Cardiac Toxicity after Matched Allogeneic Hematopoietic Cell Transplantation in the Post-Transplant Cyclophosphamide Era

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Abstract:
Graft-versus-host-disease (GVHD) is one of the leading causes of non-relapse mortality (NRM) following allogeneic hematopoietic cell transplantation (alloHCT). Post-transplant cyclophosphamide (PTCy) has shown promise in managing GVHD. However, cyclophosphamide has known cardiac toxicities and few studies have evaluated the cardiac toxicities that arise following PTCy. Here, we completed a retrospective analysis of matched alloHCT patients at our institution who received PTCy or non-PTCy-based GVHD prophylaxis, with the goal of determining the incidence of cardiac toxicities up to 100 days after alloHCT. We included 585 patients in our analysis and found that 38 patients (6.5%) experienced cardiac toxicities after alloHCT. The toxicities observed included arrhythmias (n=21), heart failure (n=14), pericardial effusions (n=10), and myocardial infarction or ischemia (n=7). Patients who received PTCy had a 7.4% incidence of cardiac toxicities, while non-PTCy patients had an incidence of 5.8% (p=0.4). We found that age > 55 years (p=0.02), history of hypertension (p=0.01), arrhythmia (p=0.003), diabetes (p=0.04), and cardiac comorbidities (p<0.001) were significant predictors of cardiac toxicity, while none of the preparative and GVHD prophylaxis regimens used were predictive of cardiac toxicity. From these findings, we proposed the use of a Cardiac Risk Stratification Score to quantify the risk of cardiac toxicity following alloHCT and found that a higher score correlated with cardiac toxicity incidence. Furthermore, the development of cardiac toxicity was associated with worse 1-yr overall survival (OS) and NRM while the use of PTCy was associated with improvements in 1-year OS and NRM rates.

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Key Points
1. The incidence of acute cardiac toxicity remains low and manageable after matched alloHCT in the era of PTCy.
2. Older age, hypertension, arrhythmia, diabetes, and cardiac comorbidities increase this risk of cardiac toxicity but PTCy did not.
Abstract

Graft-versus-host-disease (GVHD) is one of the leading causes of non-relapse mortality (NRM) following allogeneic hematopoietic cell transplantation (alloHCT). Post-transplant cyclophosphamide (PTCy) has shown promise in managing GVHD. However, cyclophosphamide has known cardiac toxicities and few studies have evaluated the cardiac toxicities that arise following PTCy. Here, we completed a retrospective analysis of matched alloHCT patients at our institution who received PTCy or non-PTCy-based GVHD prophylaxis, with the goal of determining the incidence of cardiac toxicities up to 100 days after alloHCT. We included 585 patients in our analysis and found that 38 patients (6.5%) experienced cardiac toxicities after alloHCT. The toxicities observed included arrhythmias (n=21), heart failure (n=14), pericardial effusions (n=10), and myocardial infarction or ischemia (n=7). Patients who received PTCy had a 7.4% incidence of cardiac toxicities, while non-PTCy patients had an incidence of 5.8% (p=0.4). We found that age > 55 years (p=0.02), history of hypertension (p=0.01), arrhythmia (p=0.003), diabetes (p=0.04), and cardiac comorbidities (p<0.001) were significant predictors of cardiac toxicity, while none of the preparative and GVHD prophylaxis regimens used were predictive of cardiac toxicity. From these findings, we proposed the use of a Cardiac Risk Stratification Score to quantify the risk of cardiac toxicity following alloHCT and found that a higher score correlated with cardiac toxicity incidence. Furthermore, the development of cardiac toxicity was associated with worse 1-yr overall survival (OS) and NRM while the use of PTCy was associated with improvements in 1-year OS and NRM rates.
Introduction

Allogeneic hematopoietic cell transplantation (alloHCT) is a lifesaving modality for many patients with hematologic malignancies. Over the past decade, several advances have been made to improve non-relapse mortality (NRM) associated with conditioning regimens, including the replacement of cyclophosphamide and other alkylating agents with less toxic agents, such as fludarabine. Although improvement in NRM has been shown, NRM due to graft-versus-host disease (GVHD) remains one of the leading causes of mortality in alloHCT survivors.

Currently, the standard GVHD prophylaxis regimen for alloHCT involves use of a calcineurin inhibitor (CNI) and methotrexate (MTX), with or without anti-thymocyte globulin (ATG). The use of ATG produces lower rates of GVHD without improved survival. MTX is associated with increased rates of mucositis and renal dysfunction, which ultimately leads to increased rates of NRM. Since GVHD occurs in over 50% of alloHCT recipients, investigators have recently explored other GVHD prophylaxis options, including the use of post-transplant cyclophosphamide (PTCy).

Cyclophosphamide is an alkylating agent of the nitrogen mustard class and has been used effectively in conditioning regimens for many years in alloHCT. However, cyclophosphamide has historically been associated with increased rates of cardiac toxicity, including pericarditis and cardiomyopathy, as well as increased rates of cardiac compromise after alloHCT. In recent years, PTCy has become the standard GVHD prophylaxis employed in alloHCT from haploidentical donors and has been increasingly utilized in alloHCT from matched donors. There is limited data detailing the incidence and the risk factors associated with developing cardiac toxicity in the era of PTCy-based GVHD prophylaxis.
With the increasing use of PTCy-based GVHD prophylaxis at our institution, we performed this study to evaluate both the incidence and predictors of acute cardiac toxicities after matched alloHCT. In particular, we sought to determine if the use of PTCy was associated with increased cardiac toxicity.

