TRM.

The overall incidence of NCs and the important role of CNIs and infections as causes of NCs are consistent with previous studies [5-11,14,21-24]. This is also true for some of the risk factors for the development of CNS-NCs that were identified as such in the present analysis, including age [9], TBI, and severe GVHD [8,24]. Our study also confirms the major impact of CNS-NCs on TRM and OS [5–11]. The prominent role of TAC as a risk factor for CNS-NCs, especially correlated with a higher incidence of TA-TMA with neurologic manifestations, was unexpected. We hypothesize that in previous studies, Neuro-TA-TMA might have been classified as either encephalopathy or seizures and consequently possibly underestimated.

These differences in assessing the role of TA-TMA reflect the difficulty in properly diagnosing TA-TMA and the use of different diagnostic criteria, even with a recent international effort to standardize screening and diagnostic procedures for identifying TA-TMA after allo-HSCT by introducing the harmonization criteria [35]. To verify our findings, we retrospectively determined the

**Table 3**
Multivariable Analysis of Factors Influencing the Development of CNS-NCs after Allo-HSCT

| Variable | HR | 95% CI | *P* Value |
|---|---|---|---|
| Age at allo-HSCT | 1.03 | 1.01-1.05 | **.002** |
| Sex | | | |
| Female | - | - | |
| Male | .64 | .45-.93 | **.018** |
| EBMT risk score | 1.14 | .91-1.44 | .3 |
| HCT-CI score | .93 | .77-1.14 | .5 |
| Previous auto-HSCT | 1.13 | .56-2.32 | .7 |
| Preexisting CNS condition | 1.21 | .56-2.31 | .7 |
| Donor type | | | |
| Sibling | - | - | |
| MUD | 1.5 | .94-2.41 | .09 |
| Haploidentical | 1.32 | .44-4.02 | .6 |
| Donor source | | | |
| PBSC | - | - | |
| BM | .19 | .03-1.50 | .12 |
| Conditioning regimen | | | |
| MAC | - | - | |
| RIC/NMA | .78 | .47-1.30 | .3 |
| **TBI** | | | |
| None | - | - | |
| Low-intermediate (2-8 Gy) | 2.21 | 1.18-4.14 | **.013** |
| High (12 Gy) | 3.29 | 1.72-6.28 | <**.001** |
| ATG | .8 | .48-1.34 | .4 |
| GVHD prophylaxis | | | |
| CsA | - | - | |
| TAC | 1.81 | 1.18-2.78 | **.007** |
| Engraftment | .45 | .14-1.47 | .2 |
| aGVHD | | | |
| None | - | - | |
| Grade I-II | 1.47 | .95-2.27 | .082 |
| Grade III-IV | 3.4 | 1.84-6.28 | <**.001** |
| cGVHD (any grade) | 2.01 | 1.20-3.36 | **.008** |

*P* values were calculated using the Cox proportional hazards model. Bold type indicates statistical significance.

incidence of TA-TMA in 2 time periods, 1999 to 2014 and 2015 to 2019, using the TA-TMA diagnostic criteria in use during these periods and compared the impact of TAC and CsA on the incidence and clinical manifestations of TA-TMA [18,33]. The 1-year cumulative incidence of TA-TMA of 3.06% (95% CI 1.54-4.59%) in 1999 to 2014 is consistent with the literature [36,37]. The higher 1-year cumulative incidence of 13% (95% CI, 8.83% to 17.3%) in 2015 to 2019 reflects the use of the more sensitive Jodele criteria [18] and is similar to previously reported data for pediatric and adult patients collected using these criteria [38]. The occurrence of TA-TMA in our population was independent of the type of CNI used, especially considering the more sensitive Jodele criteria with the quantitative determination of complement activation [18].

A potential interpretation of our data could be that although CNI use is a common predisposing factor for the development of TA-TMA, the type of CNI used may influence the clinical manifestations of TA-TMA. Our data suggest that TA-TMA is an underreported cause of CNS-NC following adult allo-HSCT, a finding that was previously described for pediatric patients [39]. This is very similar to the underreporting of TA-TMA as a cause of renal complications after transplantation described by Postalcioglu et al. [40]. Clearly, considering that we present here the results of a retrospective study that was not designed to explore this outcome, these data require confirmation by

prospective studies of TA-TMA incidence and clinical manifestations after adult allo-HSCT, which are currently unavailable for the adult population, in contrast to the field of pediatric transplantation [41]. The previous retrospective analyses [24,25,42] and randomized clinical studies [43] comparing TAC with CsA did not report a difference in NCs, but they did not focus on the detection of TA-TMA. This increased risk of neurotoxicity associated with TAC is not reflected in the OS data, where, in contrast, TAC prophylaxis appeared to improve OS by reducing the TRM associated with severe GVHD. Two large CIBMTR retrospective studies appear to support our findings, describing lower rates of aGVHD in patients receiving TAC as GVHD prophylaxis [24,25]. Clearly, further studies are needed to answer this question.

Our study has several limitations, including its retrospective nature, the heterogeneity of the population, and the extensive time period covered. The study's retrospective nature is particularly problematic with respect to the diagnostic criteria for TA-TMA. Another important limitation is the nonhomogeneous distribution of the use of TAC and/or CsA over the study period.

Despite these limitations, our work demonstrates that the use of TAC represents a potential risk factor for the development of CNS-NCs after allo-HSCT and is associated with a significantly higher risk of Neuro-TA-TMA compared to the use of CsA. Given that Neuro-TA-TMA as a manifestation of TA-TMA can be effectively treated with complement inhibitors such as eculizumab [44,45], a high index of suspicion with respect to TA-TMA is mandatory when administering CNIs.

In light of the results of the present analysis, with TAC emerging as a risk factor for CNS-NCs but still positively impacting TRM and OS, we suggest an intensive screening program for patients undergoing GVHD prophylaxis with TAC (lactate dehydrogenase, blood pressure, proteinuria) associated with an aggressive diagnostic approach (clinical monitoring, measuring sC5-sC9 activity, and organ biopsy with immunohistochemistry) in cases highly suspicious for TA-TMA, as proposed by Jodele et al. [18] and also considering the recently published harmonization criteria [35]. Our data also suggest that in elderly patients and/or in patients undergoing TBI-based conditioning, CsA might be more appropriate than TAC, provided that the risk of severe GVHD is not excessively high. Future prospective clinical trials comparing TAC and CsA, with a special focus on CNS-NCs after transplantation, as well as prospective and multicenter collections of data ensuring accurate follow-up and standardization of definitions of CNS-NCs, are needed to confirm these findings and better characterize potential modifiable risk factors for neurologic complications that severely impact the prognosis of transplant recipients.

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