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Post-Transplantation Cyclophosphamide Is Associated with an Increase in Non-Cytomegalovirus Herpesvirus Infections in Patients with Acute Leukemia and Myelodysplastic Syndrome

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2021.09.015.

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Abstract

The use of post-transplantation cyclophosphamide (PTCy) for graft-versus-host disease (GVHD) prophylaxis in recipients of haploidentical and fully matched transplantations is on the increase. Published studies have reported an increased incidence of cytomegalovirus (CMV) infection with the use of PTCy. Limited data exist on the incidence and outcomes of infection with non-CMV herpesviruses (NCHV) in this setting. The aim of this study was to evaluate the cumulative incidence of NCHV infections and the association of NCHV infections with transplantation-specific outcomes in recipients of haploidentical transplantation with PTCy (HaploCy), matched sibling donor transplantation with PTCy (SibCy), and matched sibling donor transplantation with calcineurin inhibitor-based prophylaxis (SibCNI). We hypothesized that, like CMV infection, HaploCy recipients of also will have a higher risk of NCHV infections. Using the Center for International Blood and Marrow Transplantation Research database, we analyzed 2765 patients

(HaploCy, n = 757; SibCNI, n = 1605; SibCy, n = 403) who had undergone their first hematopoietic stem cell transplantation (HCT) between 2012 and 2017 for acute myelogenous leukemia, acute lymphoblastic leukemia, or myelodysplastic syndrome. The cumulative incidence of NCHV at 6 months post-NCT was 13.9% (99% confidence interval], 10.8% to 17.3%) in the HaploCy group, 10.7% (99% CI, 7.1% to 15%) in the SibCy group, and 5.7% (99% CI, 4.3% to 7.3%) in the Sib CNI group ($P < .001$). This was due primarily to a higher frequency of human herpesvirus 6 viremia reported in patients receiving PTCy. The incidence of Epstein-Barr viremia was low in all groups, and no cases of post-transplantation lymphoproliferative disorder were seen in either PTCy group. The incidence of NCHV organ disease was low in all 3 cohorts. The development of NCHV infection was associated with increased treatment-related mortality, particularly in the HaploCy group. There was no association with the development of GVHD, relapse, or disease-free survival. Patients in PTCy cohorts who did not develop NCHV infection had lower rates of cGVHD. This study demonstrates that the use of PTCy is associated with an increased risk of NCHV infection. The development of NCHV infection was associated with increased nonrelapse mortality, especially in the HaploCy group. Prospective trials should consider viral surveillance strategies in conjunction with assessment of immune reconstitution for a better understanding of the clinical relevance of viral reactivation in different HCT settings.

Keywords

Non-CMV herpesvirus; Post-transplantation; cyclophosphamide; Haploidentical; HHV-6; Epstein-Barr virus

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) has curative potential for several hematologic malignancies. There has been a considerable increase in the number of partially matched (haploidentical) transplantations performed worldwide [1]. Traditionally, haploidentical HCT has been associated with substantial bidirectional alloreactivity, which often results in graft failure or severe graft-versus-host disease (GVHD). However, the use of post-transplantation cyclophosphamide (PTCy) in the haploidentical HCT platform has resulted in improved GVHD rates and overall outcomes comparable to those in fully matched donor HCT; thus, the PTCy platform is being increasingly applied in the matched donor setting [2]. With the increased use of this platform has come the identification of changes in of post-transplantation complications, including hemorrhagic cystitis, relapse, and infections [3].

Before widespread adoption of the T cell-replete graft with PTCy platform, haploidentical HCT regimens often used in vivo (antithymocyte globulin [ATG] or alemtuzumab) or ex vivo depletion of T cells (CD34 selection) from the graft, which likely contributed to poor immune reconstitution and increased risk of infections [4]. The patterns of immune reconstitution after haploidentical HCT remain poorly characterized in the PTCy era, but recent studies suggest impaired T cell and natural killer cell recovery compared with matched donor HCT [5,6].

Infection with viruses from the human herpesvirus family—herpes simplex virus (HSV)-1 and 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus-6 (HHV-6)—is a well-established cause of morbidity and mortality after HCT, especially with HLA-mismatched transplants [7]. CMV in particular is associated with an increased risk of transplantation-related mortality with all transplantation platforms [8]. Data from the Center for International Blood and Marrow Transplantation Research (CIBMTR) demonstrate that both PTCy and haploidentical donors contribute to this risk [9]. In addition, limited available data suggest a possible increased risk of non-CMV herpesvirus (NCHV) infections after haploidentical transplants with PTCy [10,11].

To address this, we designed a retrospective observational study using the large multi-institutional database of the CIBMTR to compare the incidence and outcomes of NCHV in 3 different HCT settings: haploidentical HCT using PTCy (HaploCy), matched sibling donor HCT using PTCy (SibCy), and matched sibling donor HCT using standard GVHD prophylaxis with a calcineurin inhibitor (CNI) plus methotrexate/mycophenolate mofetil (SibCNI). We hypothesized that, like CMV infection, patients receiving HaploCy will have higher risks of NCHV infections.

METHODS

Data Source

The CIBMTR is a large working group of more than 500 transplant centers worldwide that collects data on autologous transplantations, allogeneic transplantations, and other immune effector cell therapies. These data are reported to a statistical center located at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program coordinating center in Minneapolis. Participating centers are required to report all transplantations consecutively with longitudinal follow-up. Onsite audits monitor data and reporting compliance. Automated checks for discrepancies, physicians' reviews of submitted data, and onsite audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The CIBMTR collects data at 2 levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. Detailed disease and pretransplantation and post-transplantation clinical information, including infection-related data, are collected on a subset of registered patients selected for CRF data by a weighted randomization scheme. TED and CRF level data are collected pre-HCT, at 100 days and 6 months post-HCT, and annually thereafter until death. Only CIBMTR CRF data are used in this analysis, and all patients provided signed consent for CIBMTR registry data collection. Infection data collected include organism, site of infection, and date of infection. Information on screening parameters, severity, diagnostic methodology, and treatment is unavailable.