Methods

Patients

We performed a retrospective review of all patients who underwent alloHCT with an HLA-matched related donor (MRD) or matched unrelated donor (MUD) alloHCT between October 1, 2016 and April 30, 2019. We excluded patients who received an alloHCT from haploidentical or cord blood donors. MUDs were matched at HLA-A, -B, -C, and -DRB1. The majority of myeloablative preparative regimen were busulfan/fludarabine-based while the majority of reduced-intensity preparative regimens were fludarabine/melphalan-based. Both PTCy and non-PTCy GVHD prophylaxis were utilized in these preparative regimens. Cyclophosphamide and myeloablative doses of TBI were utilized in the preparative regimens of only 2.5% and 3% of patients respectively. None of these patients received concurrent PTCy. PTCy-based GVHD prophylaxis consisted of cyclophosphamide 50 mg/kg/day on days +3 and +4 and was administered with intravenous hydration and mesna, along with tacrolimus with or without mycophenolate mofetil. Non-PTCy GVHD prophylaxis primarily consisted of tacrolimus and methotrexate 5 mg/m²/day on days +1, +3, +6, and +11 with anti-thymocyte globulin (total dose of 4 mg/kg over 3 days) given to patients receiving a MUD. This study was approved by the University of Texas MD Anderson Institutional Review Board and performed in accordance with the Declaration of Helsinki.

Definitions of Cardiac Toxicity

Cardiac toxicity was defined as any new episodes of ≥ Grade 2 arrhythmia, heart failure, myocardial infarction or ischemia, pericarditis, or pericardial effusion that occurred up to Day +100. These toxicities
were recorded contemporaneously in our departmental database and reviewed during the present study. Cardiac complications were defined and graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.\textsuperscript{14} Arrhythmias included atrial fibrillation, atrial flutter, supraventricular tachycardia, and ventricular arrhythmias. Heart failure and left ventricular systolic dysfunction were combined as one toxicity. Pericarditis and pericardial effusion (including pericardial tamponade) were defined according to the NCI CTCAE. Table 1 describes the cardiac toxicity grading in more detail.

Data Collection and Analysis

Extracting data from the departmental database and by use of our electronic medical record, we obtained all patient demographics, alloHCT-related characteristics, and pertinent comorbidities including the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI), a commonly used score used to assess risk before alloHCT.\textsuperscript{15} We also reviewed history of smoking status, anthracycline exposure, hyperlipidemia, and hypertension, since these are risk factors that may impact cardiac toxicity, but are not included in the HCT-CI score.

Statistical Analysis

The primary endpoints of the study were the day +100 incidence of cardiac toxicity and risk factors associated with development of cardiac toxicities after matched alloHCT. The incidence of cardiac toxicity was estimated considering death before the development of toxicity as a competing risk. Predictors of toxicity were evaluated in univariate and multivariate analysis using Fine and Grey competing risks regression analysis. In addition, we evaluated the impact of development of cardiac toxicity on overall survival (OS) and non-relapse mortality (NRM) (using Cox’s proportional hazards and Fine and Grey regression analysis, respectively) considering the development of cardiac toxicity as a time-dependent variable. Significant predictors on univariate analysis were considered in multivariate
analysis. The use of PTCy-based GVHD prophylaxis was considered in all multivariate models irrespective of statistical significance in univariate analysis. The final regression model was determined using backward elimination. First degree interaction effects were tested for significant predictors and for the use of PTCy prophylaxis. Statistical analysis was defined at the 0.05 level. Analyses were primarily performed using STATA 14.0 (College Station).

Results

General Patient Characteristics

A total of 585 adult patients met the study eligibility criteria and received an MRD (220) or MUD (365) alloHCT from October 2016 to April 2019. Patient, alloHCT, and disease characteristics are presented in Table 2. The median age was 57 (range, 18-77) and most patients were male (58%) with AML/MDS (56%). This was a high-risk cohort, with 61% having active disease at the time of alloHCT and 66% receiving a myeloablative preparative regimen. Notably, PTCy-based GVHD prophylaxis was given to a sizable proportion of patients (46%), allowing for a robust comparison to the patients who did not receive PTCy (54%). As described in Table 2, patients who received PTCy were more often older (p<0.001) with AML/MDS (p<0.001), active disease (p=0.02), and previous anthracycline exposure (p<0.001).

Incidence of Cardiac Toxicities

From Day 0 to Day +100 following matched alloHCT, thirty-eight patients developed a total of 52 cardiac toxicities for an overall incidence of 6.5% (95% CI: 5-9) (Fig. 1). The cardiac toxicities observed included arrhythmias (n=21), heart failure (n=14), pericardial effusions (n=10), and myocardial infarction or ischemia (n=7). The median time to the development of cardiac toxicity was 20 days post-alloHCT (range, 3-95 days). Grade 2 toxicity was the maximum grade seen in 27 patients (52%), grade 3 in 11 patients (21%), grade 4 in 10 patients (19%), and grade 5 in 4 patients (8%). Patients who received PTCy-
based GVHD prophylaxis had a 7.4% incidence of developing cardiac toxicities, while non-PTCy patients had an incidence of 5.8% (p=0.4). Nine (45%) PTCy patients had multiple cardiac toxicities, compared to five (28%) of the non-PTCy patients (p=0.3). Details of cardiac toxicities are presented in Table 3.

