Incidence and Impact of Community Respiratory Viral infections in Post-Transplant Cyclophosphamide based GVHD prophylaxis and Haploidentical Stem cell transplantation

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Abstract

Community respiratory viral infections (CRVI) are associated with pulmonary function impairment, alloimmune lung syndromes, and inferior survival in HLA-matched allogeneic hematopoietic stem cell transplant (HCT) recipients. Although the incidence of viral infections in HLA-haploidentical HCT recipients who receive post-transplant cyclophosphamide (PTCy)-based GVHD prophylaxis is reportedly increased, there are insufficient data describing the incidence of CRVI and the impact of donor source and PTCy on transplant outcomes. Analyzing patients receiving their first HCT between 2012 and 2017 for AML, ALL, and MDS, we describe comparative outcomes between matched sibling transplants receiving either calcineurin-based GVHD prophylaxis (SibCNI, N=1605) or PTCy (SibCy, N=403), and related haploidentical transplants receiving PTCy (HaploCy, N=757). The incidence of CRVI was higher for patients receiving PTCy, regardless of donor type. Patients in the HaploCy cohort who developed a CRVI by day +180 had both a higher risk of treatment-related mortality (TRM) [HR 2.14 (99% CI: 1.13 – 4.07, p=0.002] and inferior two-year overall survival (OS) [HR 1.65 (99% CI: 1.11 – 2.43, p = 0.001] compared to SibCNI with no CRVI. This finding justifies further research into long-term antiviral immune recovery as well as development of preventive and treatment strategies to improve long term outcomes in such patients.

Introduction

HLA-haploidentical hematopoietic stem cell transplantation (HCT) has wide applicability as an alternative source for stem cells in patients without matched donors with the reported success of PTCy used with T-cell replete (TCR) stem cell infusions from peripheral blood or bone marrow (1–5). Prior to the development of the PTCy strategy for haploidentical HCT, alternative T-cell depletion (TCD) strategies included graft manipulation for CD34 selection as well as *in-vivo* T cell depletion with anti-thymocyte globulin (ATG) or alemtuzumab. TCD strategies in the context of haploidentical transplant were limited by severe GVHD, graft rejection, and increased infectious complications (6–8). Comparisons of TCR haploidentical strategies predominantly involving PTCy (HaploCy) to T cell depleted (TCD) haploidentical strategies demonstrate superior non-relapse mortality (NRM) accompanied by better immune reconstitution of T cell subsets in the first 6 months post–transplant for the HaploCy approach (9–14). However, reports of high rates of infections following HaploCy continue despite improvements in survival and composite outcome measures (15–19). Viral infections are reported in this setting in the range of 70% at 100 days and 77% at 1 year (19). Despite the recognition of increased risk of viral infection, there is a lack of information regarding the incidence of community respiratory viral infections (CRVI) in haploidentical stem cell transplant recipients and the impact of those infections on transplant outcomes. Furthermore, it is unknown whether the degree of mismatch, the use of PTCy, or both impacts infection and transplant outcomes, and the limited data that are available are conflicting (20–21).

Although the incidence of CRVI is reportedly low in matched allogeneic HCT recipients receiving calcineurin inhibitor (CNI) based GVHD prophylaxis, both retrospective and prospective studies have found associations between early CRVI and pulmonary function, alloimmune lung syndromes (allo-LS), and transplant related mortality (TRM). Furthermore,

co-viral infections and in particular CMV viremia has been associated with increased progression of CRVI to lower respiratory tract infections. Given the high rates of viral infections reported with HaploCy HCT, understanding the incidence and impact that CRVI has on transplant outcomes in this setting may impact the choice of donors and post-transplant management strategies relating to infection prophylaxis and treatment of graft versus host disease (GVHD).

This study aims to identify the comparative incidence of CRVI infections occurring by day +180 post-transplant by donor source and the impact of CRVI on outcomes including survival, relapse, chronic GVHD, and transplant related mortality (TRM) using the Center for International Blood and Marrow Transplant Research (CIBMTR) registry. Our target population was selected to evaluate the impact of PTCy and donor and included matched sibling transplants with calcineurin based GVHD prophylaxis (SibCNI) compared to matched siblings with PTCy based GVHD prophylaxis (SibCy) and haploidentical related transplants receiving PTCy based GVHD (HaploCy).

Materials and Methods

Study Population

A total of 11,964 patients 2 years of age or older receiving first HCT transplant for AML, ALL, and MDS between 2012 and 2017 were identified in the CIBMTR registry. Cohorts examined included recipients of related haploidentical (2 antigen/allele mismatched) donors with PTCy (HaploCy), HLA identical siblings with PTCy (SibCy), and HLA identical siblings with calcineurin based GVHD prophylaxis (SibCNI) of either tacrolimus/ cyclosporine plus MMF ± other, or tacrolimus/cyclosporine + methotrexate ± other. The HaploCy and SibCy cohorts received PTCy with other agents as GVHD prophylaxis. Patients who received ATG or alemtuzumab were excluded. Patients who received PTCy without other immune suppression were also excluded given low numbers (N=10). Other exclusion criteria included umbilical cord blood transplants, matched unrelated donor transplants, CD34 selection or other forms of *ex vivo* T cell depletion, and patients who experienced infections prior to day 0. Matched unrelated donors were excluded due to the lack of sufficient MUD PTCy comparator cohort with detailed infection data. To minimize bias, patients transplanted at centers which had no reported haploidentical HCT patients were excluded. The final patient cohort analyzed included 757 HaploCy, 403 SibCy, and 1605 SibCNI recipients (Supplemental Table 1).

