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Post-Transplantation Cyclophosphamide is Associated with Increased Bacterial Infections

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Abstract

Post-transplant cyclophosphamide (PTCy) is increasingly used to reduce graft-versus-host disease after hematopoietic cell transplantation (HCT); however, it might be associated with more infections. All patients who were ≥2 years old, receiving haploidentical or matched sibling donor (Sib) HCT for acute leukemias or myelodysplastic syndrome, and either calcineurin inhibitor (CNI)- or PTCy-based GVHD prophylaxis [Haploidentical HCT with PTCy (HaploCy), 757; Sibling with PTCy (SibCy), 403; Sibling with CNI-based (SibCNI), 1605] were included. Most bacterial infections occurred within the first 100 days; 953 patients (34.5%) had at least 1 infection and 352 patients (13%) had ≥2 infections. Patients receiving PTCy had a greater incidence of bacterial infections by day 180 [HaploCy 46%; SibCy 48%; SibCNI 35%; p<0.001). Compared with the SibCNI without infection cohort, 1.99-fold, 3.33-fold, 2.78-fold, and 2.53-fold increased TRM was seen for the HaploCy cohort without infection and HaploCy, SibCy, and SibCNI cohorts with infection, respectively. Bacterial infections increased mortality [HaploCy (HR1.84, 99%

CI: 1.45–2.33, p<0.0001], SibCy cohort (HR,1.68, 99% CI: 1.30–2.19, p<0.0001), and SibCNI cohort (HR,1.76, 99% CI: 1.43–2.16, p<0.0001)]. PTCy was associated with increased bacterial infections regardless of donor, and bacterial infections were associated with increased mortality irrespective of GVHD prophylaxis. Patients receiving PTCy should be monitored carefully for bacterial infections following PTCy.

Keywords

Post-Transplantation cyclophosphamide; allogeneic; hematopoietic cell transplantation; bacterial infections; survival; Graft-versus-host disease

Introduction

Bacterial infections in patients undergoing allogeneic stem cell transplant (alloHCT) are associated with significant morbidity and mortality.[1–5] Bacterial infections are highest during the pre-engraftment phase,[6] and are influenced by diagnosis,[7] graft source,[8] and graft-versus-host disease (GVHD) prophylaxis.[4, 9, 10]

In recent years, the use of post-transplantation cyclophosphamide (PTCy) has significantly increased in alloHCT due to its association with decreased rates of GVHD.[11–13] PTCy was first used in haploidentical donor HCT,[14] and its use has been extended to other donor type HCTs.[15] Despite the lowered incidence of GVHD in patients undergoing alloHCT with PTCy, increased viral infections have been reported in these patients.[16–18] Additionally, recent analyses from the Center for International Blood and Marrow Transplant Research (CIBMTR) demonstrated an increased risk of Cytomegalovirus (CMV), community respiratory viral infections, and non-CMV herpes viral infections following PTCy in the haploidentical and matched sibling donor setting.[19–21] Furthermore, several single-center analyses suggest increased rates of bacterial infections in patients receiving PTCy.[22–24] However, these reports are limited by small sample size and do not include pediatric alloHCT recipients.

The purpose of this study was to evaluate bacterial infections in patients receiving PTCy. To do this, we evaluated three cohorts of patients in the CIBMTR database: patients undergoing alloHCT haploidentical HCT with PTCy (HaploCy), those receiving matched sibling donor grafts with PTCy GVHD prophylaxis (SibCy), and patients who received matched sibling donor grafts and calcineurin inhibitor based GVHD prophylaxis (SibCNI).

Material and Methods

Patient Population:

The study population was previously described.[19] Briefly, we included all patients reported to the CIBMTR from 2012 to 2017 who were ≥2 years of age and undergoing first alloHCT for acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS). Cohorts were defined by GVHD prophylaxis and included the following:

- HaploCy: Individuals undergoing alloHCT and receiving a haploidentical graft from a mismatched related donor. Haploidentical HCT was defined as ≥2 antigen/allele mismatched within the loci HLA-A, -B, -C, -DRB1 and -DQB1 between donor and recipient.
- SibCy: Those receiving matched sibling donor grafts with PTCy GVHD prophylaxis (SibCy)
- SibCNI: Patients who received matched sibling donor grafts with calcineurin inhibitor based GVHD prophylaxis. This cohort included patients receiving CNI (i.e., tacrolimus or cyclosporine) with either methotrexate (MTX) ± other or mycophenolate mofetil (MMF) ± other.

Patients receiving anti-thymocyte globulin and/or alemtuzumab were excluded. Other exclusion criteria included single mismatch related donors and umbilical cord blood donors. Matched unrelated donor graft were excluded due to smaller numbers of unrelated donors with PTCy and inadequate infection data. To minimize ascertainment bias due to potentially different practices for infection screening and prophylaxis between centers, patients from centers without a patient in both the SibCNI and the HaploCy cohorts were excluded.

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.[25] Data collected include an organism, site of infection, and date of onset. There are no data on diagnostic methodology, or treatment of infection. Infection prophylaxis information is limited prior to 2017.

Outcomes and Study Definitions

The primary outcomes of this study were the cumulative incidence of any bacterial infection, excluding *Clostridioides difficile*, and bacterial infection density by day 180 for the three cohorts defined by donor and GVHD prophylaxis [HaploCy, SibCy, SibCNI]. Infection density is the number of bacterial infections per patient per days at risk during the first 180 days.[26] In addition to general bacterial infections, these outcomes were also examined for mucosal barrier injury–laboratory confirmed bloodstream infection (MBI-LCBI) and bacterial blood stream infections (BSI). MBI-LCBI used a modified definition as previously published.[7, 27, 28] Other major outcomes were acute and chronic GVHD, overall survival (OS), disease-free survival (DFS), transplant-related mortality (TRM), and infection-related

mortality (IRM). Patients were considered an event for IRM if the primary cause of death was infection either concurrent (± 30 days) with or prior to relapse.

Statistical Analysis

Patient-, disease- and transplant-related factors were compared between cohorts using the Chi-square test for categorical variables and the Wilcoxon two sample test for continuous variables. The univariate probability of OS was calculated using the Kaplan Meier estimator, with the variance estimated by Greenwood's formula. For values for other endpoints, cumulative incidence estimates to account for competing risks were calculated.