Determining Risk Factors of Cardiac Toxicity

We performed a univariate analysis to determine patient, disease, and HCT characteristics (Table 4) that would predict the development of cardiac toxicity. Age > 55 years (HR=2.3, p=0.02) and history of hypertension (HR=2.3, p=0.01) were significant predictors of cardiac toxicity. There were no associations observed regarding preparative regimen, GVHD prophylaxis (PTCy vs. non-PTCy), or history of anthracycline exposure. However, we found that several individual comorbidities in the HCT-CI score were predictive of cardiac toxicity, such as cardiac (HR=3.6, p<0.001), arrhythmia (HR=3.5, p=0.003), and diabetes (HR=2.3, p=0.04).

As expected, these cardiac comorbidities were strongly associated with age > 55 years, as well as each other. Given these correlations and the comparable hazard ratios associated with each factor (Table 4), we devised a score that reflects the sum of the number of adverse predictors, including age > 55 years, hypertension, and cardiac, arrhythmia, or diabetes comorbidities. This was termed the Cardiac Risk Stratification Score and has a range of 0-5 points, though none of the patients in our cohort had all 5 risk factors. The day +100 cumulative incidence of cardiac toxicity was 4% (95% CI: 2-8), 4% (95% CI: 2-8), 8% (95% CI: 4-13), 13% (95% CI: 7-27), 37% (95% CI: 20-71) in patients with a score of 0 (n=192), 1 (n=170), 2 (n=155), 3 (n=52), or 4 (n=16), respectively. Using multivariate analysis, we found that higher scores were associated with cardiac toxicities (scores of 0-1 (reference), score of 2 (HR=2.2, p=0.05), and scores of 3-4 (HR=5.6, p<0.001)). The cumulative incidence of cardiac toxicity increased incrementally with increasing score, as depicted in Figure 2, reaching 19% (95% CI: 12-31) for patients with scores of 3-4, compared with 8% (95% CI: 4-13) and 4% (95% CI: 2-6) for patients with scores of 2 or 0-1,
respectively. Multivariate analysis adjusting for the proposed Cardiac Risk Stratification Score and the use of PTCy-based GVHD prophylaxis showed no significant effect (HR=1.1, p=0.7) for PTCy on cardiac toxicity (Table 5).

**Determining Risk Factors of Overall Survival and Non-Relapse Mortality**

One-year OS was 71% (95% CI: 66-74) and 1-yr NRM was 10% (8-13). Results of predictors of 1-year OS and NRM are described in Table 6 and 7, respectively. As expected, the development of cardiac toxicity was associated with worse 1-yr OS (HR=2.7, p<0.001) and 1-yr NRM (HR=5.7, p<0.001). On the other hand, the use of PTCy-based GVHD prophylaxis was a predictor for improved 1-yr OS (HR=0.6, p=0.001; HR=0.5; p<0.001) and improved 1-yr NRM (HR=0.4, p<0.001; HR=0.4, p<0.001) in both univariate and multivariate analyses, respectively. Other factors for worse 1-yr OS that remained significant in both the univariate and multivariable analysis included active disease (HR=1.9, p<0.001) and HCT-CI >3 (HR=1.8, p<0.001). Likewise, other factors for worse 1-yr NRM included smoking (HR=1.6, p=0.004) and HCT-CI >3 (HR=2.6, p<0.001). Causes of death in the PTCy group included GVHD (n=3), cardiac failure (n=1), pneumonia/pulmonary failure (n=2), and viral infection (n=1). In the non-PTCy group, causes of death included GVHD (n=3), pneumonia/pulmonary failure (n=3), liver failure (n=2), cardiac failure (n=1), multi-organ failure (n=1), viral infection (n=2), and disease recurrence (n=2).

**Discussion**

In this study, we reviewed cardiac toxicities in patients at our institution who received a matched alloHCT and similar supportive care measures during the modern era of PTCy-based GVHD prophylaxis. We discovered a low incidence of acute cardiac toxicity, with a higher risk in older patients with cardiac comorbidities, arrhythmia, diabetes, and hypertension. Importantly, we did not find a difference in cardiac toxicity between patients who received PTCy-based versus non-PTCy based GVHD prophylaxis.
Cardiac toxicity after alloHCT has been reported in 0.9-43% of patients.\(^8\) The incidence in our study fits within the lower limit of this range. Numerous patient risk factors have been associated with the development of cardiac toxicity after alloHCT including age, smoking, hypertension, hyperlipidemia, coronary artery disease, arrhythmia, prior cardiac event, and heart failure.\(^8,9\) Our findings confirm the link between many of these comorbidities and the development of cardiac toxicities after alloHCT. In particular, our analysis determined that age > 55, hypertension, and 3 factors in the HCT-CI score (cardiac, arrhythmia, diabetes) were significant predictors of cardiac toxicity by Day +100. Lin, et al. performed a retrospective analysis evaluating cardiomyopathy after PTCy in 176 alloHCT patients, including 141 from haploidentical donors. The authors determined that age > 60 years and HCT-CI ≥ 4 are predictors of post-HCT cardiomyopathy.\(^7\) Our study confirms these results and suggests that age > 55, hypertension, and the cardiac, arrhythmia, and diabetes components of the HCT-CI score may be a driving force in the development of cardiac toxicity after alloHCT. In addition, our multivariate analysis demonstrated that a Cardiac Risk Stratification Score ≥ 2 is associated with a significant risk of developing cardiac toxicity compared to patients with ≤ 1 of these risk factors. HCT physicians and providers should perform a thorough evaluation of these adverse predictors and discuss the risk of cardiac toxicity with patients prior to proceeding with alloHCT. Future external studies are needed to analyze other cumulative risk factor combinations associated with cardiac toxicity and potentially validate the use of the proposed Cardiac Risk Stratification Score.