Data Source

The CIBMTR is a research consortium consisting of over 500 transplant centers internationally. Through a collaboration between the Medical College of Wisconsin and the National Marrow Donor Program, patient and outcomes data from these centers are collected and analyzed. Central auditing of the data is performed to ensure consistency and quality. The CIBMTR collects the Transplant Essential Data (TED) form and Comprehensive Report Form (CRF) prior to transplantation, at 100 days (D100), 6 months (D180), and 1 year after transplantation and annually thereafter. All patients included in this study gave written consent to participate in the CIBMTR Research Database and

to have their data included in observational research. This study was approved by the institutional review boards of the Medical College of Wisconsin and the National Marrow Donor Program.

Infection data are reported only on the CRF. Centers report infections in accordance with instructions in the forms manual (22). Data collected include an organism, site of infection, and date of onset. There are no data on prophylaxis, diagnostic methodology, or treatment of infection. Additionally, forms do not collect specifics on viral load or preemptive protocols for surveillance.

Statistical analysis

Comparative analysis was performed between three cohorts— HaploCy, SibCy, and SibCNI — to assess the impact of CRVI occurring by day +180 post-transplant. Univariate and multivariable analyses were used to determine 2-year outcomes of overall survival (OS), transplant related mortality (TRM), relapse, and chronic GVHD. The cumulative incidence function with death as a competing risk was used to estimate the probability of TRM, relapse, and chronic GVHD. OS was estimated using the Kaplan Meier analysis.

CRVI is a time-dependent variable and events may occur early after HCT. To account for impacts of CRVI prior to day 180, univariate analyses for outcomes were examined applying dynamic landmark analyses using multiple landmark time points based on the median and interquartile range for CRVI (23). This approach allows appropriate categorization of the patient as infection/no infection for patients still alive at the landmarks examined. Multivariable analyses employed the Cox proportional hazard models for outcomes by 2 years post-transplant. The main effect of the presence/absence of respiratory viral infection was kept in all models as a time-dependent variable. Variables examined in the Cox model are shown in Table 1. The proportional hazards assumptions for each factor in the Cox model were tested. If covariates violated the proportional hazards assumptions, time-dependent covariates were added. A stepwise selection procedure was used to identify significant risk factors with the significance level of 0.01. Interactions between main effect and significant covariates were tested. Center effects were tested using the score test and all models were adjusted for center effect (24).

Results

Table 2 shows the patient characteristics. The identified CRVI included rhinovirus, parainfluenza virus, respiratory syncytial virus, influenza, adenovirus, enterovirus, human metapneumovirus, and coronavirus. Rhinovirus, parainfluenza, and respiratory syncytial virus accounted for approximately 70% of all CRVI reported (Table 3). Some patients had multiple viruses; however, more patients receiving PTCy developed a CRVI [HaploCy 14%; SibCy 16%; SibCNI 9%; p <0.001). Notably, the frequency of individual viruses was not statistically different among groups.

The cumulative incidences of CRVI in the HaploCy, SibCy and SibCNI at day 30 were: 3% (99% CI, 1.6–4.8), 3% (1.3–5.5) and 2.4 % (1.5–3.5) respectively (P =0.649). However, the incidence of CRVI at day 180 was notably higher at 15.5% (12.3–19) for HaploCy,

16.2% (11.7–21.2) for SibCy, and 9.4 %(7.6–11.4) for SibCNI at 6 months (P<.001) post-transplant, with incidence of CRVI in SibCy and HaploCy significantly higher than seen with SibCNI. (Figure 1).

HaploCy + CRVI was associated with a decreased overall survival and increased treatment related mortality (TRM) by day 180. On multivariable analysis, the HaploCy cohort who develop a CRVI (n = 114) by day +180 have an inferior OS [HR 1.65 (99% CI: 1.11 – 2.43), p< .002] and increased TRM [HR 2.14 (995 CI: 1.13 – 4.07) p=0.0022] compared to reference group, SibCNI with no CRVI (n = 1421) (Figures 2A–B, Table 4, supplemental 2). The SibCy cohort (n = 65) also demonstrated an inferior overall survival [HR 1.48 (99% CI: 0.96 – 2.27), p = 0.02] and increased TRM [HR 1.84 (99% CI: 0.80 – 4.21), p = 0.057] but did not meet statistical significance. Additional factors associated with inferior overall survival include transplant for high/very high risk MDS; higher HCT-CI; and older age. Additional factors associated with an increase TRM include female donor to male recipient; older age; and development of grade II-IV aGVHD. Relapse of primary disease was the primary cause of death across the 3 cohorts. Infection as a primary or contributory cause of death occurred in 131 (35%) patients following HaploCy, 45 (25%) patients following SibCy, and 193 (26%) in the SibCNI cohort (Supplemental table 3).