Patients

This study included patients age >2 years of age with a diagnosis of acute myelogenous leukemia (AML), acute lymphoblastic leukemia, or myelodysplastic syndrome (MDS) who underwent HCT with a haploidentical donor and PTCy (HaploCy), a matched sibling donor

receiving PTCy (SibCy), or a matched sibling donor treated with calcineurin inhibitor and methotrexate/mycophenolate mofetil (SibCNI) reported to the CIBMTR between 2012 and 2017. Because of the small sample size, patients who underwent matched unrelated donor HCT with PTCy were excluded. Patients receiving an umbilical cord blood transplant, single-mismatch related donor transplant, transplant with CD34 selection or ex vivo T cell depletion, antithymocyte globulin and/or alemtuzumab were also excluded. To minimize center bias for viral surveillance, patients transplanted at centers with no reported haploidentical transplants were also excluded. The data were locked on January 1, 2019, with a 2-year completeness index of 91% in the HaploCy cohort, 93% in the SibCy cohort, and 95% in the SibCNI cohort.

Statistical Analysis

Because the 3 groups were defined by the presence or absence of infection at day 180, baseline patient-, disease-, and transplantation-related factors are descriptive. Cumulative incidence estimates to account for competing risks were calculated. The day 180 cumulative incidence of NCHV (HSV, VZV, EBV, and HHV-6) by donor group was measured, with death as a competing risk. For all other analyses, as the main effect variable was time-dependent; dynamic landmark studies were used by choosing 3 landmark time points comprising the median and interquartile range (IQR) for the development of NCHV infection [12]. Owing to interactions between the donor type, GVHD prophylaxis with PTCy (or not), and variables of interest in each analysis, composite variables were used. For each of the 6 groups defined by donor, GVHD prophylaxis, and infection status, outcomes described included overall survival (OS), disease-free survival (DFS), nonrelapse mortality (NRM), relapse, and chronic GVHD at 2 years. Supplementary Table S1 lists the variables considered in the Cox proportional hazards regression models.

Acute GVHD occurring before onset of infection was included as a time-dependent variable in the Cox models. The assumption of proportional hazards for each factor in the Cox models was tested. When the proportional hazards assumption was violated, a time-dependent variable was added to the model. The stepwise variable selection method was used to identify significant risk factors associated with the outcomes. Factors significantly associated with the outcome variable at a significance level of 0.01 were kept in the final model. Interactions between the main effect and significant covariates were tested. Center effects were examined, and all reported multivariable analyses were adjusted for center effects using the score test [13]. Because infections are expected to have the greatest impact around the time of transplantation, all outcomes were examined to 2 years post-HCT.

RESULTS

Patient Demographics

This study included 757 HaploCy patients from 100 centers, 403 SibCy patients from 77 centers, and 1605 SibCNI patients from 100 centers. Table 1 describes the patient, disease, and transplantation characteristics classified by the development of NCHV infection by day 180.

Irrespective of infection occurrence, SibCy patients were younger (HaploCy: median, 58 [IQR, 3 to 78] years; SibCy: median, 46 [IQR, 3 to 75] years; SibCNI: median, 57 [IQR, 2 to 78] years; $P < .001$), and the HaploCy group had a greater representation of African Americans (HaploCy, 18%; SibCy, 15%, SibCNI: 7%) and a younger donor population (HaploCy: median, 36 [range, 9 to 76] years; SibCy: median, 45 [range, 4 to 72] years; SibCNI: median, 54 [range, 2 to 82]; $P < .001$). Most transplantations were performed in patients with AML in first complete response with intermediate cytogenetics. The HaploCy group had more bone marrow grafts, use of reduced-intensity conditioning (RIC) regimens, low-dose total body irradiation, and use of granulocyte colony-stimulating factor (G-CSF). Absolute lymphocyte count at days 100 and 180 were similar in the 3 cohorts; however, data were missing in 5% of patients at day 100 and in 20% at day 180.

Infection Outcomes

The cumulative incidence of NCHV at day 30 was 6.9% (99% CI, 5% to 9% in the HaploCy cohort, 3.2% (99% CI, 1% to 6%) in the SibCy cohort, and 1.7% (99% CI, 1% to 3%) in the SibCNI cohort. This increased to 13.9% (99% CI, 11% to 17%), 10.7% (99% CI, 7% to 15%), and 5.7% (99% CI, 4% to 7%) ($P < .001$) by 6 months post-HCT (Figure 1).

The median onset of NCHV infections for the entire study population was 40 days (IQR, 23 to 98 days). HHV-6 viremia contributed to the majority of NCHV in both the HaploCy and SibCy arms (HaploCy, 9.3%; SibCy, 5.7%; SibCNI, 1.9%); however, the incidence of HHV6 end-organ disease was low in all 3 cohorts. The incidence of EBV viremia was low in all 3 cohorts (HaploCy, 2.9%; SibCy, 3.7%; SibCNI, 1.8%). Only 1 case of EBV-end organ disease was reported, occurring in the SibCNI cohort. The incidence of NCHV organ disease was low in all 3 cohorts (HaploCy, 2%; SibCy, 1%; SibCNI, 2%). The majority of NCHV organ disease was related to HSV and VZV infections. Table 2 presents the characteristics of NCHV infections in these cohorts.