To our knowledge, this is the first study to review cardiac toxicities in only the matched alloHCT setting during the current era of PTCy-based GVHD prophylaxis. Even though cyclophosphamide has been associated with cardiac toxicity, we found no significant difference in the incidence of cardiac toxicities between the patients receiving PTCy and non-PTCy GVHD prophylaxis. Additionally, the patients who received PTCy in our study were older and more often had active disease, factors that are often associated with increased toxicities and worse outcomes after alloHCT. These results suggest that
PTCy-based GVHD prophylaxis may not increase acute cardiac toxicities after matched alloHCT. Lin, et al. also found no significant difference in the incidence of post-HCT cardiomyopathy between patients who received PTCy versus non-PTCy. Although 21.9% of the patients in this study developed cardiomyopathy after HCT with PTCy, the authors described this cardiomyopathy to be transient, reversible, and often sepsis-induced.\(^7\) The patient populations reviewed in Lin, et al. and our present study are different in that the Lin, et al. study was primarily in haploidentical HCT recipients while our study excluded haploidentical HCT recipients. PTCy has established itself as the standard GVHD prophylaxis utilized after haploidentical HCT with acceptable rates of GVHD, relapse, and survival.\(^16\) Standard GVHD prophylaxis in the matched alloHCT setting has historically utilized a calcineurin inhibitor with methotrexate, with or without ATG, with recent studies proposing that PTCy may be more beneficial in this setting as well.\(^5\) Our results are significant since cardiovascular risk is a current consideration in the decision of what GVHD prophylaxis platform to utilize in the matched donor alloHCT setting. PTCy is often avoided in patients with a history of cardiac comorbidities. With similar rates of cardiac toxicities seen between the PTCy and non-PTCy groups, our results suggest the preferred GVHD prophylaxis platform may not need to be altered due to cardiac comorbidities alone, however this would need to be confirmed in prospective trials.

The improvement in outcomes for patients who received PTCy-based GVHD prophylaxis is an interesting finding that appears to be driven by a significant difference in NRM. Reviewing the causes of death amongst the two groups does reveal a numerically higher number of deaths attributed to infectious causes, liver failure, and disease recurrence in the non-PTCy group. Although these numbers are small, we postulate that PTCy could provide an improvement in immune reconstitution of memory T-cells that can protect against opportunistic infections.\(^17\) Another potential factor in the improvement of OS in the PTCy group could be related to the use of antithymocyte globulin (ATG) in the non-PTCy group. Ten out of the 14 non-PTCy patients who died were recipients of MUD alloHCT and received ATG...
as part of their preparative regimen and GVHD prophylaxis. The use of ATG has been associated with delayed immune reconstitution and higher incidence of infections. These factors may have contributed to the worse NRM and lower survival seen in the non-PTCy group.

Limitations of this study include its retrospective, single-center study design and lack of long-term follow-up. We focused on acute cardiac toxicities up to Day +100 post-alloHCT and utilized objective definitions. Routine electrocardiograms or echocardiograms after alloHCT are not routinely performed before Day +100 at our institution, and the lack of these data is a major limitation of our retrospective comparison. Thus, the rates of cardiac toxicity may be underestimated due to potential asymptomatic cardiac toxicities that were not captured in our review. Longer follow-up is needed to evaluate for long-term cardiac toxicities, which have been shown to place a significant burden on survivors of alloHCT. In addition, we were unable to consistently record other possible pre-HCT risk factors such as cardiac biomarkers or analysis from cardiac imaging with details of diastolic function. Furthermore, the retrospective study design did not account for physician preference to avoid PTCy-based GVHD prophylaxis in patients with known cardiac comorbidities.

BMTCTN 1703 is a phase 3, prospective, randomized trial that compares tacrolimus/methotrexate to PTCy-based GVHD prophylaxis in alloHCT. In addition to this study’s primary endpoint, it will also be important to review the acute and long-term cardiac toxicities developed by patients in this trial. This will add to the paucity of prospective data that currently exists concerning cardiac toxicities with PTCy-based GVHD prophylaxis in the matched alloHCT setting.

In conclusion, the results of our study suggest that the incidence of cardiac toxicities is low in this current era of PTCy-based GVHD prophylaxis and that PTCy does not impact the development of acute cardiac toxicities after matched alloHCT. The improved survival and toxicity outcomes in our study provides further support that PTCy may be utilized in patients with limited cardiac comorbidities.
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Authorship Contributions

J.Y. and L.W.: designed the research, collected data, analyzed data, and wrote the manuscript
R.M.S.: designed and performed statistical analyses, interpreted data, and wrote the manuscript
G.R.: collected data
J.B., E.S., and R.C.: analyzed data and edited the manuscript
U.P.: designed the research, analyzed data, and wrote the manuscript

Disclosures of Conflicts of Interest

None of the authors has a relevant conflict of interest to disclose.