There was no association of relapse risk based upon the main effect variable of CRVI and donor type with or without PTCy (p=0.119) (Figure 2C, Supplemental table 2). Patients without CRVI and receiving PTCy have a lower risk of cGVHD, regardless of donor (p<.001) (Figures 2D, Supplemental table 2). A higher risk of relapse was associated with transplant for high/very high risk MDS or advanced acute leukemia, as well as NMA/RIC conditioning. Development of grade II-IV aGVHD was protective against relapse (Table 4). Factors associated with increased cGVHD included receipt of peripheral blood stem cells, female donor for a recipient of either gender, and the development of grade II-IV aGVHD (Table 4).

Discussion

In this retrospective registry study our goal was to 1) determine the comparative incidence of community respiratory virus infections (CRVI) occurring by day +180 post-transplant in 3 cohorts defined by donor source and GHVD prophylaxis; and 2) determine the impact of CRVI on outcomes including survival, TRM, relapse, and chronic GVHD within the cohorts. We found a statistically significant increase in the 6-month cumulative incidence of CRVI in the cohorts who received PTCy regardless of donor type. The occurrance of CRVI in the HaploCy prior to day 180 was associated with an increase in TRM and decrease in OS. These findings did not extend to the SibCy group, although the small number of patients with CRVI in this cohort may have prevented findings of significance at 99% confidence. This suggests, that for CRVI, the increased risk of TRM and decrease in OS is driven predominantly by the platform of haploidentical donor and PTCy, rather than just PTCy alone. The findings from our analysis evaluated in the context of previously reported CRVI related phenomena following allogeneic HCT highlight the importance of understanding the impact of viral infection and immune recovery in haploidentical HCT with PTCy.

Recipients of allogeneic HCT are particularly susceptible to severe respiratory viral infections. Several previously identified factors contribute to the development and severity of respiratory viral infection following allogeneic HCT (25–28). Cytomegalovirus (CMV) seropositivity is a risk factor for CRVI following HCT and CMV viremia is associated with increased mortality in this setting. Progression of CRVI from upper tract disease to lower tract disease appears to impact mortality and long term pulmonary complications. Conversion from upper tract infections (URI) to lower tract infections (LRTI) is associated with CMV viremia, CRVI within the first 100 days of HCT (29), high-dose steroids at the time of CRVI, GVHD, cord blood, or antigen mismatch allo-HCT. Prospective studies reported by EBMT in 1997 showed high mortality rates from fatal pneumonias following RSV and Adenovirus (28). Subsequent studies suggest that these infections contribute to morbidity and mortality in the short and long term with increases in non-infectious pulmonary syndromes including obstructive airway disease and bronchiolitis obliterans (25, 27, 30).

Pulmonary complications represent a major cause of morbidity and mortality after allogeneic HCT, with alloimmune lung syndromes (allo-LS) including Idiopathic pneumonia syndrome (IPS), bronchiolitis obliterans syndrome (BOS), and bronchiolitis obliterans and organizing pneumonia (BOOP). Both retrospective and prospective studies have found associations between early CRVI associated airflow decline (30) and short- and long-term pulmonary function as well as the development of allo-LS, and data show that this complication contributes to transplant related outcomes (31). In allogeneic HCT as a whole, improvements in care associated with prospective interventional clinical surveillance programs for CRVI have suggested that all-cause mortality is substantially reduced with intervention when compared to retrospective controls (32). Addressing the higher rates of viral infections, as seen in HaploCy HCT, and understanding the characteristics of immune reconstitution provide opportunities for improving transplant outcomes by focusing on infection control measures and early identification of patients at risk for increased morbidity and mortality from the sequelae of these infections.

Our study supports the importance of respiratory viral infections in transplant outcome and particularly in the setting of HaploCy. While the cumulative incidences of community respiratory viral infections following allogeneic HCT in our population is relatively low particularly within the first 30 days after HCT, CRVI increases in frequency over subsequent months. This timing correlates with patients leaving the protection of the transplant center and early isolation measures and resultant increased exposure to community based pathogens. By day 180 post HCT there is a statistically significant increase in community respiratory viral infections in the patients who received post-transplant cyclophosphamide as compared to standard calcineurin inhibitor based GVHD prophylaxis, regardless of donor type. We saw decreased survival and increased treatment related mortality in HaploCy cohort as compared to SibCNI with no CRVI. Our findings suggest that the degree of mismatch as well as the use of PTCy may impact the incidence of CRVI and, subsequently, transplant outcome. The small number of patients in the SibCy cohort who developed CRVI likely contributed to the inability to find statistical significance at the 99% confidence level making it difficult to evaluate the contributions of mismatch versus PTCy with respect to

outcomes. Ongoing efforts to better define immune reconstitution in the setting of PTCy and different donor sources are needed.

There are clear limitations to this analysis. These data are collected retrospectively across multiple institutions and could be impacted by substantial variation related to practice patterns. Testing for CRVI is not done pre-emptively and there are no data captured on indications nor the methodology utilized for CRVI testing. For patients who have left the transplant center, even if tested, the results may not be reported to the transplant center for subsequent CIBMTR reporting. These limitations are likely to underestimate the absolute incidence of CRVI as testing is more likely to be completed in patients with more persistent or severe symptoms or those seen at the transplant center instead of in the community. In addition, the data available through the CIBMTR do not define the severity of infection including a lack of information on the progression from upper tract infection to lower tract infection, duration of infection, or requirement for hospitalization or more intensive support. Furthermore, we were unable to comment on correlations to immune reconstitution due to limited reported data for quatitative immunoglobulins and lymphocyte subsets.