Outcomes were examined in six groups defined by cohort and the presence/absence of infection. Because neutropenia and infection as well as acute GVHD (aGVHD) and infection are intertwined time-dependent events, it was necessary to examine the interaction using a dynamic landmark analysis at three landmark times for each univariate analysis, defined as the median and interquartile range for the event [MBI-LCBI, BSI, any bacterial infection, acute GVHD (aGVHD), or neutrophil recovery].[29] Death was the competing risk for cumulative incidence of infection, acute and chronic GVHD. Relapse was a competing risk for IRM and TRM.

Cox proportional hazards regression was used for outcomes of OS, TRM, IRM, chronic GVHD (cGVHD), and relapse. The variables considered in the multivariable regression models are listed (Supplemental materials) and all results were examined for center effect.[30] The assumption of proportional hazards for each factor in the Cox model was tested. When the proportional hazards assumption was violated, time-dependent variable was added in the model. The stepwise variable selection method was used to identify significant risk factors which associated with the outcomes. Factors significantly associated with the outcome variable at a 1% level were kept in the final model. As infections were expected to have the greatest impact around the time of infection, all outcomes were examined between day 100 to 2 years from transplant.

Data Sharing Statement

The final analysis dataset will be posted to the CIBMTR website at: https://cibmtr.org/CIBMTR/Resources/Publicly-Available-Datasets1#.

Results

Patient Characteristics

Detailed characteristics of 2765 HCTs (HaploCy, 757; SibCy, 403; and SibCNI, 1605) previously published in another CIBMTR study evaluating CMV are provided in Table 1.[19] The median age of patients in the SibCNI cohort was significantly lower and had less patients with performance scores <80% than the other two groups. However, the HCT-CI was similar between the three cohorts. The SibCNI cohort received more myeloablative conditioning (MAC) and peripheral blood stem cells (PBSC) but less TBI-based conditioning and lower reported use of growth factor after HCT [HaploCy 82% vs SibCy 79% vs SibCNI 24%, p <0.001]. The SibCNI cohort also had a shorter time from

diagnosis to HCT. Finally, in addition to PTCy, 99% of patients in the HaploCy cohort, and 95% in the SibCy cohort, received a calcineurin inhibitor (CNI).

Incidence of Bacterial Infections

A total of 1108 patients (40%) had at least one infection by day 180, with most infections occurring within the first 100 days. The median time to any bacterial infection was 12 – 13 days, which was similar between the three cohorts (p=0.595). Additionally, 5 to 6% of patients in each cohort had a new bacterial infection between days 100 and 180. (Figure 1A).

Patients receiving PTCy had a higher cumulative incidence of bacterial infections within first 180 days (HaploCy, 46.1% vs. SibCy, 48% vs. SibCNI, 35.3%; p<0.001) (Figure 1A and 1B). MBI-LCBI occurred more commonly in patients receiving PTCy (MBI-LCBI: HaploCy, 15.5% vs. SibCy,15.4% vs. SibCNI, 7.7%; p<0.001) (Figure 2A and B). Similarly, any bacterial BSI were more common in the PTCy cohorts (HaploCy, 24.7% vs. SibCy, 26.1% vs. SibCNI, 17.7%; p<0.001) within 180 days after alloHCT (Figure 2A and C).

The median day of neutrophil engraftment was 16 days (IQR: 14 – 19) in the entire population [HaploCy: 17 days (range, 1 – 125 days); SibCy: 16 days (<1 – 61 days); SibCNI:15 days (1 – 73 days)]. Using 14 days (lower bound IQR) as the landmark, the cumulative incidence of any bacterial infection by 100 days was higher for patients receiving PTCy, irrespective of donor compared to patients in the SibCNI cohort [HaploCy 19.1% (99% CI, 14 – 24.9%); SibCy 19.4% (12.7–27.2%); SibCNI 12.2% (9.5 – 15.1%); p = 0.002]. Notably, this impact waned by day 180. Furthermore, examining the landmark of the median (16 days) and the upper bound of the IQR (19 days), significance was lost (16 days, p=0.013; 19 days p=0.04). When examining specifically for MBI-LCBI or any BSI, there was no difference between the cohorts at day 100 or day 180 for the median or the upper IQR; however, BSI at the day 14 landmark was higher in the PTCy cohorts [HaploCy 10% (6.5 – 14.1); SibCy 8.2% (4.2 – 13.4); SibCNI 5.1% (3.4 – 7); p = 0.006] (Supplemental Table 1).

Acute GVHD and infection are overlapping time-dependent events. Therefore, dynamic landmark analysis (DLA) was again used to examine the cumulative incidence of infection with the left truncation landmarks of the onset of acute GVHD [median: 38 days, IQR: 26 – 63 days]. There was no difference in the cumulative incidence of any bacterial infection, MBI-LCBI, or BSI between the cohorts at day 100 or day 180 at any of the landmarks assessed (Supplemental Table 2). Of note, in a separate landmark analysis, the impact of infections on acute or chronic GVHD was evaluated and found no impact on acute GVHD or chronic GVHD (Supplemental Table 3 and 4).

As noted previously, 517 patients (19%) had more than one bacterial infection in the first 100 days. To account for multiple infections and varied time evaluable due to early deaths, infection density was examined by cohort to establish the rate of infection in the first 180 days. For any bacterial infection, MBI-LCBI, and any BSI, infections were more likely in the PTCy cohorts irrespective of donor source. The rate of any bacterial infection was 0.884, 0.855, 0.604 (p<0.001) in HaploCy, SibCy, and SibCNI, respectively (Table 2). Overall

MBI-LCBSI rates were 0.194, 0.177, and 0.092 (p<0.001) and any bacterial BSI rates were 0.36, 0.36, and 0.24 (p<0.001) in HaploCy, SibCy, and SIBCNI, respectively.

Pathogens—In terms of bacteria type, vancomycin-resistant Enterococcus (VRE) and gram-negative rods (GNR) were more common in the PTCy cohorts by day 180. The frequency of VRE was 6%, 5%, and 3% in HaploCy, SibCy, and SibCNI, p<0.001, respectively. The frequency of GNR was 21%, 25%, and 15% in HaploCy, SibCy, and SibCNI, p=<.001, respectively. This was true for non-Enterobacteriaceae as well as Enterobacteriaceae GNR. (Supplemental Table 5 and Supplemental Figure 1).