NRM

For patients still alive and developing an NCHV infection before day 40 (median onset), the estimated 2-year NRM was 37.6% (99% CI, 22% to 55%) for the HaploCy cohort, 26.1% (99% CI, 3% to 61%) for the SibCy cohort, and 24% (99% CI, 8% to 46%) for the SibCNI cohort (Supplementary Figure S1).

Conversely, for those patients alive and without NCHV infection by day 40, the NRM was lower: HaploCy, 17.5% (99% CI, 14% to 22%); SibCy, 15.9% (99% CI, 1% to 21%); SibCNI, 12.4% (99% CI, 10% to 15%). Multivariable analysis for NRM performed using a group of SibCNI without NCHV infection as the reference group found that development of NCHV infection was associated with higher NRM (Figure 2).

GVHD

Univariate analysis at each of the landmark times for NCHV infection demonstrated no impact of NCHV infection on grade II-IV acute GVHD development by 6 months post-HCT (Supplementary Figure S2).

Multivariable analysis for cGVHD showed that patients in both PTCy cohorts who did not develop NCHV infection by day 180 had a decreased risk of developing cGVHD compared with the reference group of SibCNI without infection (HaploCy: hazard ratio [HR], 0.62 [99% CI, 0.46 to 0.82], $P < .0001$; SibCy: HR, 0.59 [99% CI, 0.39 to 0.88], $P = .0006$) (Figure 2). Notably, patients receiving PTCy regardless of donor type and who developed NCHV infection had a similar risk of developing chronic GVHD as seen in the infected and noninfected SibCNI cohorts (HaploCy: HR, 0.97 [99% CI, 0.61 to 1.55], $P = .87$; SibCy: HR, 0.89 (99% CI, 0.38 to 2.13], $P = .74$). Other factors associated with an increased risk of cGVHD include receipt of peripheral blood stem cells (HR, 2.25; 99% CI, 1.68 to 3.02; $P < .0001$), a female donor and male recipient (HR, 1.26; 99% CI, 1.03 to 1.53; $P < .003$) or a female donor and female recipient (HR, 1.25; 99% CI, 1.02 to 1.54; $P = .006$), and development of grade II-IV aGVHD prior to infection (HR, 1.32; 99% CI, 1.08 to 1.61; $P = .0003$) (Table 3).

Relapse

There was no impact on the risk of relapse based on the main effect variable of development of a NCHV by day 180 and donor type with/without PTCy (Figure 2). As shown in Table 3, factors associated with increased risk of relapse by 2 years post-HCT included transplantation for high/very high risk MDS (HR, 2.12; 99% CI, 1.19 to 3.80; $P < .001$) or advanced acute leukemia (HR, 1.80; 99% CI, 1.06 to 3.07; $P = .004$) and nonmyeloablative/RIC conditioning (HR, 1.51; 99% CI, 1.27 to 1.79; $P < .001$). A longer interval from diagnosis to HCT was associated with a lower risk of relapse during the first 4 months post-transplantation, but the effect was lost beyond 4 months. The development of grade II-IV aGVHD was protective against relapse (HR, 0.80; 99% CI, 0.68 to 0.93; $P = .0001$).

OS

In the first 2 years post-HCT, mortality was 49.5% (n = 375) in the HaploCy cohort, 44.4% (n = 179) in the SibCy cohort, and 46.9% (n = 753) in the SibCNI cohort. Supplementary Table S2 lists the causes of death in the 3 cohorts.

Thirty-eight percent of deaths in the HaploCy cohort were due to infection of any kind, as either the primary or secondary cause, compared with 27% of the deaths in both the SibCy and SibCNI cohorts ($P < .001$). Compared to SibCNI patients without NCHV infection, patients in the HaploCy cohort had a higher risk of death irrespective of NCHV infection (HaploCy with infection: HR, 1.82 [99% CI, 1.18 to 2.80], P = .0004; HaploCy without infection: HR, 1.31 [99% CI, 1.02 to 1.67], P = .006) (Figure 2). Patients in the SibCy cohort did not have a higher risk of death compared with the SibCNI without NCHV infection cohort. Additional factors associated with decreased survival included HCT for high/very high-risk MDS (HR, 2.04; 99% CI, 1.10 to 3.80; $P = .003$), higher Hematopoietic Cell Transplantation-specific Comorbidity Index; age >60 years (HR, 1.61; 99% CI, 1.08 to 2.40; $P = .002$); and development of aGVHD grade II-IV prior to infection (HR, 1.54; 99% CI, 1.25 to 1.89; $P < .001$) (Table 3).

DISCUSSION

This is the largest study reported to date comparing the incidence and outcomes of NCHV infections in the setting of 3 different HCT platforms: HaploCy, SibCy, and SibCNI. Our data show that the incidence of NCHV infection was highest in the HaploCy cohort, followed by the SibCy and SibCNI cohorts. HHV-6 viremia was the primary contributor to this higher incidence. The development of NCHV infection was associated with increased NRM in all 3 cohorts; however, the magnitude was greatest in the HaploCy cohort and was associated with an inferior OS. We found very low rates of NCHV organ involvement in all 3 cohorts.

