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The Impact of Beta-Blocker Use at the Time of Hematopoietic Cell Transplantation on the Development of Acute and Chronic Graft-Versus-Host Disease

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Abstract

Sympathetic nervous system activation plays a role in the development of acute and chronic graft-versus-host disease (GVHD) following allogeneic hematopoietic cell transplantation (HCT). The primary objective was to compare the cause-specific hazard of grade II-IV and III-IV acute GVHD (aGVHD) and chronic GVHD (cGVHD) in the context of ß-blocker use and type (selective vs. non-selective). Secondary objectives included overall survival (OS), relapse-free survival (RFS), and cumulative incidence of relapse, non-relapse mortality (NRM), and grade II-IV and III-IV aGVHD and cGVHD. The current study included 151 patients ages 18 and older diagnosed with hematological malignancies who underwent reduced intensity conditioning allogeneic HCT from HLA matched related or unrelated donors between January 2014 and 2017. 31 patients were on a ß-blocker of which 71% were on a selective ß-blocker. The incidence of aGVHD was not different among groups. Results show a non-significant trend in the association between ß-blocker use and reduction in the risk of developing cGVHD (cause-specific hazard ratio 0.49, p = 0.060), with no negative impact on survival or relapse. The current data are supportive of a potential ß-adrenergic influence on the pathogenesis of GVHD, consistent with the inflammatory etiology of GVHD and the anti-inflammatory effects of ß-adrenergic antagonists.

Keywords: ß-blockers, Graft-versus-host disease, Allogeneic hematopoietic cell transplantation, Clinical outcomes

1. Introduction

Both acute and chronic graft-versus-host disease (GVHD) are significant complications of allogeneic hematopoietic cell transplantation (allo-HCT) and major causes of morbidity and mortality [1,2]. 30–70% of HCT recipients develop acute GVHD (aGVHD) and 20–50% develop chronic GVHD (cGVHD) [2]. According to the Center for International Blood and Marrow Transplant Research, approximately 14–16% of deaths among HLA-matched sibling and unrelated donor transplant recipients from 2016-2017 were due to GVHD [3]. The overall survival of aGVHD has improved in recent years; however, the 1-year survival of aGVHD grade III-IV is 40% [4]. The occurrence of aGVHD confers a greater than threefold increase in mortality as well as significantly longer length of stay and greater median costs per stay [5].

First line therapy for GVHD with corticosteroids can be highly effective with response rates of 40–60%, though steroid efficacy wanes with increased GVHD severity, where mortality rates are 70–80% [1]. Increased risk for infection, organ impairment, reduced quality of life, chronic health

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conditions, and frailty are particularly concerning in cGVHD given the need for prolonged immunosuppression [6–8]. Therefore, there remains a need for the development and improvement of prophylaxis to further reduce GVHD incidence and improve transplant related mortality (TRM) [9–11].

As GVHD is largely an inflammatory process, studies have focused on investigation of medications that target inflammation as potential prophylactic adjuncts. Statins have been explored for their anti-inflammatory properties; 10% vs. 40% of patients who received vs. did not receive a high-dose statin prior to allo-HCT developed aGVHD [12]. Though not traditionally considered an anti-inflammatory approach, the immunosuppressant tocilizumab blocks the effects of the pro-inflammatory cytokine IL-6 and is associated with a lower incidence and higher disease-free survival of grade II-IV aGVHD [13]. Tocilizumab is also associated with achieving complete remission in patients with severe corticosteroid refractory aGVHD [14].

ß-adrenergic receptor antagonists (ß-blockers) are another medication class with anti-inflammatory properties. Increased sympathetic nervous system (SNS) activity, as occurs in physiologically stressed states including both depression and GVHD, results in increased ß-adrenergic receptor (ß-AR) activation that stimulates inflammatory and other related pathways associated with the development and persistence of various cancers [15–18]. ß-AR activation leads to increased IL-6, IL-8 [19,20], and VEGF [16,18] expression and prevents apoptosis [17] in solid organ tumor cells, with evidence in multiple cancer populations that ß-blockers are also associated with increased OS [21–25]. With regard to hematopoiesis, ß-blockers are implicated in the upregulation of myelopoiesis and production of immature pro-inflammatory monocytes [26].