TRM and Infection related mortality (IRM)—Patients diagnosed with a bacterial infection had a higher TRM by 2 years after HCT [HaploCy 27% (19–36); SibCy 20% (11–32%); SibCNI 19% (13 – 26%)] compared with those patients without a bacterial infection by day 16 [HaploCy 20% (15 – 24); SibCy 16% (11 – 23%); SibCNI 12% (10 – 15%); p=0.002] (Supplemental Table 6). The 2-year TRM was higher in the cohorts with any bacterial infection, irrespective of the landmark of median, lower (9 days), or upper (63 days) quartile examined. These findings were consistent when examining by BSI (median onset 48 days) and MBI-LCBI (median onset 10 days). Similar to 2-year TRM, 2-year IRM was lowest in the SibCNI without infection cohort [2.9% (1.7 – 4.5%)] and highest for the HaploCy with infection cohort [10.5% (4.7 – 18.1%)] and intermediate for the other 4 cohorts [with bacterial infection: SibCy 3.4% (0.2 – 10.4); SibCNI 7.1% (3 – 12.7%); without bacterial infection HaploCy 6.9% (4.1 – 10.5); SibCy 5.5% (2.2 – 10); p = 0.002] (Supplemental Table 7).

In multivariable analysis, development of bacterial infection increased TRM 3.33-fold, 2.78-fold, and 2.53-fold higher risk of TRM for the HaploCy, SibCy, and SibCNI cohorts (Table 3). The HaploCy cohort, even without bacterial infection, had a 1.99-fold higher risk of TRM. Additional risk factors associated with increased TRM were female-to-male-donor HCT, transplant for intermediate or high/very high risk MDS, development of acute GVHD, and lack of neutrophil engraftment (Table 3). Bacterial infections were the primary cause of death in 5%, 4%, and 4% of patients in HaploCy, SibCy, and SibCNI, respectively.

Overall Survival—Relapse was the main cause of all mortalities in each cohort (>60%) (Supplemental Table 8). By the landmark of 16 days, patients with any bacterial infection had a lower OS by 1 year after HCT [HaploCy 61% (51 – 70); SibCy 68% (55–79%); SibCNI 61% (53 – 69%)] compared with those patients without a bacterial infection in the same period [HaploCy 66% (61 – 71); SibCy 68% (60 – 75%); SibCNI 71% (68 – 74%); p<0.001] (Supplemental Table 9). Although the difference became less prominent, inferior survival persisted at 2 years. These findings were consistent when examining by BSI (median onset 48 days). Notably, the 1- and 2-year OS was not impacted by the development of MBI-LCBI by 10 days post-HCT

In multivariable analysis, compared with the SibCNI without bacterial infection cohort, development of bacterial infection increased mortality for the HaploCy, SibCy, and SIBCNI cohorts (Table 3 and Figure 3). The HaploCy cohort, even without bacterial infection, had a 1.32-fold higher risk of mortality. Additional factors increasing the risk of death in the MVA

included age of recipient >60 years, advanced acute leukemia, high/very high risk MDS, development of acute GVHD prior to infection, and lack of neutrophil engraftment prior to infection.

Discussion

In this large study, our main finding is that bacterial infections are more common with PTCy regardless of donor type (i.e., haploidentical siblings or HLA-matched siblings). In addition, we demonstrated that early bacterial infections are associated with increased TRM as well as overall mortality in all 3 types of transplantation investigated.

Many studies showed a high incidence of bacterial infections (e.g., 40% to 64%) after HaploCy following PTCy prophylaxis within 1 year.[31–33] The preponderance of these bacterial infections (approximately 30–40%) occurred in early phase (e.g., 30 days).[31–33] This is likely increased risk of infections in the pre-engraftment period given that median time to neutrophil engraftment is approximately 3 weeks after HaploCy.[31, 33, 34]

It is well-known that bacterial infections after an allogeneic HCT are associated with mortality.[5] Most studies also showed bacterial infections after Haploidentical HCT following PTCy was associated with a higher mortality. Slade et al reported that risk of mortality increases by 2.32 (95%CI, 1.23–4.3) times when bacterial infection occurred after haploidentical HCT.[33] In a Spanish Group for Hematopoietic Stem Cell Therapy study, IRM at year 1 was found to be 17% after HaploCy, and bacterial infections were the most common cause of IRM (51%). Likewise, the French stem cell transplantation group showed that bacterial infections constituted 46% of TRM.[32] In a comparison study, patients with acute lymphoblastic leukemia receiving HaploCy (>90% patients receiving PTCy) had significantly higher IRM compared with those receiving SibCNI (>90% patients receiving non-PTCy) (33.1% vs. 19.7%).[35]

Following studies that used PTCy not only in Haploidentical HCT but also in other donor types shed some light whether this increased bacterial infections and higher IRM primarily due to donor type, GVHD prophylaxis or both. Khimani et al showed similar results in a relatively smaller single center study from Moffit Cancer Center.[36] PTCy was used in 75 haploidentical and in 38 MUD HCTs whereas a CNI-based GVHD prophylaxis was used in 470 MUD HCTs. Overall infection density was significantly more common in PTCy patients (5.0 vs approximately 2 per 1000-person days; $p<0.01$) within the first year of alloHCT, and this difference resulted from higher bacterial and viral infections. Immune reconstitution analysis showed that PTCy led to slower CD4+ cell but faster CD19+ cell recovery. Salas et al. recent study revealed 2.4 times higher BSI in the first 30 days after PTCy compared with other GVHD prophylaxis regimens in 330 patients receiving an alloHCT from various donors, including in MRD, MUD, and MMUD, and Haploidentical an alloHCT.[37]

Supporting further the suggestion that GVHD prophylaxis has a more prominent impact than donor per se on infections, the study by Ciurea et al evaluated haploidentical HCT patients' outcomes in two cohorts; the ones received PTCy and unmanipulated stem cells vs. those received antithymocyte globulin (ATG) and CD34+ selected stem cells.[38] IRM