Additional limitations of this study include our inability to determine outcome of specific viral infections and whether infections associated with adenovirus were primary infections or reactivation. While the outcome for individual respiratory viral infections are expected to differ by organism, even a CRVI with a less virulent organism has potential to lead to LRTI and additional morbidity. Therefore we included all common CRVI regardless of expected virulence. Rhinovirus progression to LRTI in allogeneic HCT recipients is significant ranging from 17–29% in recent publications (37, 38). Similarly, human coronavirus infections are common causes of CRVI in allogeneic HCT recipients and have been reported to progress to LRTI in 5–30% of cases (39, 40). While we are unable to determine whether adenoviral infections were related to primary infections or reactivation, the incidence of adeniviral infections in allogeneic HCT recipients is significant with high mortality rates in the setting of LRTI and disseminated infections (29, 41). Consequently, inclusion of all reported CRVI is supported.

The higher overall mortality for HaploCy patients developing CRVI warrants consideration for pre-emptive, therapeutic, and long term follow up studies of such patients in an effort to identify strategies for improving outcomes. Antiviral options for treatment of respiratory viral infections, with the exception of influenza, remain limited. However, evolving and expanding treatment for respiratory viral infections are in clinical trials, including the use of antiviral cytotoxic T cells, virus-specific monoclonal antibodies or nanobodies. Other novel antiviral therapies such as the new fusion or entry inhibitors may offer potential for improvement in high risk settings. The development of bronchiolitis obliterans, which has been associated with early respiratory viral infections after allogeneic HCT is frequently not diagnosed until substantial airway obstruction has occurred and the patient has experienced irreversible lung damage causing progressive respiratory impairment, increased infections and an increase in non-relapse mortality (20, 25, 29). Strategies for early detection of developing allo-LS such as bronchiolitis obliterans are critical to prevent irreversible consequences of advanced bronchiolitis obliterans. Application of prevention and treatment strategies may be more effective once the important deficits in immune recovery are better

defined. Pro-active surveillance, aggressive efforts to limit the incidence of CRVI, including wearing masks, and detection of early disease may offer opportunities to intervene and prevent adverse outcomes related to the immunologic sequela of CRVI in these patients. (32–36)

Conclusion

In conclusion, the findings from this retrospective registry study show that the use of PTCy increases the incidence of CRVI and composite viral infections regardless of donor type. The occurrence of CRVI in the setting of PTCy impacts OS and TRM and is statistically significant in the HaploCy cohort. While we are unable to comment on the specific pathophysiology, previously reported studies related to CRVI in allogeneic HCT are intriguing and suggest that there are opportunities to develop pre-emptive and therapeutic strategies that may have substantial impact on outcome in this setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Community Respiratory Viral Infection by Donors

Cumulative Incidence			
HaploCy	3 (1.6-4.8)%	9.6 (7.1-12.6)%	15.5 (12.3-19)%
SibCy	3 (1.2-5.5)%	11.4 (7.7-15.8)%	16.2 (11.7-21.2)%
SibCNI	2.4 (1.5-3.5)%	6.4 (4.9-8)%	9.4 (7.6-11.4)%
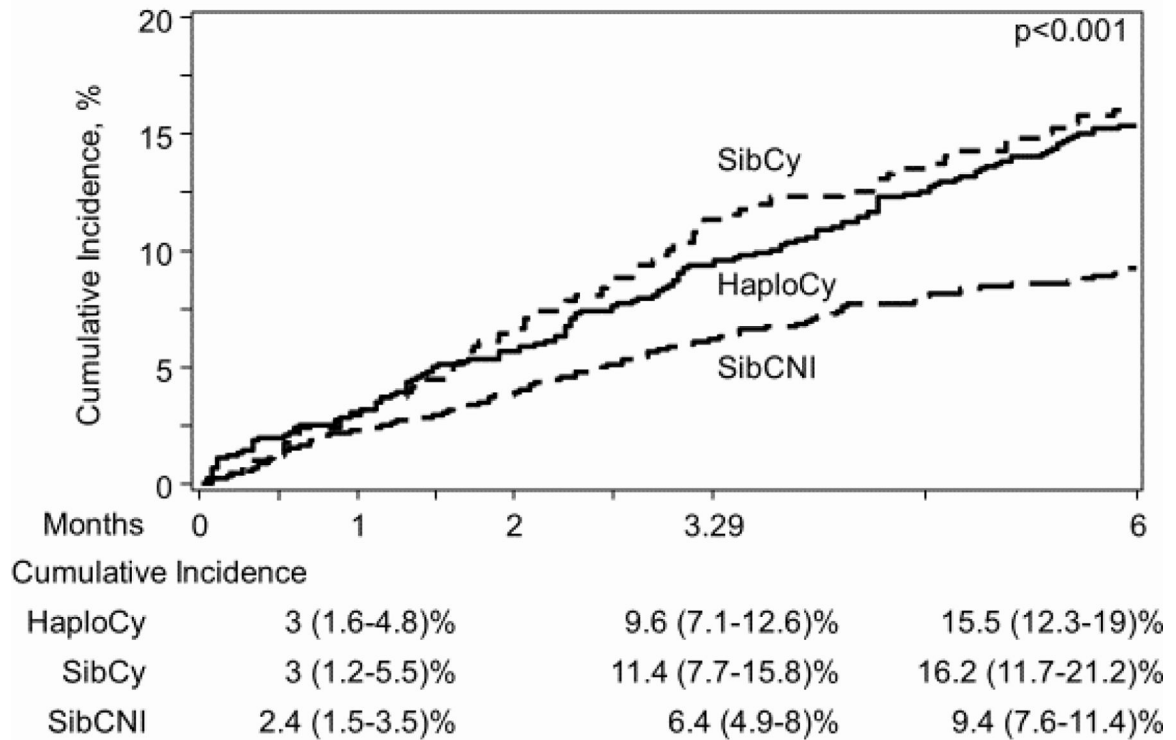
Figure 1:

The Incidence of CRV infections based on donor type

The cumulative incidences of CRVI in the HaploCy, SibCy and SibCNI at day 30 were: 3% (99% CI, 1.6–4.8), 3% (1.3–5.5) and 2.4 %(1.5–3.5) respectively (P =0.649). However, the incidence of CRVI at day 180 was notably higher at 15.5% (12.3–19) for HaploCy, 16.2% (11.7–21.2) for SibCy, and 9.4 %(7.6–11.4) for SibCNI at 6 months (P<.001) post-transplant, with incidence of CRVI in SibCy and HaploCy significantly higher than seen with SibCNI
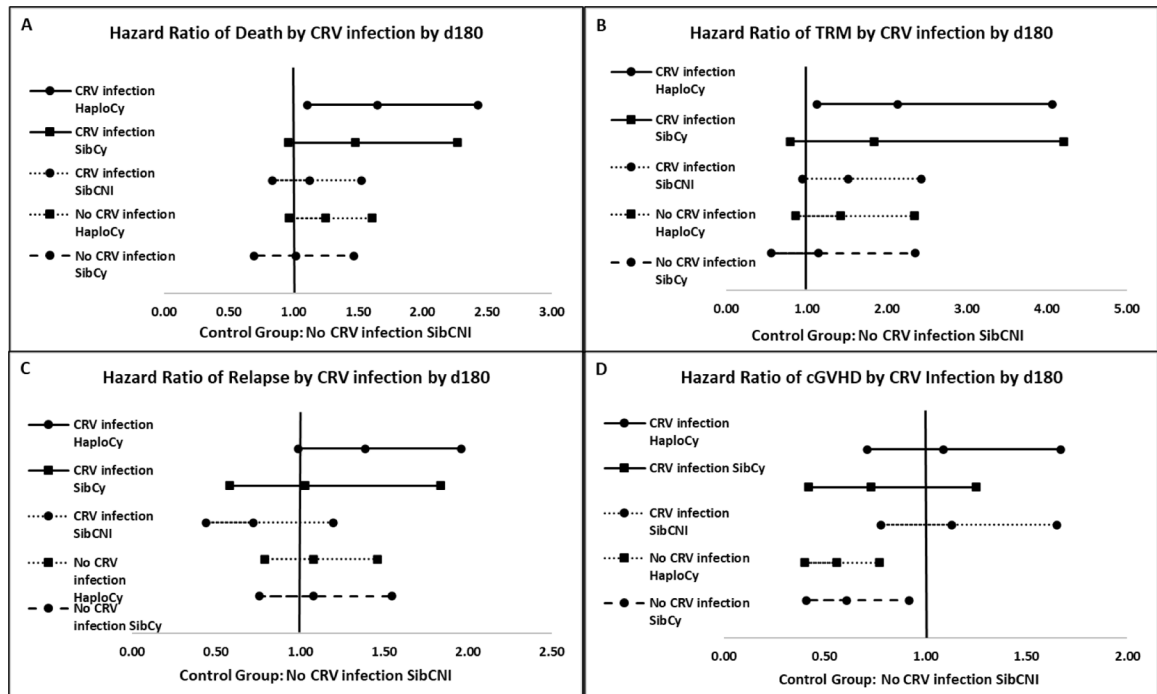
Figure 2:
Forest plots of the main effect variable of the presence/absence of infection by HaploCy, SibCy, and SibCNI cohorts. The reference group for each panel is the SibCy cohort without infection. Hazard ratio for death (A), transplant related mortality (B), relapse (C), and chronic GVHD (D) are shown.

Table 1:

Variables included in the MVA

Analyses: 2y OS, 2y DFS, 2y Rel, 2y NRM, 2y cGVHD

Main Effect Variable: Groups by CRV infection
• HaploPTCy with CRV infection vs Haplo PTC no CRV infection vs MRDPTCy with CRV infection vs MRD PTCy no CRV infection vs MRD no PTCy with CRV infection vs MRD no PTCy no CRV infection (ref)