In the context of hematological malignancies, Hwa et al. demonstrated improved OS and disease specific survival in multiple myeloma patients concurrently on ß-blocker therapy at the time of HCT [27]. Importantly, the non-selective ß-blocker propranolol was efficacious at improving molecular risk and inflammatory markers in a phase 2 randomized controlled trial of multiple myeloma patients undergoing autologous HCT, with early indication it may also be associated with earlier engraftment [28]. Wang et al. evaluated the intricate relationship between GVHD and graft-versus-tumor (GVT), and found that $ß_2$ adrenergic signaling blockade improved donor T-cell reconstitution, leading to enhanced GVT effect without increasing GVHD [29,30]. Finally, ß-blocker administration is not only feasible and tolerated in the HCT setting, but it is cost effective as well [31].

Despite the increasing use of HCT to treat hematologic malignancies, its efficacy remains dampened by significant morbidity and mortality, including GVHD [32]. Heightened SNS activity and increased inflammatory activation in the peri-HCT period, along with early evidence that ß-blockers may be helpful with cancer and HCT outcomes, support investigating the effect of this drug class on GVHD. Therefore, we evaluated the association between ß-blocker exposure at the time of HCT and a/cGVHD (primary outcome) as well as survival and relapse (secondary outcomes) in HCT patients.

2. Materials and methods

2.1. Patient population

This is a single center retrospective study approved by the Medical College of Wisconsin Institutional Review Board (IRB). Patient consent for research-directed access to their medical records was waived during IRB application. This study included hematological malignancy patients 18 and older who underwent a reduced intensity conditioning (RIC) allo-HCT from either HLA matched related or unrelated donors at Froedtert/Medical College of Wisconsin between January 2014 and January 2017. Data were extracted from the cohort as reported by Guru et al that evaluated outcomes of RIC allogeneic HCT performed in the inpatient versus outpatient setting [33]; please see this publication for additional detail.

Additional data retrieved from the medical record for the current study included ß-blocker usage, defined as patients receiving an oral or IV dose of either a selective or non-selective ß-blocker at least a day prior to HCT, at the time of HCT, and at least a day after HCT. This modality of ß-blocker use assessment was utilized to maximize obtaining participants who were exposed to a ß-blocker throughout a longer duration of the peri-HCT period, without including patients whose ß-blocker use was initiated or terminated as a result of their transplant. Selective ß-blockers included metoprolol and atenolol, and non-selective ß-blockers included carvedilol, propranolol, and sotalol. Data abstracted for current use from the prior study[33] included age, gender, race, in- vs. outpatient HCT, disease type, disease risk index (DRI) classification, HCT comorbidity index (HCT-CI), donor type, RIC regimen, GVHD prophylaxis, stem cell source, Karnofsky performance status (KPS), acute or

chronic GVHD onset and staging, time of death, cause of death, and time of relapse.

2.2. Clinical outcomes and statistical analysis

The primary objective of the current study was to compare the cause-specific hazard of grade II-IV and grade III-IV acute and chronic GVHD between patients on a ß-blocker and patients not on a ß-blocker at the time of RIC allo-HCT as well as the type of ß-blocker used (selective vs. non-selective). Secondary objectives included assessing differences between overall survival (OS), relapse-free survival (RFS), and the cumulative incidence of relapse, non-relapse mortality (NRM), and grade II-IV and grade III-IV acute GVHD and chronic GVHD between patients exposed vs. not exposed to ß-blocker therapy.