(although mainly due to viral and fungal infections) was significantly higher in the latter group (9% vs.24%, p=0.01). This indicates that GVHD prophylaxis affects infections and IRM even in the same donor type HCT (i.e., HaploHCT). Indeed, Goldsmith et al using our same CIBMTR patient population showed that cumulative incidences of CMV infection by day 180 in patients receiving HaploCy, (n = 757), SibCy (n = 403) and SibCNI (n= 1605) were 42%, 37%, and 23%, respectively (p <0.001).[19] PTCy also increased other viral infections in the haploidentical and matched sibling donor setting.[20, 21] This observation is further supported by other studies using PTCy in different donor types; a single center, recent study used PTCy for 3 different donor type HCTs (i.e., haploidentical, MRD, and 1-allele mismatched unrelated donor, n=117).[34] In this study, neither bacterial infections nor IRM was different among the donor types. Another study from Italy investigated PTCy in 235 patients, including 62% Hapto-PTCy, 21% MUD-PTCy, and 17% SibCy.[24]

Donor type had no effect on pre-engraftment bacterial infections although impacted viral and fungal infections. IRM at day 180 was 8%, patients had pre-engraftment bacterial infection had a higher mortality: GN BSI, 14% vs. GP BSI,7% vs. no BSI,2%, (Gray's test: p =0.010). IRM was not impacted by donor type.[24]

In this study, we showed that PTCy increases bacterial infections and TRM regardless of donor type. However, it is also important to note that patients receiving HaploCy, irrespective of bacterial infection, had a higher risk of death compared to the SibCNI cohort that did not develop bacterial infections. Furthermore, looking at the patients who developed any bacterial infection, there was no impact of donor or PTCy as all patients had a higher risk of death ranging for 1.68x – 1.84x that of the SibCNI cohort without infection. This effect of infection did not seem related to increased acute or chronic GVHD in our study.

Risk factors for IRM after PTCy were found to be delayed neutrophil engraftment, older age, lymphoid malignancy, and the presence of severe GVHD also increased IRM.[24, 34] In our study, we showed that the neutropenia following PTCy increased bacterial infections but that the incidence of bacterial infections was not different between the cohorts following the onset of aGVHD.

Enterobacteriaceae seemed to be more in PTCy patients in our study. Similar to our findings, in another HaploCy study, gram-negative bacilli were the most prevalent bacteria (59.3%) with a majority of Enterobacteriaceae.[32] In another study, Enterobacteriaceae species were the most common documented gram-negative (66%) and all bacteria (31.6%) after HaploCy.[33] The majority of gram-negative bacterial infection occurred after engraftment[32, 34] and associated with more mortality[34] whereas gram-positive bacteria were more common in the pre-engraftment period.[24, 34] Although it is logical to think that gram-negative infections were associated with acute GVHD, the findings in the literature remain controversial.[33, 34] In fact, given that PTCy is generally associated with less GVHD, this also undermines the potential relation between acute GVHD and gram negative bacteremia observed in the later phases of HCTs.

Our study limitations are inherent to the retrospective nature of the study including lacking the the reasons a center chose to use a PTCy for GVHD prophylaxis in a matched sibling

transplant. Another limitation is that data on antibiotic prophylaxis, treatment, or evidence of multidrug-resistance were not captured in this transplant registry. Lack of these data might limit our interpretation of the results and outcomes following HCT. Our goal was to create as homogeneous population as possible to discern if PTCy or a haploidentical donor or both increased the risk of infection. The number of patients receiving MUD with PTCy was limited, therefore the effect of PTCy could not be evaluated. Similarly, there were low number of patients who received ATG; thus, to avoid additional confounders, these patients were not included in the study. However, our study has several important strengths including, first, a robust sample size from 102 centers from diverse geographic locations and reflecting current transplant practices. The inclusion of multiple centers provides a diverse population of all ages (our study included pediatric population as well), most of the common stem cell sources and transplant types; however, it also results in a small percentage of missing data. Given that it is less than 5% for nearly all pertinent variables, these data are unlikely to change the overall outcomes in this large dataset. It is also likely to minimize over or underreporting biases inherent in single center studies. Uniform definitions were used for data collection stipulated by CIBMTR and long term follow up is ensured. Second bacterial infections especially in 180 days are significant clinical events that are likely to be reported, even if the patient is no longer at the HCT center.

In conclusion, PTCY is a risk factor for early bacterial infections, TRM and OS regardless of donor type. As PTCy is almost always used with a combination of immunosuppressive drugs (e.g., CNI), increased infections may be more expected compared with only CNI-based regimens. A subset of patients enrolled in the BMT CTN 1703 trial co-enrolled in the BMT CTN 1801 trial which prospectively captured detailed infectious complications including antimicrobial prophylaxis and treatment.[39] These forthcoming results will add to the literature and include MUD HCT patients. Regardless, this study shows that PTCy (another great GVHD prophylaxis option e.g., decreased chronic GVHD) has adverse effects on infections. Therefore, appropriate preventions and close monitoring of patients for high-risk infections are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

Materials described in the manuscript, including all relevant raw data, belongs to CIBMTR and will be freely available to any researcher wishing to use them for non-commercial purposes, without breaching participant confidentiality per discussion with CIBMTR.