The most common NHCV infection reported in our analysis was HHV-6. HHV-6 has 2 distinct virus species, HHV-6A and HHV-6B, with a combined seroprevalence of >90% in adults [14]. Studies have reported incidence rates of 30% to 70% of post-transplantation HHV-6 reactivation, which has been associated with encephalitis, fever, rash, bone marrow failure, pneumonitis, acute GVHD, and CMV reactivation [15–21]. A unique feature of the HHV-6 virus is its ability for chromosomal integration in the host DNA, with resulting vertical transmission [22,23]. In a transplantation study, chromosomally integrated HHV6 was found in 1.4% of the recipients and in 0.9% of the donors and was associated with a higher incidence of acute GVHD (adjusted HR, 1.7 to 1.9; $P = .004$ to .001) [24]. We found a lower incidence of HHV-6 infection in all 3 study cohorts compared with some previously reported studies [21,25]. The use of prospective screening of all patients in some of these studies likely resulted in many asymptomatic viremia cases contributing to the higher incidence. Because the CIBMTR does not collect data on institutional practices for viral detection, it is not possible to confirm whether the HHV-6 testing in this population was driven by clinical concerns or more aggressive screening. Many transplant centers do not use standard screening for HHV6, because there is no documented efficacy in treatment for isolated viremia. There is no evidence that low-level HHV-6 viremia increases the risk of encephalitis, the most clearly established complication of HHV-6 reactivation [26,27].

Because of this study's retrospective design, we cannot determine whether the association of HHV-6 infection with increased NRM is a direct association or a result of increased viral testing in otherwise sick patients. We also do not have data on the prevalence of chromosomally integrated HHV-6 in this cohort. The higher incidence of infection in both PTCy cohorts raises concerns about impaired T cell and natural killer cell reconstitution resulting from PTCy [5,28]. There is also evidence that a high level of HHV-6 viremia itself may affect T cell reconstitution [29].

The low incidence of EBV infection in the HaploCy cohort is in sharp contrast to previous reports in non-PTCy haploidentical HCT showing a high incidence of EBV infection and subsequent post-transplantation lymphoproliferative disorder [30,31]. This difference is likely related to impaired early T cell reconstitution secondary to the use of in vivo or ex vivo T cell depletion in previous haploidentical HCT platforms. A large retrospective study using PTCy as GVHD prophylaxis for both haploidentical and matched donor transplantations reported no cases of EBV-associated PTLD at 1 year [32]. The exact mechanism responsible for this protection from EBV is unclear; hypotheses include PTCy-

induced destruction of EBV-infected B cells with relative sparing of EBV-specific memory T cells [32].

The cumulative incidence of HSV and VZV infection was low in all cohorts in this study. The near-universal use of acyclovir/valacyclovir prophylaxis has resulted in a low incidence of HSV and VZV in all HCT settings. This study's infection rate may represent breakthrough infections, discontinuation of prophylaxis, or patient noncompliance with prophylaxis; however, this cannot be determined in the absence of prophylaxis data.

Even though this study's primary objective was to assess the incidence of NCHV infections and their effect on NRM, we also analyzed the association of NCHV infection with GVHD, overall mortality, and relapse rates. We did not find an association of NCHV infection with the development of grade II-IV acute GVHD, which has been reported previously [33]. This study also found lower OS in the HaploCy cohort compared with the SibCNI cohort, irrespective of the development of NCHV infection. A recent CIBMTR publication reported similar OS in HaploCy and SibCNI groups of AML patients [34]. Our study also included patients with MDS and acute lymphoblastic leukemia, suggesting that outcomes between transplantation platforms also could be disease-dependent. There was no impact on relapse rate based on the main effect variable of developing an NCHVinfection by day 180 and donor type with or without PTCy. Interestingly, although multivariable analysis showed that patients in the PTCy cohorts with no NCHV infection by day 180 had a decreased risk of developing cGVHD, the PTCy cohorts with NCHV infection by day 180 had a similar risk of cGVHD compared with the SibCNI cohort. The exact mechanism by which PTCy is protective against cGVHD has not been established, and the role of regulatory T cells in promoting tolerance is under clinical investigation [6].

This study has several limitations, starting with the retrospective design. Even though the data were collected from a large prospective observational database, granular information on infections is not reported. The CIBMTR does not collect data on antiviral prophylaxis, institutional standards for monitoring virus levels in blood, and antiviral therapy threshold. Similarly, institutions differ regarding the definition of criteria for clinically significant infection; however, the multivariable analyses are all adjusted for center effect to minimize these differences.

We also were not able to assess the immunosuppression burden and the relationship to infections. Modifications to the current CIBMTR data collection forms should improve our understanding of viral infections and response to treatment. The CIBMTR does not collect data on the reasons for choosing PTCy over CNI for prophylaxis in sibling donor HCT. A future study also should include matched unrelated donor transplants with PTCy and conventional GVHD prophylaxis. There is an ongoing prospective clinical trial comparing outcomes including immune reconstitution and infectious complications between patients randomized to receive either CNI-based or PTCy-based GVHD prophylaxis in patients undergoing RIC allogeneic HCT [35].

In summary, in our study cohort, HaploCy HCT was associated with an increased incidence of NCHV infections, with a predominance of HHV-6 viremia. This was associated with