Demographic and disease characteristics were summarized using descriptive statistics and compared between the study cohorts using Wilcoxon rank-sum test for continuous and ordinal measures and chi-square tests for categorical outcomes. Patients were followed for survival from the time of transplant to death or last follow-up. Survival curves were estimated using the Kaplan-Meier method and compared between groups via the log-rank test. Cox regression was used for the multivariable analysis of survival. In the presence of competing risks (GVHD, TRM), Nelson-Aalen estimate of the cumulative incidence was presented. Log-rank test and Gray's test, respectively, were used for unadjusted group comparisons. The effect of ß-blocker on the cause-specific hazard of acute and chronic GVHD was evaluated using a Cox proportional hazards regression, with acute or chronic GVHD as the event time and censoring at time of death or end of follow-up. The Cox regression was stratified by disease type and adjusted for HLA-match (matched unrelated donor vs. matched related donor), disease risk index (low, intermediate, high), age, and HCT-Comorbidity Index. The effect of non-selective ß-blockers was evaluated by comparing them to the combined group of patients taking selective ß-blockers or no ß-blocker. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

The power of the cause-specific hazards regression is driven by the number of events. Assuming that 25% of the study population would have aGVHD, 40% would develop cGVHD, and that one-third of patients would be using ß -blockers, with 150 patients, the study could detect with 80% power a hazard ratio of 0.38 or 0.46 for the effect of ß-blockers on aGVHD and cGVHD, respectively.

3. Results

3.1. Baseline characteristics

Table 1 describes patient, disease, and treatment characteristics for patients taking vs. not taking a ß-blocker at the time of transplant. The study included 151 patients of which 31 were on a ß-blocker at the time of transplant; 22 patients were on a selective ß-blocker and 9 on a non-selective ß-blocker. The median age of patients in these two categories was the same (65 years). There were no significant differences based on gender or race, with the majority of patients in both cohorts predominantly male and Caucasian. The most common indication for HCT in both cohorts was acute leukemia (28.3% vs. 41.9%) and the least common indication was lymphoma (18.3% vs. 12.9%). The ß-blocker usage cohort had a significantly higher median HCT-CI (2.0 vs. 1.0, $p = 0.035$). The two cohorts did not significantly differ in DRI, sex match, conditioning regimen, GVHD prophylaxis, stem cell source, KPS, or donor type, as described in Table 1.

3.2. Transplant outcomes

Patients who were on a ß-blocker at the time of transplant had a lower cause-specific hazard (hazard ratio [HR] = 0.49, 95% confidence interval [CI] = 0.23 to 1.03, $p = 0.060$) and cumulative incidence of cGVHD at 1-, 2-, and 3-year follow-up (overall $p = 0.17$) as compared to those not on a ß-blocker, with a greater reduction of the cause-specific hazard (HR = 0.19, CI = 0.025 to 1.37, $p = 0.099$) and cumulative incidence ($p = 0.070$) for those on a non-selective ß-blocker, though these associations did not reach statistical significance (Table 2, Figs. 1a and 1b). The hazard ratio measured the multiplicative effect of ß-blockers on the instantaneous risk of developing cGVHD. With an HR of 0.49, patients that were on ß-blockers developed cGVHD at an approximately two times lower rate compared to those that were not on ß-blockers. There was no significant difference in OS, RFS, incidence of relapse, and incidence of NRM based on ß-blocker usage or type (Table 2).

There was no significant difference in the overall cumulative incidence of grade II-IV and grade III-IV aGVHD and cGVHD at day 100 in terms of ß-blocker usage and type (selective vs. non-selective) (Table 3).

4. Discussion

The current data suggest that ß-blocker usage may be associated with a reduction in the risk of

Table 1. Patient, disease, and treatment characteristics by ß-blocker use.