Other variables to be examined
• Graft type: Marrow (ref) vs PB
• D/R Gender: M-M (ref) vs M-F v F-F v F-M
• HCT-CI: 0 (ref) vs 1 −2 vs 3–4 vs 5+
• Disease risk: AL favorable cyto, early/intermediate stage (ref) vs AL intermediate/nl cyto, early stage, vs AL poor cyto, early stage; vs AL int/nl cyto, intermediate stage vs AL poor cyto, intermediate stage vs AL advanced (all cyto categories) vs MDS very low/low vs MDS intermediate vs MDS high/very high
• Recipient Age: 20 (ref) vs 21 – 40 vs 41 – 60 v >60
• KPS: 90 (ref) vs 80 – 89 vs <80
• Conditioning intensity: Myeloablative (ref) vs RIC/NMA
• TBI: No (ref) vs Yes
• Time from dx to HCT: <6 m (ref) vs 6 – 12 m vs >12 m
• Year of HCT: 2012 – 2014 (ref) vs 2015 – 2017
• Neutrophil engraftment prior to infection (time dependent)
• # of Viral infections: None vs 1 vs 2 vs 3+
• Co-Infection: No infection (ref) vs Viral + Co-infection vs Viral + Co-infection vs other infection by day 180
• Acute GVHD grade 2 – 4 (time dependent)

Table 2:

Characteristics of the three cohorts as defined by presence/absence of CRVI by day 180.

Variable	CRV Infection by day 180			No CRV infection		
	HaploCy N(%) N = 117	SibCy N(%) N = 65	SibCNI N(%) N = 151	HaploCy N(%) N = 640	SibCy N(%) N = 338	SibCNI N(%) N = 1454
Number of centers	46	34	56	97	72	99
Patient Related						
Gender, Male	77 (66)	39 (60)	79 (52)	382 (60)	204 (60)	854 (59)
Age at transplant, years						
10	8 (7)	1 (2)	11 (7)	27 (4)	3 (<1)	30 (2)
11–20	12 (10)	4 (6)	4 (3)	39 (6)	19 (6)	81 (6)
21–30	12 (10)	16 (25)	13 (9)	56 (9)	53 (16)	102 (7)
31–40	5 (4)	10 (15)	8 (5)	39 (6)	52 (15)	129 (9)
41–50	17 (15)	9 (14)	22 (15)	54 (8)	58 (17)	183 (13)
51–60	25 (21)	11 (17)	35 (23)	127 (20)	71 (21)	357 (25)
61–70	29 (25)	12 (18)	51 (34)	226 (35)	73 (22)	498 (34)
>70	9 (8)	2 (3)	7 (5)	72 (11)	9 (3)	74 (5)
Karnofsky/Lansky performance status						
90	64 (55)	37 (57)	91 (60)	326 (51)	196 (58)	855 (59)
80–89	34 (29)	18 (28)	45 (30)	195 (30)	84 (25)	404 (28)
<80	16 (14)	10 (15)	15 (10)	103 (16)	55 (16)	185 (13)
Missing	3 (3)	0	0	16 (3)	3 (<1)	10 (<1)
HCT-CI						
0	32 (27)	10 (15)	37 (25)	167 (26)	93 (28)	355 (24)
1–2	29 (25)	17 (26)	40 (26)	180 (28)	107 (32)	407 (28)
3–4	38 (32)	18 (28)	48 (32)	173 (27)	86 (25)	428 (29)
5+	18 (15)	20 (31)	26 (17)	119 (19)	51 (15)	259 (18)
Missing	0	0	0	1 (<1)	1 (<1)	5 (<1)
Donor Related						
Donor/recipient gender match						
Male-Male	49 (42)	24 (37)	47 (31)	240 (38)	132 (39)	460 (32)
Male-Female	21 (18)	19 (29)	32 (21)	159 (25)	80 (24)	315 (22)
Female-Male	28 (24)	15 (23)	32 (21)	142 (22)	72 (21)	394 (27)
Female-Female	19 (16)	7 (11)	40 (26)	99 (15)	54 (16)	284 (20)
Missing	0	0	0	0	0	1 (<1)
Disease Related						
Disease						
AML	87 (74)	53 (82)	105 (70)	441 (69)	257 (76)	920 (63)