an increase in overall mortality for the infected HaploCy cohort. This information should aid transplant physicians in selecting the donor and transplantation platform, as well as in considering risk-adapted screening and preemptive strategies. Prospective studies are needed to understand the true incidence and outcomes of clinically significant infections in relation to unique immune reconstitution with different HCT platforms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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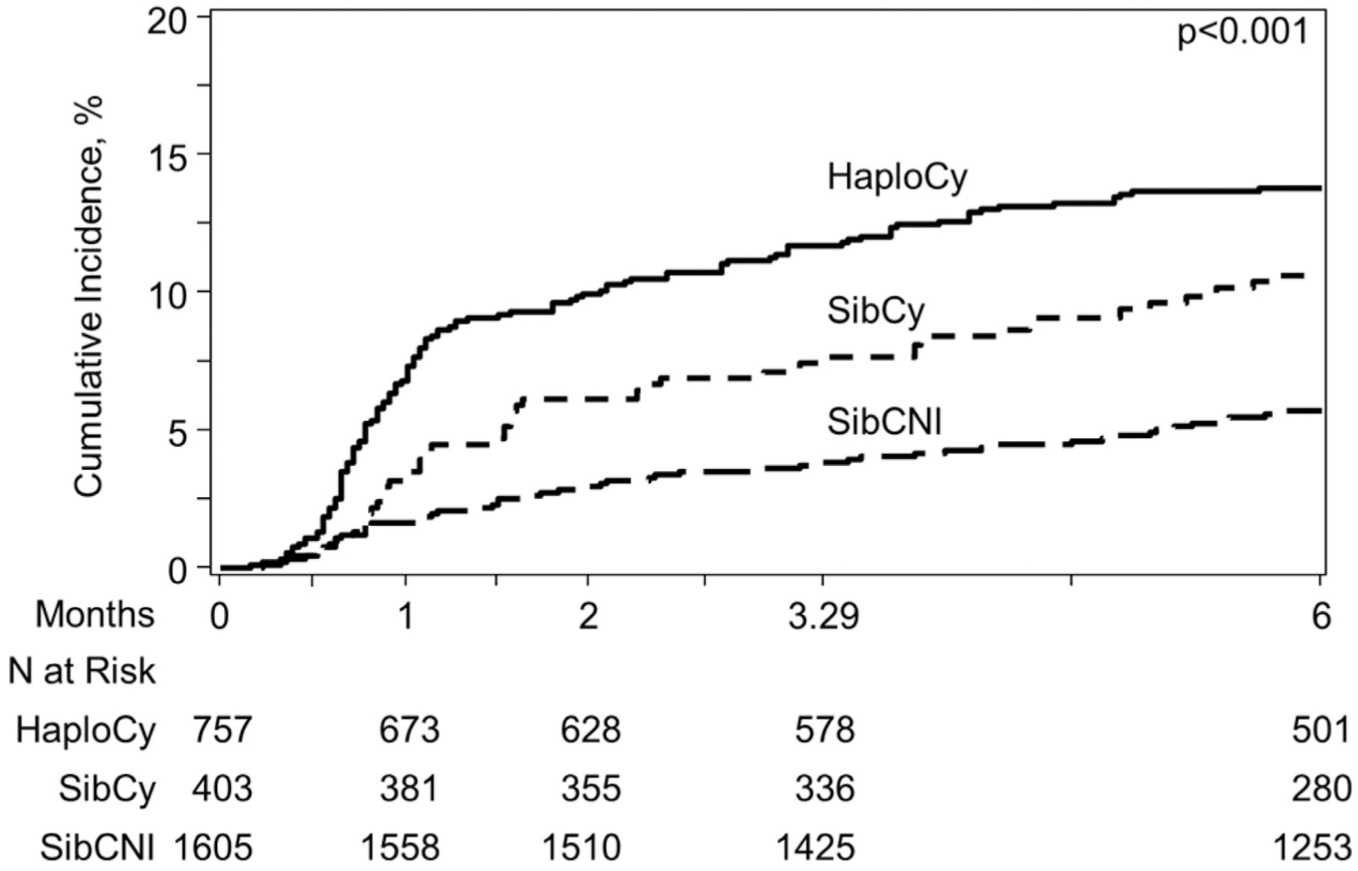

Figure 1.

Cumulative incidence of NCHV infection across the 3 HCT cohorts.

The cumulative incidence of NCHV at day 30 was 6.9% (99% CI, 5% to 9%) in the HaploCy cohort, 3.2% (99% CI, 1% to 6%) in the SibCy cohort, and 1.7% (99% CI, 1% to 3%) in the SibCNI cohort. This increased to 13.9% (99% CI, 11% to 17), 10.7% (99% CI, 7% to 15%), and 5.7% (99% CI, 4% to 7%), respectively ($P < .001$) by 6 months post-HCT.