Data sharing statement

For data sharing, contact the corresponding author: upopat@mdanderson.org.
Table 1. Grading of Cardiac Toxicities after alloHCT

| Cardiac Toxicity                          | Grade 1                                                                 | Grade 2                                                                 | Grade 3                                                                 | Grade 4                                                                 | Grade 5                                                                 |
|------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Arrhythmia (including atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular arrhythmia) | Asymptomatic; intervention not indicated                              | Non-urgent medical intervention indicated                              | Symptomatic and incompletely controlled medically, or controlled with device, or ablation | Life-threatening consequences; urgent intervention indicated          | Death                                                                  |
| Heart failure (including left ventricular systolic dysfunction) | Asymptomatic with laboratory or cardiac imaging abnormalities | Symptoms with mild to moderate activity or exertion                    | Severe with symptoms at rest or with minimal activity or exertion; intervention indicated | Life-threatening consequences; urgent intervention indicated       | Death                                                                  |
| Myocardial infarction or ischemia (including acute coronary syndrome) | -                                                                      | Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction | Life-threatening consequences; hemodynamically unstable                 | Death                                                                  |
| Pericardial Effusion (including pericardial tamponade) | Asymptomatic effusion size small to moderate                         | Effusion with physiologic consequences                                | Life-threatening consequences; urgent intervention indicated           | Death                                                                  |
| Pericarditis                              | Asymptomatic, ECG or physical findings consistent with pericarditis | Symptomatic pericarditis                                             | Pericarditis with physiologic consequences                              | Life-threatening consequences; urgent intervention indicated | Death                                                                  |

Adapted from Common Terminology Criteria for Adverse Events, version 4.0
### Table 2. Patient Characteristics

| Characteristics                   | Total N=585 (%) | PTCy-based N=272 (%) | Non-PTCy N=313 (%) | P   |
|-----------------------------------|-----------------|----------------------|--------------------|-----|
| **Sex**                           |                 |                      |                    |     |
| Female                            | 243 (42)        | 120 (44)             | 123 (39)           | 0.2 |
| Male                              | 342 (58)        | 152 (56)             | 190 (61)           |     |
| **Age, median (Interquartile range) years** |                 |                      |                    |     |
| Age >55                            | 309 (53)        | 180 (66)             | 129 (41)           |     |
| Age ≤55                            | 276 (47)        | 92 (34)              | 184 (59)           | <0.001|
| **Diagnosis**                     |                 |                      |                    |     |
| AML / MDS                         | 327 (56)        | 189 (69)             | 138 (44)           | <0.001|
| ALL                               | 76 (13)         | 9 (3)                | 67 (21)            |     |
| CML / MPD                         | 82 (14)         | 50 (18)              | 32 (10)            |     |
| CLL                               | 24 (4)          | 4 (1)                | 20 (6)             |     |
| Lymphoma                          | 52 (9)          | 12 (4)               | 40 (13)            |     |
| Other                             | 24 (4)          | 8 (3)                | 16 (5)             |     |
| **Donor type**                    |                 |                      |                    | 0.1 |
| MUD                               | 365 (62)        | 179 (66)             | 186 (59)           |     |
| MRD                               | 220 (38)        | 93 (34)              | 127 (41)           |     |
| **Stem Cell Source**              |                 |                      |                    | 0.08|
| Peripheral Blood                  | 475 (81)        | 229 (84)             | 246 (79)           |     |
| Bone Marrow                       | 110 (19)        | 43 (16)              | 67 (21)            |     |
|                          | Disease status | Preparative regimen | History of Anthracycline | History of Hypertension | History of Hyperlipidemia | Smoker | KPS |
|--------------------------|----------------|---------------------|--------------------------|-------------------------|--------------------------|--------|-----|
| Active                   | 356 (61)       | 201 (34)            | 335 (57)                 | 235 (40)                | 115 (20)                 | 227 (39)| 230 (39)|
| Remission                | 229 (39)       | 384 (66)            | 250 (43)                 | 350 (60)                | 470 (80)                 | 356 (61)| 287 (49)|
| Active Remission         | 179 (66)       | 82 (30)             | 122 (45)                 | 81 (30)                 | 60 (22)                  | 112 (41)| 117 (43)|
| Remission                | 136 (43)       | 194 (62)            | 200 (64)                 | 191 (70)                | 212 (78)                 | 160 (59)| 133 (49)|
| Active Remission         | 177 (57)       | 119 (38)            | 113 (36)                 | 114 (36)                | 55 (18)                  | 115 (37)| 113 (36)|
| Remission                | 136 (43)       | 194 (62)            | 200 (64)                 | 199 (64)                | 258 (82)                 | 196 (63)| 154 (49)|
| History of Anthracycline|                |                     |                          |                         |                          |        |      |
| Yes                      | 335 (57)       |                     | 122 (45)                 |                         |                          |        |      |
| No                       | 250 (43)       |                     | 150 (55)                 |                         |                          |        |      |
| History of Hypertension  |                |                     |                          |                         |                          |        |      |
| Yes                      | 235 (40)       |                     | 81 (30)                  |                         |                          |        |      |
| No                       | 350 (60)       |                     | 191 (70)                 |                         |                          |        |      |
| History of Hyperlipidemia|               |                     |                          |                         |                          |        |      |
| Yes                      | 115 (20)       |                     | 60 (22)                  |                         |                          |        |      |
| No                       | 470 (80)       |                     | 212 (78)                 |                         |                          |        |      |
| Smoker                   |                |                     |                          |                         |                          |        |      |
| Yes                      | 227 (39)       |                     | 112 (41)                 |                         |                          |        |      |
| No                       | 356 (61)       |                     | 160 (59)                 |                         |                          |        |      |
| Missing                  | 2 (0)          |                     | 0 (0)                    |                         |                          |        |      |
| KPS                      |                |                     |                          |                         |                          |        |      |
| <90                      | 230 (39)       |                     | 117 (43)                 |                         |                          |        |      |
| ≥90                      | 287 (49)       |                     | 133 (49)                 |                         |                          |        |      |
| Missing                  | 68 (12)        |                     | 22 (8)                   |                         |                          |        |      |
| Condition      | Yes | No     | p-value |
|---------------|-----|--------|---------|
| **HCT-CI**    |     |        |         |
| >3            | 195 (33) | 81 (30) | 0.09 |
| ≤3            | 390 (67) | 191 (70) | 199 (64) |
| **Cardiac**   |     |        | 0.4    |
| Yes           | 54 (8) | 22 (8) | 32 (10) |
| No            | 531 (92) | 250 (92) | 281 (90) |
| **Arrhythmia** |    |        | 0.7    |
| Yes           | 39 (7) | 17 (6) | 22 (7) |
| No            | 546 (93) | 255 (94) | 291 (93) |
| **Heart valve** |   |        | 0.6    |
| Yes           | 11 (2) | 5 (2) | 6 (2) |
| No            | 574 (98) | 267 (98) | 307 (98) |
| **Diabetes**  |     |        | 0.8    |
| Yes           | 63 (11) | 30 (11) | 33 (11) |
| No            | 522 (89) | 242 (89) | 280 (89) |
| **Pulmonary** |     |        | 0.2    |
| 0             | 335 (57) | 166 (61) | 169 (54) |
| 2             | 190 (33) | 82 (30) | 108 (34) |
| 3             | 60 (10) | 24 (9) | 36 (11) |
| **Obesity**   |     |        | 0.5    |
| Yes           | 76 (13) | 38 (14) | 38 (12) |
|                  | No        | Yes       | No        | Yes       | 0.01   |
|------------------|-----------|-----------|-----------|-----------|--------|
| **Infection**    |           |           |           |           |        |
| Yes              | 509 (87)  | 234 (86)  | 275 (88)  | 78 (13)   |        |
| No               | 507 (87)  | 246 (90)  | 261 (83)  | 507 (87)  | 261 (83)|
| **Hepatic**      |           |           |           |           | 0.7    |
| 0                | 423 (72)  | 197 (72)  | 226 (72)  | 423 (72)  |        |
| 1                | 123 (21)  | 59 (22)   | 64 (20)   | 123 (21)  |        |
| 3                | 39 (7)    | 16 (6)    | 23 (7)    | 39 (7)    |        |