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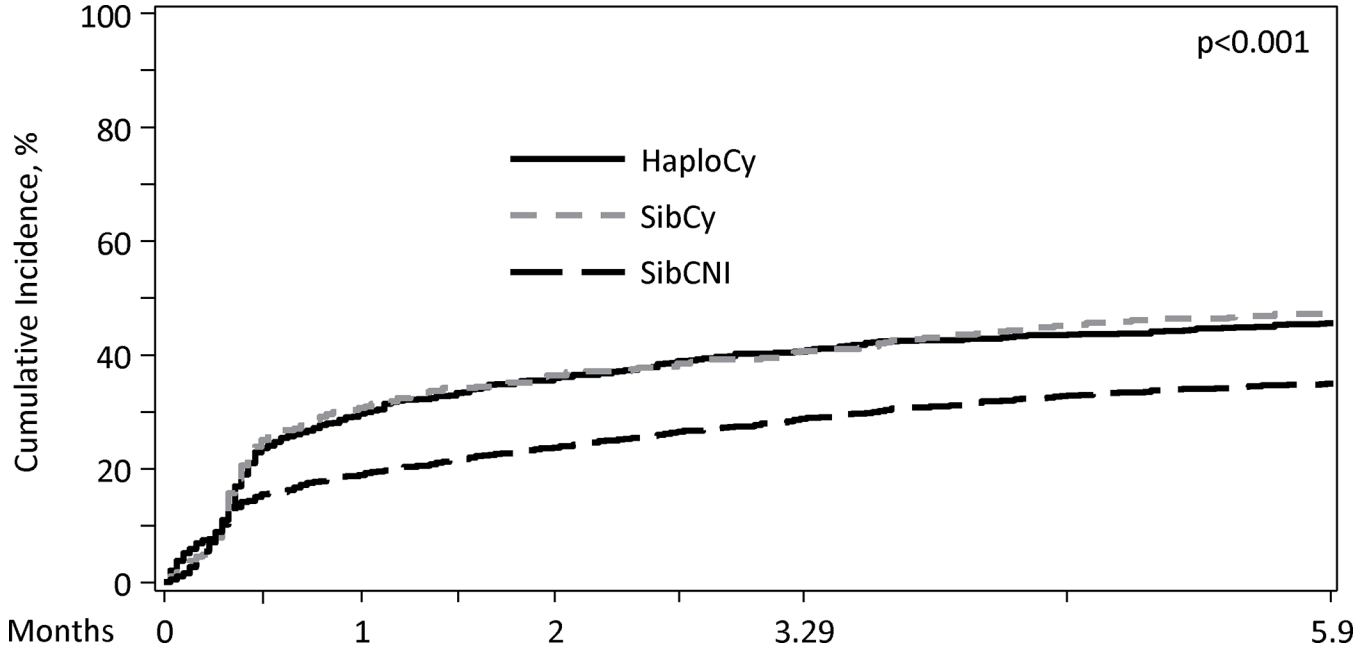

Figure 1A. Cumulative Incidence of Bacterial Infections by Donor Type/GVHD Prophylaxis in Day 180

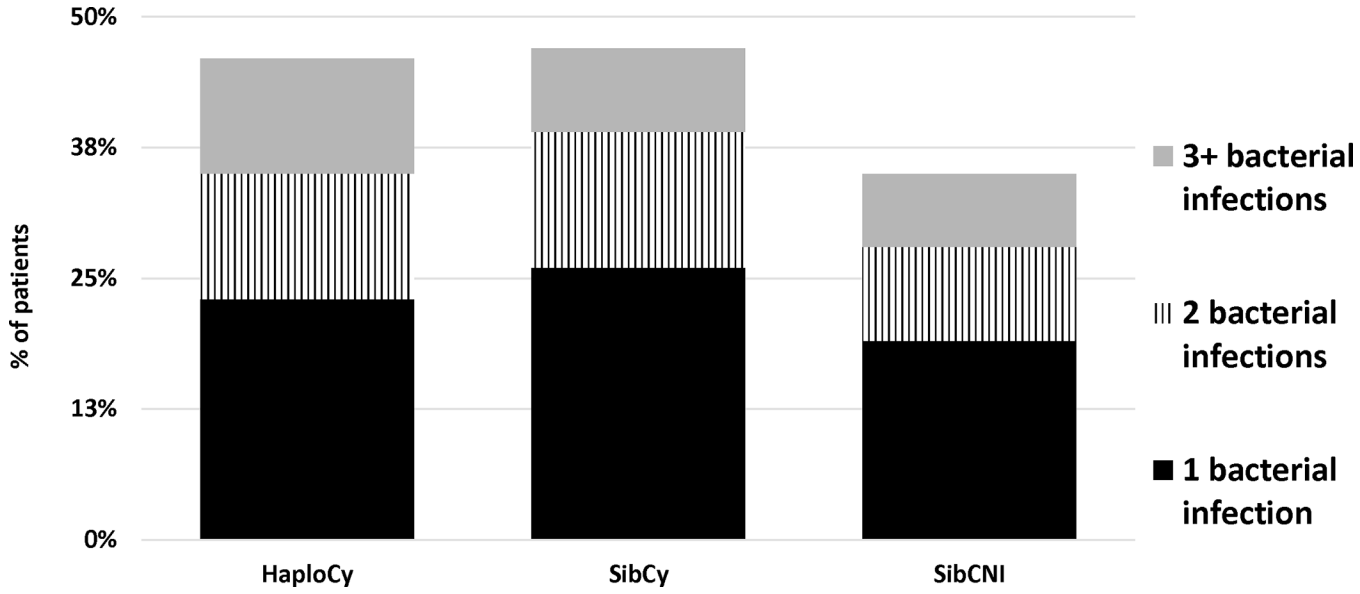

Figure 1B. Frequency ofOne or More Bacterial Infection by Donor Type/GVHD Prophylaxis inDay 180