	CRV Infection by day 180			No CRV infection		
Variable	**HaploCy N(%) N = 117**	**SibCy N(%) N = 65**	**SibCNI N(%) N = 151**	**HaploCy N(%) N = 640**	**SibCy N(%) N = 338**	**SibCNI N(%) N = 1454**
ALL	5 (4)	2 (3)	7 (5)	21 (3)	17 (5)	53 (4)
MDS	25 (21)	10 (15)	39 (26)	178 (28)	64 (19)	481 (33)
Disease status						
AML/ALL, early	49 (42)	31 (48)	59 (39)	259 (40)	158 (47)	660 (45)
AML/ALL, intermediate	27 (23)	11 (17)	27 (18)	116 (18)	66 (20)	183 (13)
AML/ALL, advanced	15 (13)	13 (20)	22 (15)	82 (13)	48 (14)	122 (8)
AML/ALL, unknown	1 (<1)	0	5 (3)	5 (<1)	2 (<1)	10 (<1)
MDS, early	12 (10)	3 (5)	10 (7)	64 (10)	21 (6)	169 (12)
MDS, advanced	13 (11)	7 (11)	28 (19)	114 (18)	43 (13)	310 (21)
Cytogenetics for AML/ALL						
Normal	10 (9)	3 (5)	7 (5)	32 (5)	25 (7)	76 (5)
Favorable	3 (3)	2 (3)	2 (1)	20 (3)	16 (5)	37 (3)
Intermediate	36 (31)	20 (31)	54 (36)	220 (34)	120 (36)	464 (32)
Poor	42 (36)	28 (43)	40 (26)	161 (25)	104 (31)	334 (23)
Other	1 (<1)	1 (2)	7 (5)	19 (3)	5 (1)	42 (3)
Not tested/Missing	0	1 (2)	2 (1)	10 (2)	4 (1)	20 (1)
MDS N/A	25 (21)	10 (15)	39 (26)	178 (28)	64 (19)	481 (33)
IPSS-R prior to transplant (MDS only)						
Very low	1 (<1)	3 (5)	1 (<1)	18 (3)	11 (3)	59 (4)
Low	9 (8)	4 (6)	11 (7)	58 (9)	18 (5)	122 (8)
Intermediate	8 (7)	3 (5)	13 (9)	45 (7)	19 (6)	147 (10)
High	6 (5)	0	7 (5)	24 (4)	10 (3)	66 (5)
Very high	0	0	4 (3)	13 (2)	3 (<1)	34 (2)
Missing	1 (<1)	0	3 (2)	20 (3)	3 (<1)	53 (4)
AML/ALL N/A	92 (79)	55 (85)	112 (74)	462 (72)	274 (81)	973 (67)
		Transplant Related				
Graft type						
Bone Marrow	51 (44)	24 (37)	22 (15)	257 (40)	107 (32)	178 (12)
Peripheral blood	66 (56)	41 (63)	129 (85)	383 (60)	231 (68)	1276 (88)
Conditioning regimen intensity						
Myeloablative	53 (45)	38 (58)	89 (59)	261 (41)	184 (54)	846 (58)
RIC/NMA	64 (55)	27 (42)	62 (41)	379 (59)	154 (46)	608 (42)
TBI, yes	78 (67)	40 (62)	48 (32)	453 (71)	194 (57)	388 (27)
Time from diagnosis to transplant						
<6 month	49 (42)	33 (51)	81 (54)	266 (42)	147 (43)	809 (56)
6 month-12 months	30 (26)	17 (26)	30 (20)	165 (26)	100 (30)	318 (22)

	CRV Infection by day 180			No CRV infection		
Variable	**HaploCy N(%)** **N = 117**	**SibCy N(%)** **N = 65**	**SibCNI N(%)** **N = 151**	**HaploCy N(%)** **N = 640**	**SibCy N(%)** **N = 338**	**SibCNI N(%)** **N = 1454**
>12 months	38 (32)	15 (23)	39 (26)	208 (32)	90 (27)	324 (22)
Missing	0	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Year of transplant						
2012 – 2014	24 (21)	13 (20)	101 (68)	146 (23)	74 (22)	718 (49)
2015 – 2017	93 (79)	52 (80)	63 (42)	494 (67)	264 (68)	736 (51)

Table 3

CRV type and frequency based on donor type. The values (n, %) for the organisms in the table are for the patients with the individual infections by a specific organism. Some patients had more than one CRVI reported and a patient may be included in more than one organism group. The percentages noted represent the percent for individual organisms of the total number of CRVI. The p-value for each organism is from the Chi-squared analysis of the organism based upon the number of total patients with infection for that specific organism.

Organism	HaploCy n=757 (%)	SibCy n=403 (%)	SibCNI n=1605 (%)	P-value
Number of patients with CRVI	**107 (14%)**	**63 (16%)**	**147 (9%)**	**<0.001**
Organisms Reported (not mutually exclusive)				
Rhinovirus	27 (25%)	30 (48%)	53 (36%)	0.011
Parainfluenza	24 (22%)	15 (24%)	41 (28%)	0.588
Respiratory syncytial virus	32 (30%)	10 (16%)	35 (24%)	0.118
Influenza	16 (15%)	8 (13%)	24 (16%)	0.796
Adenovirus	20 (19%)	12 (19%)	15 (10%)	0.098
Enterovirus	6 (6%)	5 (8%)	7 (5%)	0.660
Human Metapneumovirus	2 (2%)	0	4 (3%)	0.415
Coronavirus	3 (3%)	0	3 (2%)	0.425

Table 4:

Multivariable analyses for events by 2 years

Variable	N	Hazard Ratio [99% CI]	p-value
Overall Mortality (adjusted for center effects)			
Main Effect Variable, Infection			**0.0017**
SibCNI, no infection	1421	1.00	
HaploCy <u>with</u> infection	114	**1.65 [1.11 – 2.43]**	**0.0010**
SibCy <u>with</u> infection	65	1.48 [0.96 – 2.27]	0.0203
SibCNI <u>with</u> infection	148	1.13 [0.84 – 1.53]	0.2787
HaploCy no infection	615	1.25 [0.97 – 1.61]	0.0246
SibCy no infection	330	1.20 [0.70 – 1.47]	0.8979
Disease/Stage/Cytogenetics (IPSS)			**< 0.0001**
AL, early/intermediate, favorable cyto	68	1.00	
AL early, normal/intermediate cyto	667	1.00 [0.56–1.78]	0.9892
AL early, poor cyto	434	0.96 [0.55–1.69]	0.8655
AL intermediate, normal/intermediate cyto	213	1.07 {0.59 – 1.92]	0.7695
AL intermediate, poor cyto	124	1.27 [0.69 – 2.33]	0.3208
AL advanced, any cyto	291	**1.97 [1.08 – 3.60]**	**0.0036**
MDS very low/low	307	0.90 [0.51 – 1.59]	0.6248
MDS intermediate	229	1.54 [0.87 – 2.72]	0.0539
MDS high/very high	162	**2.05 [1.09 – 3.86]**	**0.0034**
Missing	198	1.29 [0.66 – 2.50]	0.3255
HCT-CI			**0.0004**
0	679	1.00	
1 – 2	762	0.95 [0.67 – 1.34]	0.6945
3 – 4	768	1.12 [0.80 – 1.56]	0.3815
5+	484	1.32 [0.94 – 1.85]	0.0380
Age at HCT, years			**<0.0001**
0 – 20	234	1.00	
21 – 40	479	0.88 [0.60 – 1.30]	0.4042
41 – 60	945	1.27 [0.89 – 1.82]	0.0790
60	1035	**1.62 [1.08 – 2.42]**	**0.0023**
Treatment Related Mortality (adjusted for center effects)			
Main Effect Variable, Infection			**0.0164**
SibCNI, no infection	1415	1.00	
HaploCy <u>with</u> infection	116	**2.14 [1.13 – 4.07]**	**0.0022**
SibCy <u>with</u> infection	65	1.84 [0.80 – 4.21]	0.0574
SibCNI <u>with</u> infection	146	1.52 [0.95 – 2.43]	0.0223
HaploCy no infection	621	1.42 [0.86 – 2.35]	0.0736