**Note:**

- **Cardiac** = coronary artery disease (≥ 1 vessel coronary artery stenosis requiring medical treatment, stent, or bypass graft), congestive heart failure, myocardial infarction, or EF ≤ 50%
- **Arrhythmia** = atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias
- **Heart valve** = any heart valve disease except mitral valve prolapse
Table 3. Cardiac Toxicities after alloHCT

|                                | Overall (N=585) | PTCy (N=272) | Non-PTCy (N=313) | P     |
|--------------------------------|----------------|--------------|------------------|-------|
| Incidence of cardiac toxicities (Day +100) (95% CI) | 6.5% (5-9) | 7.4% (4.7-10.9) | 5.8% (3.5-8.7) | 0.4   |
| # of patients with cardiac toxicities, n | 38 | 20 | 18 |       |
| Number of episodes/patients |               |              |                  |       |
| 1                              | 24 (63)       | 11 (55)      | 13 (72)          | 0.3   |
| ≥ 2                            | 14 (37)       | 9 (45)       | 5 (28)           |       |
| Type of cardiac toxicities     | N=52          | N=29         | N=23             |       |
| Arrhythmia                     | 21 (40)       | 13 (45)      | 8 (35)           | 0.5   |
| Heart Failure                  | 14 (27)       | 8 (28)       | 6 (26)           | 0.9   |
| Myocardial infarction or ischemia | 7 (13)       | 4 (14)       | 3 (13)           | 0.6   |
| Pericardial effusion           | 10 (19)       | 4 (14)       | 6 (26)           | 0.2   |
Table 4. Predictors of Cardiac Toxicity – Univariate Analysis