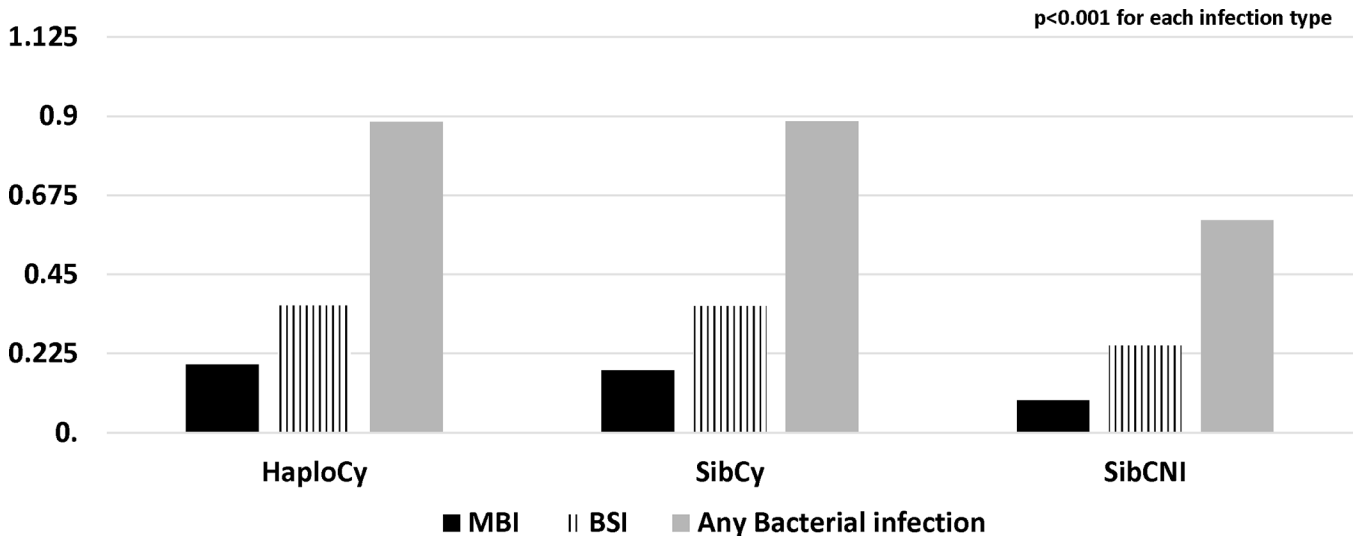

Figure 2A. Rate of MBI, BSI and All Bacterial Infections by Donor Type/GVHD Prophylaxis in Day 180