Variable	N	Hazard Ratio [99% CI]	p-value
SibCy no infection	329	1.15 [0.56 – 2.36]	0.6290
Donor/Recipient Gender Match			**<0.0001**
Male/Male	927	1.00	
Male/Female	616	1.05 [0.77 – 1.43]	0.6610
Female/Male	**658**	**1.45 [1.13 – 1.87]**	**0.0002**
Female/Female	491	0.82 [0.56 – 1.19]	0.1631
Age at HCT, years			**0.0025**
0 – 20	234	1.00	
21 – 40	477	0.80 [0.47 – 1.37]	0.2857
41 – 60	946	1.23 [0.68 – 2.25]	0.3673
> 60	1035	1.77 [0.88 – 3.55]	0.0341
Acute GVHD, grade II-IV			**<0.0001**
No	1837	1.00	
Yes	855	**2.66 [1.79 – 3.96]**	
Relapse (adjusted for center effects)			
Main Effect Variable, Infection			0.1185
SibCNI, no infection	1407	1.00	
HaploCy <u>with</u> infection	113	1.39 [0.99 – 1.96]	0.0118
SibCy <u>with</u> infection	65	1.03 [0.58 – 1.84]	0.8883
SibCNI <u>with</u> infection	146	0.72 [0.44 – 1.20]	0.0992
HaploCy no infection	605	1.08 [0.79 – 1.46]	0.5416
SibCy no infection	326	1.08 [0.76 – 1.55]	0.5700
Disease/Stage/Cytogenetics (IPSS)			**<0.0001**
AL, early/intermediate, favorable cyto	67	1.00	
AL early, normal/intermediate cyto	659	0.69 [0.40 – 1.21]	0.0890
AL early, poor cyto	430	0.96 [0.54 – 1.70]	0.8366
AL intermediate, normal/intermediate cyto	208	0.75 [0.43 – 1.33]	0.1945
AL intermediate, poor cyto	124	1.03 [0.55 – 1.94]	0.8889
AL advanced, any cyto	**289**	**2.00 [1.18 – 3.40]**	**0.0007**
MDS very low/low	305	1.03 [0.61 – 1.76]	0.8827
MDS intermediate	227	1.20 [0.67 – 2.16]	0.4246
MDS high/very high	**159**	**2.27 [1.25 – 4.10]**	**0.0004**
Missing	194	1.12 [0.62 – 2.01]	0.6141
Conditioning Intensity			**<0.0001**
Myeloablative	1419	1.00	
RIC/NMA	**1243**	**1.46 [1.23 – 1.73]**	
Acute GVHD, grade II-IV			**<0.0001**
No	1816	1.00	

Variable	N	Hazard Ratio [99% CI]	p-value
Yes	846	**0.78 [0.67 – 0.91]**	
Chronic GVHD (adjusted for center effects)			
Main Effect Variable, Infection			**<0.0001**
SibCNI, no infection	1433	1.00	
HaploCy <u>with</u> infection	117	1.09 [0.71 – 1.67]	0.6031
SibCy <u>with</u> infection	65	0.73 [0.42 – 1.25]	0.1283
SibCNI <u>with</u> infection	148	1.13 [0.78 – 1.65]	0.3971
HaploCy no infection	632	**0.56 [0.40 – 0.77]**	**<0.0001**
SibCy no infection	332	**0.61 [0.41 – 0.92]**	**0.0017**
Graft Type			**<0.0001**
Bone Marrow	636	1.00	
Peripheral Blood	2091	**2.23 [1.66 – 3.00]**	
Donor/Recipient Gender Match			**0.0005**
/Male	937	1.00	
Male/Female	623	1.01 [0.82 – 1.25]	0.8804
Female/Male	670	**1.26 [1.04 – 1.54]**	**0.0021**
Female/Female	496	**1.24 [1.01 – 1.53]**	**0.0074**
Acute GVHD, grade II-IV			**0.0004**
No	1820	1.00	
Yes	907	**1.30 [1.07 – 1.58]**	