| Characteristics                  | N=585 adults | HR  | 95% CI    | P    |
|----------------------------------|--------------|-----|-----------|------|
| **Age, years**                   |              |     |           |      |
| Age >55                          | 309 (53)     | 2.3 | 1.1-4.5   | 0.02 |
| Age ≤55                          | 276 (47)     | 1.0 |           |      |
| **Disease status**               |              |     |           |      |
| Active                           | 356 (61)     | 2.1 | 1.0-4.5   | 0.05 |
| Remission                        | 229 (39)     | 1.0 |           |      |
| **GVHD prophylaxis**             |              |     |           |      |
| PTCy-based                       | 272 (46)     | 1.3 | 0.7-2.4   | 0.4  |
| Non-PTCy                         | 313 (53)     | 1.0 |           |      |
| **Preparative regimen**          |              |     |           |      |
| Reduced Intensity                | 201 (34)     | 0.9 | 0.5-1.9   | 0.9  |
| Myeloablative                    | 384 (66)     | 1.0 |           |      |
| **Stem Cell Source**             |              |     |           |      |
| Peripheral Blood                 | 475 (81)     | 0.9 | 0.4-1.9   | 0.7  |
| Bone Marrow                      | 110 (19)     | 1.0 |           |      |
| **Hx Anthracycline**             |              |     |           |      |
| Yes                              | 335 (57)     | 0.9 | 0.5-1.7   | 0.8  |
| No                               | 250 (43)     | 1.0 |           |      |
| **Hx of HTN**                    |              |     |           |      |
| Yes                              | 235 (40)     | 2.3 | 1.2-4.5   | 0.01 |
|                  | No   | 350 (60) | 1.0 |                  |                  |
|------------------|------|----------|-----|------------------|------------------|
| History of Hyperlipidemia | Yes  | 115 (20) | 1.5 | 0.7-2.9          | 0.3              |
|                  | No   | 470 (80) | 1.0 |                  |                  |
| Smoker           | Yes  | 227 (39) | 1.6 | 0.8-3.0          | 0.1              |
|                  | No   | 356 (61) |     |                  |                  |
| KPS              | <90  | 230 (39) | 0.7 | 0.4-1.4          | 0.3              |
|                  | ≥90  | 287 (49) | 1.0 |                  |                  |
| Specific HCT-CI Comorbidity | Cardiac<sup>a</sup> | Yes | 54 (9) | 3.6 | 1.8-7.1 | <0.001 |
|                  | No   | 531 (91) | 1.0 |                  |                  |
|                  | Arrhythmia<sup>b</sup> | Yes | 39 (7) | 3.5 | 1.5-7.9 | 0.003 |
|                  | No   | 546 (93) | 1.0 |                  |                  |
|                  | Heart valve<sup>c</sup> | Yes | 11 (2) | Not |                | 0.4 |
|                  | No   | 574 (98) | evaluable |        |            |      |
|                  | Diabetes | Yes | 63 (11) | 2.3 | 1.1-5 | 0.04 |
|                  | No   | 522 (89) |        |                |                  |
| Pulmonary |   |   |   |   |
|-----------|---|---|---|---|
| 0         | 335 (57) | 1.01.2 |   |   |
| 2         | 190 (33) | 0.8 | 0.6-2.3 | 0.6 |
| 3         | 60 (10) | 0.2-2.6 | 0.7 |   |
| Obesity   |   |   |   |   |
| Yes       | 76 (13) | 1.8 | 0.8-3.9 | 0.1 |
| No        | 509 (87) | 1.0 |   |   |

HR: Hazard Ratio, CI: Confidence Interval

*a* Cardiac= coronary artery disease (≥ 1 vessel coronary artery stenosis requiring medical treatment, stent, or bypass graft), congestive heart failure, myocardial infarction, or EF ≤ 50%

*b* Arrhythmia= atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias

*c* Heart valve= any heart valve disease except mitral valve prolapse
Table 5. Predictors of Cardiac Toxicity – Multivariate Analysis

| Co-variable                          | HR (95% CI)    | P       |
|--------------------------------------|----------------|---------|
| **Cardiac Risk Stratification Score*** |                |         |
| 0-1                                  | 1              |         |
| 2                                    | 2.2 (1.0-4.8)  | 0.05    |
| 3-4                                  | 5.6 (2.6-11.9) | <0.001  |
| **PTCy**                             | 1.1 (0.6-2.1)  | 0.7     |

HR: Hazard Ratio, CI: Confidence Interval

*Proposed Cardiac Risk Stratification Score includes 5 predictors of cardiac toxicity: age > 55, hypertension, cardiac\(^a\), arrhythmia\(^b\), diabetes

\(^a\)Cardiac= coronary artery disease (≥ 1 vessel coronary artery stenosis requiring medical treatment, stent, or bypass graft), congestive heart failure, myocardial infarction, or EF ≤ 50%

\(^b\)Arrhythmia= atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias

Score 3-4 vs 2: HR=2.5 (95% CI 1.2-5.5), p=0.02
Table 6. Predictors of 1-yr Overall Survival