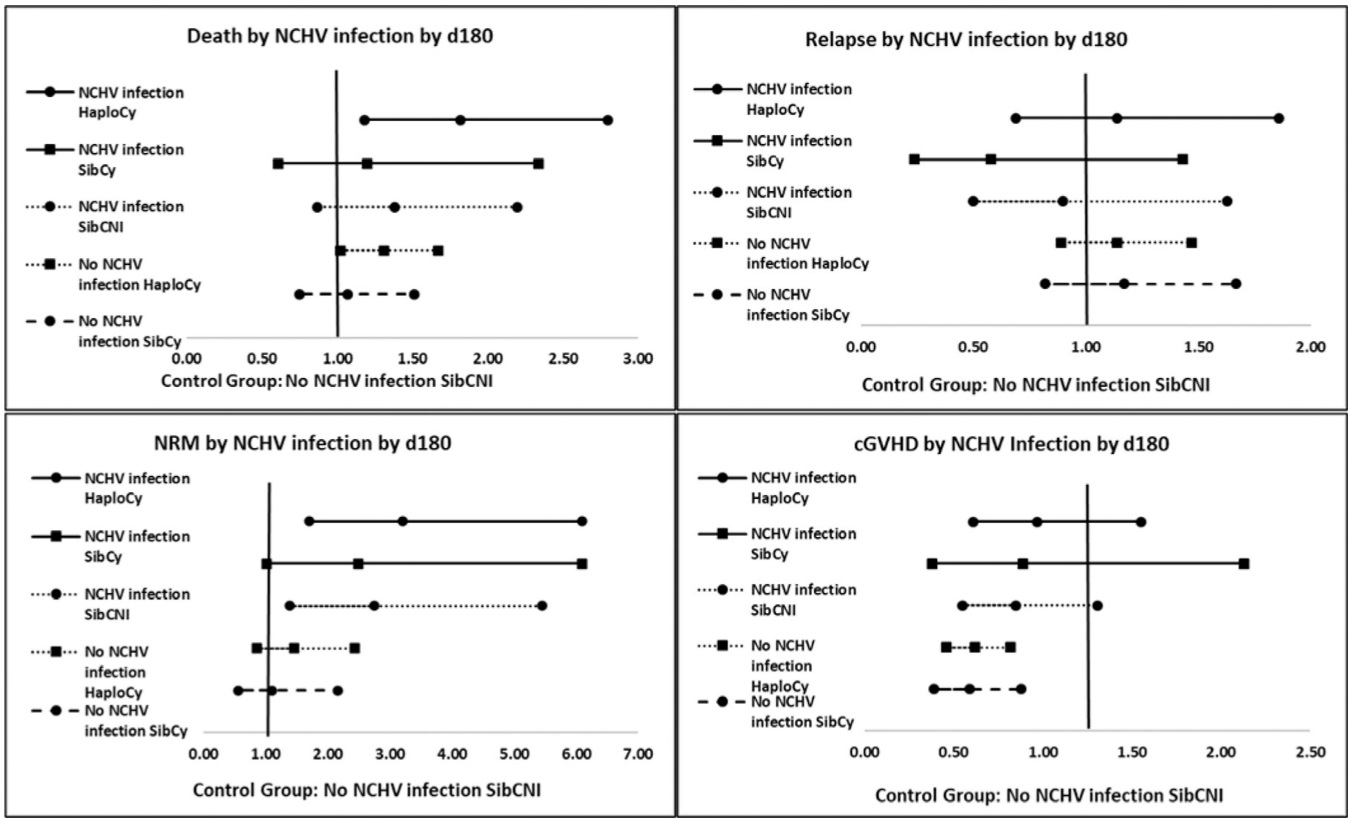

Figure 2.

Multivariable analysis of outcomes with NCHV infection. Values are HR (99% CI) from Cox models for risk of death, relapse, NRM, and chronic GVHD. The reference group is SibCNI without NHCV infection. The highest risk is seen in the HaploCy cohort (HR, 3.21; 99% CI, 1.70 to 6.09; $P < .001$); however, increased NRM was also seen in the SibCy (HR, 2.50; 99% CI, 1.02 to 6.09; $P = .008$) and SibCNI (2.75; 99% CI, 1.39 to 5.45; $P < .001$) cohorts. Other factors associated with increased NRM included HCT from a female donor to a male recipient (HR, 1.46; 99% CI, 1.14 to 1.88; $P < .0001$), older age ($P = .0021$), and development of grade II-IV aGVHD (HR, 2.67; 99% CI, 1.83 to 1.91; $P < .0001$) (see Table 3).

Table 1

Characteristics of Patients by Donor/PTCy Status and NCHV Type Reported to the CIBMTR, 2012 to 2017

Variable	NCHV Infection by Day 180			No NCHV Infection		
	HaploCy (N = 105)	SibCy (N = 43)	SibCNI (N = 92)	HaploCy (N = 652)	SibCy (N = 360)	SibCNI (N = 1513)
Number of centers	38	25	35	95	69	100
Male sex, n (%)	75 (71)	25 (58)	43 (47)	384 (59)	218 (61)	890 (59)
Age, yr, median (range)	53 (3–75)	43 (13–65)	57 (5–73)	58 (3–78)	47 (3–75)	57 (2–78)
KPS ≥ 90, n (%)	49 (47)	31 (72)	51 (55)	341 (52)	202 (56)	895 (59)
Race/ethnicity, n (%)						
Caucasian, non-Hispanic	60 (57)	25 (58)	57 (62)	384 (59)	214 (59)	1052 (70)
African American	25 (24)	7 (16)	15 (16)	106 (16)	49 (14)	92 (6)
Others	19 (18)	9 (21)	18 (20)	115 (18)	71 (20)	244 (16)
Missing	1 (<1)	2 (5)	2 (2)	47 (7)	26 (7)	125 (8)
HCT-CI, n (%)						
0	26 (25)	8 (19)	22 (24)	173 (27)	95 (26)	370 (24)
1–2	20 (19)	15 (35)	21 (23)	189 (29)	109 (30)	426 (28)
3–4	42 (40)	13 (30)	31 (34)	169 (26)	91 (25)	445 (29)
5+	16 (15)	7 (16)	18 (20)	121 (19)	64 (18)	267 (18)
Missing	1 (<1)	0	0	0	1 (<1)	5 (<1)
Donor age, yr, median (range)	35 (17–68)	39 (12–63)	53 (2–74)	36 (9–76)	46 (4–72)	54 (3–82)
Donor/recipient sex match, n (%)						
Male-male	48 (46)	15 (35)	24 (26)	241 (37)	141 (39)	483 (32)
Male-female	19 (18)	14 (33)	22 (24)	161 (25)	85 (24)	325 (21)
Female-male	27 (26)	10 (23)	19 (21)	143 (22)	77 (21)	407 (27)
Female-female	11 (10)	4 (9)	27 (29)	107 (16)	57 (16)	297 (20)
Missing	0	0	0	0	0	1 (<1)
Donor/recipient CMV serostatus, n (%)						
+/+	45 (43)	16 (37)	48 (52)	281 (43)	156 (43)	636 (42)
+/−	10 (10)	4 (9)	6 (7)	44 (7)	32 (9)	157 (10)