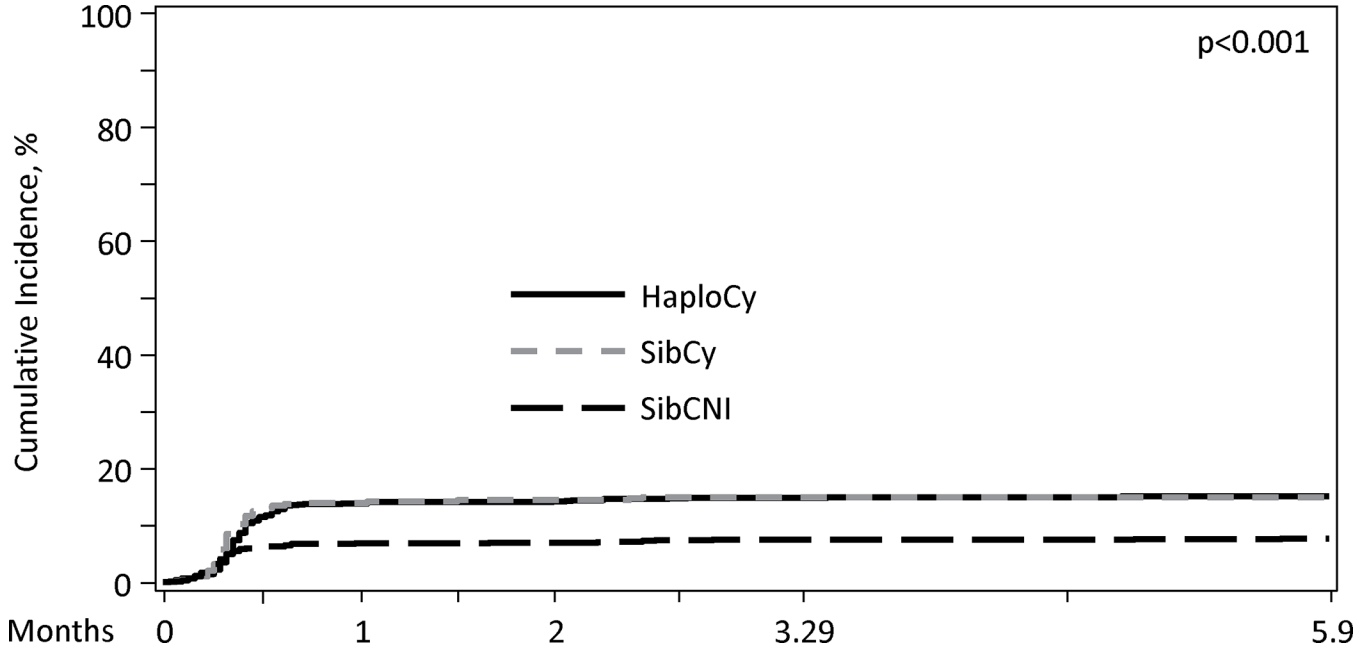

Figure 2B. Cumulative Incidence of MBI by Donor Type/GVHD Prophylaxis in Day 180

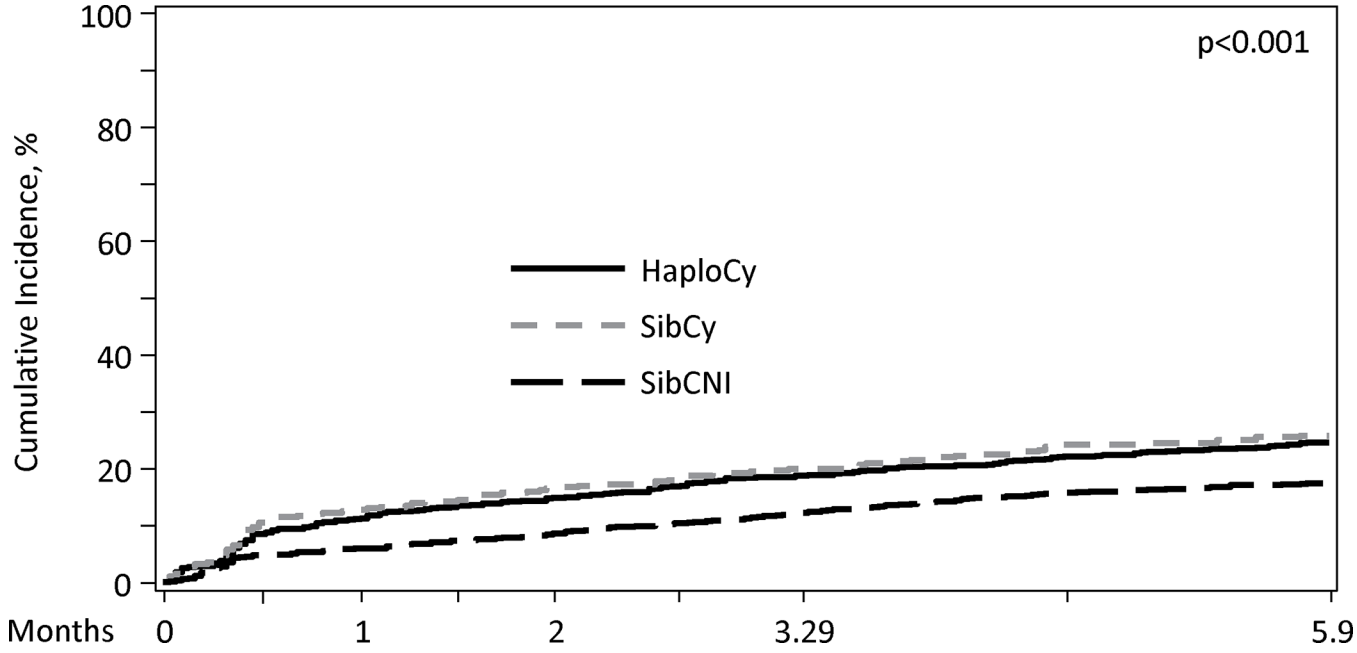

Figure 2C. Cumulative Incidence of any BSI by Donor Type/GVHD Prophylaxis in Day 180

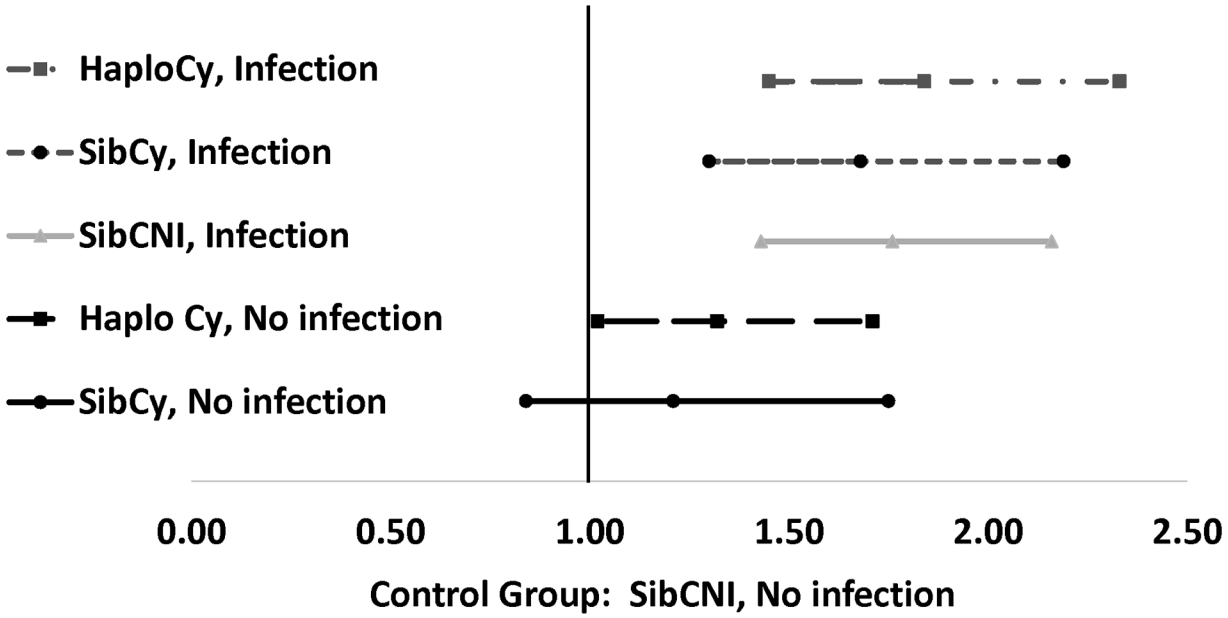

Figure 3. 2-year Hazard Ratio of Mortality by Bacterial Infection by Day 180

Table 1.

Characteristics of patients receiving first Allogeneic HCT with or without PTCy conditioning regimen, reported to the CIBMTR, from 2012 to 2017

Variable	Haplo-PTCy N(%)	SibCy N(%)	SibCNI N(%)	P value
Number of patients	757	403	1605	
Male	459 (61)	243 (60)	933 (58)	
Age, median(range), years	58 (3 – 78)	46 (3 – 75)	57 (2 – 78)	<0.001
KPS/LPS <80	119 (16)	65 (16)	200 (12)	<0.001
HCT-CI =>3	348 (46)	175 (44)	761 (48)	0.817
Prior Fungal Infection, Yes	63 (8)	44 (11)	125 (8)	0.138
Race/Ethnicity				<0.001
Caucasian, non-Hispanic	444 (59)	239 (59)	1109 (69)	
African-American, non-Hispanic	131 (17)	56 (14)	107 (7)	
Asian, non-Hispanic	52 (7)	29 (7)	97 (6)	
Hispanic, Caucasian	72 (10)	45 (11)	134 (8)	
Other	10(1)	6 (1)	31 (2)	
Missing	48 (6)	28 (7)	127 (8)	
Donor age, median(range), years	36 (9 – 76)	45 (4 – 72)	54 (2 – 82)	<0.001
Donor/Recipient CMV status				0.04
+/+ or −/+	543 (72)	273 (68)	1067 (67)	
+/− or −/−	185 (24)	115 (29)	490 (30)	
Disease Status				<0.001
AML/ALL, early	308 (41)	189 (47)	719 (45)	
AML/ALL, intermediate	143 (19)	77 (19)	210 (13)	
AML/ALL, advanced	97 (13)	61 (15)	144 (9)	
AML/ALL, unknown	6 (<1)	2 (<1)	15 (<1)	
MDS, early	76 (10)	24 (6)	179 (11)	
MDS, advanced	127 (17)	50 (12)	338 (21)	
Peripheral blood stem cells	449 (59)	272 (67)	1405 (88)	<0.001
MAC	314 (41)	222 (55)	935 (58)	<0.001
TBI (cGy)				<0.001
No	226 (30)	169 (42)	1169 (73)	
Yes and >800	115 (15)	80 (20)	264 (16)	
Growth Factor, Yes	620 (82)	319 (79)	379 (24)	<0.001
Time from diagnosis to transplant, median(range), months	7 (1 – 165)	7 (<1 – 396)	5 (1 – 556)	<0.001
Year of transplant				<0.001
2012–2014	170 (22)	87 (22)	806 (50)	
2015–2017	587 (78)	316 (78)	799 (50)	
Median follow-up of survivors, months	25 (3 – 74)	25 (3 – 69)	37 (2 – 75)	

Table 2.