| Characteristics                  | Univariate |            |          |            | Multivariate |          |            |
|----------------------------------|------------|------------|----------|------------|--------------|----------|------------|
|                                  | N=585 adults | HR | 95% CI  | P   | HR | 95% CI  | P   |
| Toxicity (time dependent)        |            | 2.8 | 1.7-4.5 | <0.001 | 2.7 | 1.7-4.4  | <0.001 |
| Age, years                       |            |      |          |        |    |          |      |
| Age >55                          |            | 1.1 | 0.8-1.5 | 0.6   |    |          |      |
| Age ≤55                          |            | 1.9 | 1.4-2.8  | <0.001 | 1.9 | 1.3-2.8  | <0.001 |
| Disease status                   |            |      |          |        |    |          |      |
| Active                           |            | 1.9 | 1.4-2.8  | <0.001 | 1.9 | 1.3-2.8  | <0.001 |
| Remission                        |            | 0.6 | 0.4-0.8  | 0.001  | 0.5 | 0.4-0.7  | <0.001 |
| GVHD prophylaxis                 |            |      |          |        |    |          |      |
| PTCy-based                       |            | 0.6 | 0.4-0.8  | 0.001  | 0.5 | 0.4-0.7  | <0.001 |
| Non-PTCy                         |            | 1.0 | 0.9-1.8  | 0.08   |    |          |      |
| Preparative regimen              |            |      |          |        |    |          |      |
| Reduced Intensity                |            | 2.7 | 1.7-4.4  | <0.001 | 2.7 | 1.7-4.4  | <0.001 |
| Myeloablative                    |            | 1.0 | 0.9-1.8  | 0.08   |    |          |      |
| Stem Cell Source                 |            |      |          |        |    |          |      |
| Peripheral Blood                 |            | 356 | 1.9 | 1.4-2.8  | <0.001 | 1.9 | 1.3-2.8  | <0.001 |
| Bone Marrow                      |            | 229 | 1.0 | 0.9-1.8  | 0.08   |    |          |      |
| Hx of HTN                        |            |      |          |        |    |          |      |
| Yes                              |            | 235 | 1.5 | 1.1-2.1  | 0.008  |    |          |      |
| No                               |            | 350 | 1.0 | 1.03-1.9  | 0.03   |    |          |      |
| History of Hyperlipidemia        |            |      |          |        |    |          |      |
| Yes                              |            | 115 | 1.0 | 0.7-1.5  | 0.8    |    |          |      |
| No                               |            | 470 | 1.0 | 1.03-1.9  | 0.03   |    |          |      |
| Smoker                           |            |      |          |        |    |          |      |
| Yes                              |            | 227 | 1.4 | 1.03-2.1  | 0.03   |    |          |      |
| No                               |            | 356 | 1.0 | 1.03-2.1  | 0.03   |    |          |      |
| KPS                              |            |      |          |        |    |          |      |
| <90                              |            | 230 | 1.4 | 1.03-2.1  | 0.03   |    |          |      |
| ≥90                              |            | 287 | 1.0 | 1.03-2.1  | 0.03   |    |          |      |
| HCT-CI >3                        |            | 265 | 1.5 | 1.1-2.1  | 0.008  |    |          |      |

HR: Hazard Ratio, CI: Confidence Interval
Table 7. Predictors of 1-yr Non-Relapse Mortality

| Characteristics                | Univariate | Multivariate |
|-------------------------------|------------|--------------|
|                               | N=585 adults | HR | 95% CI | P | HR | 95% CI | P |
| Toxicity (time dependent)     |            | 4.9 | 2.7-8.6 | <0.001 | 5.7 | 3.1-10.5 | <0.001 |
| Age, years                    |            |     |         |       |     |         |     |
| Age >55                       | 309 (53)   | 1.3 | 0.9-2.1 | 0.2 |
| Age ≤55                       | 276 (47)   | 1.0 |         |     |
| Disease status                |            |     |         |       |     |         |     |
| Active                        | 356 (61)   | 1.6 | 0.9-2.5 | 0.05 |
| Remission                     | 229 (39)   | 1.0 |         |     |
| GVHD prophylaxis              |            |     |         |       |     |         |     |
| PTCy-based                    | 272 (46)   | 0.4 | 0.2-0.7 | <0.001 |
| Non-PTCy                      | 313 (53)   | 1.0 |         |     |
| Preparative regimen           |            |     |         |       |     |         |     |
| Reduced Intensity             | 201 (34)   | 1.5 | 0.9-2.3 | 0.05 |
| Myeloablative                 | 384 (66)   | 1.0 |         |     |
| Stem Cell Source              |            |     |         |       |     |         |     |
| Peripheral Blood              | 475 (81)   | 0.6 | 0.4-1.0 | 0.06 |
| Bone Marrow                   | 110 (19)   | 1.0 |         |     |
| Hx of HTN                     |            |     |         |       |     |         |     |
| Yes                           | 235 (40)   | 1.6 | 1.1-2.5 | 0.02 |
| No                            | 350 (60)   | 1.0 |         |     |
| History of Hyperlipidemia     |            |     |         |       |     |         |     |
| Yes                           | 115 (20)   | 0.9 | 0.5-1.6 | 0.7 |
| No                            | 470 (80)   | 1.0 |         |     |
| Smoker                        |            |     |         |       |     |         |     |
| Yes                           | 227 (39)   | 1.6 | 1.05-2.4 | 0.03 |
| No                            | 356 (61)   | 1.0 |         |     |
| KPS                           |            |     |         |       |     |         |     |
| <90                           | 230 (39)   | 1.5 | 0.9-2.3 | 0.1 |
| ≥90                           | 287 (49)   | 1.0 |         |     |
| HCT-CI >3                     |            |     |         |       |     |         |     |
|                               | 195 (33)   | 2.8 | 1.8-4.3 | <0.001 |
|                               | 390 (67)   | 1.0 |         |     |


Figure Legends

Figure 1. Incidence of cardiac toxicity from day 0 to day +100 post-alloHCT.

Figure 2. Incidence of cardiac toxicity between cardiac risk stratification scores following alloHCT.
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Figure 1. Incidence of cardiac toxicity from day 0 to day +100 post-alloHCT
Figure 2. Incidence of cardiac toxicity between cardiac risk stratification scores following alloHCT

Cumulative Incidence of Cardiotoxicity

Number at risk

| Score 0-1 | 362 | 355 | 349 | 340 | 327 | 309 |
|-----------|-----|-----|-----|-----|-----|-----|
| Score 2   | 155 | 145 | 141 | 139 | 132 | 121 |
| Score 3-4 | 68  | 62  | 59  | 52  | 49  | 47  |

p=0.005

p<0.001