Variable	NCHV Infection by Day 180			No NCHV Infection		
	HaploCy (N = 105)	SibCy (N = 43)	SibCNI (N = 92)	HaploCy (N = 652)	SibCy (N = 360)	SibCNI (N = 1513)
−/+	30 (29)	14 (33)	18 (20)	187 (29)	87 (24)	365 (24)
−/−	17 (16)	7 (16)	16 (17)	114 (17)	72 (20)	311 (21)
Recipient missing	0	0	2 (2)	3 (<1)	2 (<1)	13 (<1)
Donor missing	3 (3)	2 (5)	2 (2)	23 (4)	11 (3)	31 (2)
Disease, n (%)						
AML	67 (64)	35 (81)	61 (66)	461 (71)	275 (76)	964 (64)
ALL	7 (7)	2 (5)	1 (1)	19 (3)	17 (5)	59 (4)
MDS	31 (30)	6 (14)	30 (33)	172 (26)	68 (19)	490 (32)
Graft type, n (%)						
Bone marrow	49 (47)	21 (49)	18 (20)	259 (40)	110 (31)	182 (12)
Peripheral blood	56 (53)	22 (51)	74 (80)	393 (60)	250 (69)	1331 (88)
Conditioning regimen intensity, n (%)						
Myeloablative	60 (57)	29 (67)	59 (64)	254 (39)	193 (54)	876 (58)
RIC/NMA	45 (43)	14 (33)	33 (36)	398 (61)	167 (46)	637 (42)
GVHD prophylaxis, n (%)						
Cyclophosphamide	105	43	0	652	360	0
CNI + MMF ± others	0	0	28 (30)	0	0	334 (22)
CNI + MTX ± others	0	0	64 (70)	0	0	1179 (78)
TBI	66 (63)	24 (56)	39 (42)	465 (71)	210 (58)	397 (26)
Growth factors post-transplantation, n (%)	86 (82)	36 (84)	23 (25)	534 (82)	283 (79)	356 (24)
Time from diagnosis to HCT, mo, median (range)	9 (2–165)	8 (3–291)	5 (1–57)	7 (1–160)	7 (<1–396)	6 (1–556)
Year of transplantation, n (%)						
2012–2014	23 (22)	9 (21)	49 (53)	147 (23)	78 (22)	757 (50)
2015–2017	82 (78)	34 (79)	43 (47)	505 (77)	282 (78)	756 (50)

KPS indicates Karnofsky Performance Status; HCT-CI, Hematopoietic Cell Transplantation-specific Comorbidity Index; ALL, acute lymphoblastic leukemia; NMA, non-myeloablative; MMF, mycophenolate mofetil; MTX, methotrexate; TBI, total body irradiation.

Table 2

NCHV Infections by 180 Days

Variable	HaploCy (N = 757), n (%)	SibCy (N = 403), n (%)	SibCNI (N = 1605), n (%)	*P* Value
Number of viral infections (any) by day 180				<.001
None	331 (44)	201 (50)	1035 (64)	
1	221 (29)	114 (28)	383 (24)	
2	138 (18)	49 (12)	128 (8)	
3+	67 (9)	39 (10)	59 (4)	
NCHV				
Viremia	92 (12)	38 (9)	60 (4)	<.001
HSV	4 (<1)	0	3 (<1)	.394
HHV-6	71 (9)	23 (6)	31 (2)	.004
EBV	22 (3)	15 (4)	30 (2)	.004
NCHV organ involvement (± viremia)	18 (2)	6 (1)	34 (2)	.600
HSV	11 (1)	4 (<1)	16 (1)	.496
VZV	3 (<1)	2 (<1)	11 (<1)	.458
HHV-6	4 (<1)	0	6 (<1)	.457
EBV	0	0	1 (<1)	.698
Sites other than blood (not mutually exclusive)				
Gastrointestinal	7 (<1)	3 (<1)	13 (<1)	.860
Lung	2 (<1)	1 (<1)	3 (<1)	.837
Liver	0	0	1 (<1)	.698
Sinus/upper respiratory	3 (<1)	1 (<1)	8 (<1)	.817
Central nervous system	1 (<1)	0	4 (<1)	.547
Lower genitourinary	1 (<1)	0	2 (<1)	.832
Upper genitourinary	3 (<1)	2 (<1)	2 (<1)	.126
Skin	4 (<1)	2 (<1)	10 (<1)	.813
Other sites	2 (<1)	0	2 (<1)	0.607

The values for the organisms in the table are for the patients with the individual infections by a specific organism. Some patients had more than 1 NCHV reported, and a patient may be included in more than 1 organism group.

Table 3

Multivariable Analysis Results for Events by 2 Years Post-HCT, Adjusted for Center Effects

Variable	N	HR (99% CI)	*P* Value
Overall mortality			
Main effect variable			.0002
SibCNI, no NCHV infection	1480	1.00	
HaploCy with NCHV infection	101	1.82 (1.18–2.80)	.0004
SibCy with NCHV infection	43	1.20 (0.61–2.34)	.4872
SibCNI with NCHV infection	89	1.38 (0.87–2.20)	.0705
HaploCy, no NCHV infection	628	1.31 (1.02–1.67)	.0057
SibCy, no NCHV infection	352	1.07 (0.75–1.51)	.6405
Disease/cytogenetics/stage			<.0001
Leukemia, favorable cytogenetics, early/intermediate	68	1.00	
Leukemia, intermediate/normal cytogenetics, early	667	1.02 (0.58–1.80)	.9287
Leukemia, poor cytogenetics, early	434	0.99 (0.57–1.71)	.9604
Leukemia, intermediate/normal cytogenetics, intermediate	213	1.10 (0.63–1.92)	.6745
Leukemia, poor cytogenetics, intermediate	124	1.31 (0.72–2.36)	.2429
Leukemia, any cytogenetics, advanced	291	1.94 (1.09–3.45)	.0030
MDS, very low/low	307	0.91 (0.51–1.62)	.6594
MDS intermediate	229	1.57 (0.89–2.75)	.0400
MDS high/very high	162	2.04 (1.10–3.80)	.0029
Missing	198	1.33 (0.70–2.53)	.2529
HCT-CI			.0007
0	679	1.00	
1–2	762	0.94 (0.66–1.34)	.6504
3–4	768	1.08 (0.77–1.53)	.5540
5+	484	1.30 (0.92–1.84)	.0543
Age at HCT, yr			<.0001
0–20	234	1.00	
21–40	479	0.86 (0.60–1.25)	.3001