Infection density* by 180 days by cohort.

Variable (by day 180)	HaploCy N(%)	SibCy N(%)	SibCNI N(%)	P value
Infection Density Scores				
Any bacterial infection	0.884	0.855	0.604	<0.001
MBI-LCBI overall density score	0.194	0.177	0.092	<0.001
BSI overall density score	0.361	0.36	0.248	<0.001

*Infection density accounts for multiple infections and normalizes for survival to 180 days

Table 3.

Multivariate analysis for OS and TRM

	OS				TRM			
	N	**HR (99% CI)**	**P-value**	**Overall P-value**	**N**	**HR (99% CI)**	**P-value**	**Overall P-value**
Bacterial Infection								
BI no, SibCNI	1027	1.00		**<.0001**	1016	1.00		**<.0001**
BI yes, Haplo-PTCy	345	1.84 (1.45 – 2.33)	<.0001		342	3.33 (2.09– 5.29)	<.0001	
BI yes, SibCy	191	1.68 (1.30 – 2.19)	<.0001		191	2.78 (1.79 –4.33)	<.0001	
BI yes, SibCNI	558	1.76 (1.43 – 2.16)	<.0001		551	2.53 (1.57 – 4.08)	<.0001	
BI no, Haplo-PTCy	396	1.32 (1.02 – 1.71)	0.0058		389	1.99 (1.24 – 3.18)	0.0002	
BI no, SibCy	205	1.21 (0.84 – 1.75)	0.1727		201	1.69 (0.88 – 3.25)	0.0400	
Donor-Recipient Sex Match								
Male-Male					924	1.00		0.0001
Male-Female					618	0.94 (0.68 – 1.30)	0.6041	
Female-Male					655	1.33 (1.01 –1.77)	0.0082	
Female-Female					493	0.76 (0.53 – 1.10)	0.0601	
Age at transplant, Years								
0–20	236	1.00		**<.0001**				
21–40	487	0.90 (0.61 – 1.32)	0.4660					
41–60	955	1.34 (0.91 – 1.97)	0.0482					
>60	1044	1.70(1.09 – 2.66)	0.0021					
Disease Risk by disease status and cytogenetic risks								
AL favorable cytogenetic early/intermediate stage	69	1.00		**<.0001**	68	1.00		**0.0001**
AL intermediate/nl cytogenetic early stage	675	1.02 (0.58 – 1.81)	0.9267		667	1.32 (0.58 – 3.00)	0.3822	
AL poor cytogenetic early stage	439	0.99 (0.58 – 1.68)	0.9598		435	0.97 (0.44 – 2.12)	0.9219	
AL int/nl cytogenetic intermediate stage	215	1.19 (0.68 – 2.09)	0.4269		210	1.28 (0.57 – 2.89)	0.4275	
AL poor cytogenetic intermediate stage	126	1.32 (0.72 – 2.42)	0.2306		126	1.16 (0.45 – 3.00)	0.6963	
AL advanced (all cytogenetic categories)	296	1.93 (1.07 – 3.50)	0.0044		294	1.26 (0.56 – 2.82)	0.4691	
MDS very low/low	312	0.94 (0.54 – 1.66)	0.7911		310	1.67 (0.68 – 4.09)	0.1437	
MDS intermediate	227	1.69 (1.00 – 2.88)	0.0105		225	2.24 (0.92 – 5.45)	0.0198	
MDS high/very high	164	2.11 (1.15 – 3.87)	0.0016		160	2.49 (0.99 – 6.25)	0.0108	
Other/not test/missing	199	1.28 (0.67 – 2.46)	0.3287		195	1.44 (0.55 – 3.78)	0.3353	
Acute GVHD, grade II - IV								
No	1744	1.00		<.0001	1724	1.00		<.0001
Yes	978	1.56 (1.28 – 1.91)			966	2.60 (1.71 – 3.96)		
Neutrophil engraftment								

	OS				TRM			
	N	**HR (99% CI)**	**P-value**	**Overall P-value**	**N**	**HR (99% CI)**	**P-value**	**Overall P-value**
No	69	1.00		<.0001	69	1.00		<.0001
Yes	2653	0.20 (0.11 – 0.35)			2621	0.12 (0.07 – 0.22)		
Contrasts								
BI yes, Haplo-PTCy vs. BI yes, SibCy		1.09 (0.81 – 1.47)	0.4475			1.19 (0.77 – 1.86)	0.3027	
BI yes, Haplo-PTCy vs. BI yes, SibCNI		1.05 (0.83 – 1.33)	0.6173			1.32 (0.90 – 1.93)	0.0635	
BI yes, Haplo-PTCy vs. BI no, Haplo-PTCy		1.39 (1.01 – 1.91)	0.0072			1.67 (0.97 – 2.90)	0.0159	
BI yes, Haplo-PTCy vs BI no, SibCy		1.51 (1.06 – 2.17)	0.0029			1.97 (1.11 – 3.50)	0.0023	
BI yes, SibCy vs . BI yes, SibCNI		0.96 (0.75 – 1.23)	0.6616			1.10 (0.74 – 1.63)	0.5243	
BI yes, SibCy vs BI no, HaploCy		1.27 (0.92 – 1.77)	0.0552			1.40 (0.84 – 2.35)	0.0933	
BI yes, SibCy vs. BI no, SibCNI		1.39 (0.93 – 2.07)	0.0342			1.65 (0.91 – 3.01)	0.0313	
BI yes, SibCNI vs BI no, Haplo-PTCy		1.33 (1.00 – 1.76)	0.0098			1.27 (0.75 –2.16)	0.2445	
BI yes, SibCNI vs. BI no, SibCy		1.45 (1.03 – 2.02)	0.0046			1.50 (0.82 – 2.74)	0.0854	
BI no, HaploCy vs BI no, SibCy		1.09 (0.75 – 1.58)	0.5560			1.18 (0.62 – 2.25)	0.5106	