Variable	N	HR (99% CI)	P Value
41–60	945	1.27 (0.90–1.79)	.0800
>60	1035	1.61 (1.08–2.40)	.0019
Acute GVHD grade II-IV			<.0001
No	1797	1.00	
Yes	896	1.54 (1.25–1.89)	
Main effect variable			.2551
SibCNI, no NCHV infection	1462	1.00	
HaploCy with NCHV infection	100	1.14 (0.69–1.86)	.5031
SibCy with NCHV infection	42	0.58 (0.24–1.43)	.1222
SibCNI with NCHV infection	87	0.90 (0.50–1.63)	.6434
HaploCy, no NCHV infection	617	1.14 (0.89–1.47)	.1697
SibCy, no NCHV infection	348	1.17 (0.82–1.67)	.2664
Disease/cytogenetics/stage			<.0001
Leukemia, favorable cytogenetics, early/intermediate	67	1.00	
Leukemia, intermediate/normal cytogenetics, early	658	0.59 (0.34–1.05)	.0180
Leukemia, poor cytogenetics, early	430	0.82 (0.46–1.46)	.3724
Leukemia, intermediate/normal cytogenetics, intermediate	208	0.86 (0.50–1.49)	.4855
Leukemia, poor cytogenetics, intermediate	124	1.16 (0.62–2.17)	.5502
Leukemia, any cytogenetics, advanced	289	1.80 (1.06–3.07)	.0043
MDS, very low/low	305	0.98 (0.57–1.68)	.9132
MDS intermediate	227	1.14 (0.63–2.06)	.5663
MDS high/very high	159	2.12 (1.19–3.80)	.0009
Missing	189	1.04 (0.58–1.88)	.8533
Conditioning intensity			<.0001
Myeloablative	1417	1.00	
RIC/NMA	1239	1.51 (1.27–1.79)	
Time from diagnosis to HCT (≤ 4 months)			<.0001
<6 mo	325	1.00	
6 mo-1 yr	149	0.72 (0.56–0.93)	.0008

Variable	N	HR (99% CI)	P Value
≥1 yr	145	0.47 (0.32–0.67)	<.0001
Time from diagnosis to HCT (>4 months)			.2843
<6 mo	1339	1.00	
6 mo-1 yr	637	1.05 (0.79–1.41)	.6460
≥1 yr	680	0.88 (0.66–1.18)	.2661
Acute GVHD grade II-IV			<.001
No	1812	1.00	
Yes	844	0.79 (0.68–0.92)	
NRM			
Main effect variable			<.001
SibCNI, no NCHV infection	1473	1.00	
HaploCy with NCHV infection	103	3.21 (1.70–6.09)	<.0001
SibCy with NCHV infection	42	2.50 (1.02–6.09)	.0083
SibCNI with NCHV infection	88	2.75 (1.39–5.45)	.0001
HaploCy, no NCHV infection	634	1.46 (0.87–2.44)	.0579
SibCy, no NCHV infection	352	1.10 (0.56–2.17)	.7231
Donor-recipient sex match			.0021
Male-male	927	1.00	
Male-female	616	0.85 (0.50–1.44)	.4153
Female-male	658	1.32 (0.72–2.43)	.2317
Female-female	491	1.89 (0.93–3.86)	.0212
Age at HCT, yr			.0021
0–20	234	1.00	
21–40	477	0.85 (0.50–1.44)	.4153
41–60	946	1.32 (0.72–2.43)	.2317
>60	1035	1.89 (0.93–3.86)	.0212
Acute GVHD, grade II-IV			<.0001
No	1837	1.00	
Yes	855	2.67 (1.83–3.91)	

Variable	N	HR (99% CI)	*P* Value
Chronic GVHD			
Main effect variable			<.0001
SibCNI, no NCHV infection	1486	1.00	
HaploCy with NCHV infection	104	0.81 (0.49–1.36)	.3035
SibCy with NCHV infection	43	0.73 (0.30–1.78)	.3689
SibCNI with NCHV infection	90	0.71 (0.45–1.10)	.0419
HaploCy, no NCHV infection	644	0.58 (0.44–0.78)	<.0001
SibCy, no NCHV infection	354	0.58 (0.38–0.87)	.0005
Graft type			<.0001
Bone marrow	635	1.00	
Peripheral blood	2086	2.26 (1.69–3.02)	
Donor-recipient sex match			.0006
Male-male	936	1.00	
Male-female	621	1.01 (0.82–1.25)	.9195
Female-male	669	1.26 (1.03–1.55)	.0027
Female-female	495	1.24 (1.00–1.54)	.0084
Number of viral infections (any) by day 180			.0063
None	1545	1.00	
1	699	1.16 (0.96–1.40)	.0412
2	312	1.16 (0.90–1.51)	.1378
3+	165	1.54 (1.06–2.25)	.0032
Acute GVHD, grade II-IV			.0018
No	1817	1.00	
Yes	904	1.27 (1.04–1.56)	