Variable	ß-blocker use		P-value
	No	Yes	
No. of patients	120	31	
ß-blocker Class			
Non-selective	0	9 (29.0)	
Selective	0	22 (71.0)	
Age			0.317
Median (range)	65.0 (27.0−78.0)	65.0 (25.0−77.0)	
Mean ± SD	61.2 ± 10.4	62.8 ± 10.9	
Gender			0.770
Female	46 (38.3)	11 (35.5)	
Male	74 (61.7)	20 (64.5)	
Race			0.454
Asian	3 (2.5)	0 (0.0)	
Black	1 (0.8)	1 (3.2)	
Hispanic	1 (0.8)	0 (0.0)	
White	115 (95.8)	30 (96.8)	
KPS			0.855
Median (range)	80.0 (50.0−100.0)	80.0 (50.0−100.0)	
Mean ± SD	80.7 ± 9.2	80.0 ± 11.0	
Disease group			0.390
Acute Leukemia	34 (28.3)	13 (41.9)	
Lymphoma	22 (18.3)	4 (12.9)	
MDS/MPN	37 (30.8)	10 (32.3)	
MM	27 (22.5)	4 (12.9)	
DRI			0.445
High	18 (15.3)	6 (19.4)	
Intermediate	92 (78.0)	19 (61.3)	
Low	8 (6.8)	6 (19.4)	
HCT-CI			0.022
0	28 (23.3)	3 (9.7)	
1	35 (29.2)	4 (12.9)	
2	22 (18.3)	12 (38.7)	
3+	35 (29.2)	12 (38.7)	
HCT-CI			0.035
Median (range)	1.0 (0.0−10.0)	2.0 (0.0−7.0)	
Mean ± SD	1.9 ± 1.8	2.4 ± 1.5	
Missing	0	0	
Conditioning regimen			0.865
BEAM	1 (0.8)	0 (0.0)	
Flu Bu	80 (66.7)	22 (71.0)	
Flu Mel	39 (32.5)	9 (29.0)	
Sex match			0.774
F-F	19 (15.8)	4 (12.9)	
F-M	31 (25.8)	11 (35.5)	
M-F	28 (23.3)	6 (19.4)	
M-M	42 (35.0)	10 (32.3)	
GVHD prophylaxis			0.187
FK/MTX	91 (75.8)	24 (77.4)	
FK/MTX/ATG	1 (0.8)	0 (0.0)	
FK/MTX/atorvastatin	11 (9.2)	6 (19.4)	
FK/MTX/tocilizumab	17 (14.2)	1 (3.2)	
Stem cell source			1.000
BM	4 (3.3)	1 (3.2)	
PB	116 (96.7)	30 (96.8)	
Donor type			0.381
MRD	57 (47.5)	12 (38.7)	
MUD	63 (52.5)	19 (61.3)	

Data presented in % unless otherwise indicated. SD indicates standard deviation. KPS, Karnofsky performance score. MDS, myelodysplastic syndrome. MPN, myeloproliferative neoplasm. DRI, disease risk index. HCT-CI, hematopoietic cell transplantation comorbidity index. BEAM, carmustine, etoposide, cytarabine, and melphalan. Flu, fludarabine. Bu, busulfan. Mel, melphalan. F, female. M, male. FK, tacrolimus. MTX, methotrexate. ATG, anti-thymocyte globulin. BM, bone marrow. PB, peripheral blood. MRD, matched related donor. MUD, matched unrelated donor.

Table 2. Cause-specific hazard regression comparing ß-blocker use/type and GVHD and relapse outcomes, stratified by disease type. Adjusted for HLA-match, disease risk, age, and HCT-CI.

Outcomes	ß-blocker use		Non-selective ß-blocker use	
	aHR (95% CI)	P-value	aHR (95% CI)	P-value
Grade II-IV acute GVHD	1.15 (0.54–2.43)	0.72	1.26 (0.37–4.34)	0.71
Grade III-IV acute GVHD	1.12 (0.34–3.68)	0.85	1.99 (0.41–9.66)	0.39
Chronic GVHD	0.49 (0.23–1.03)	0.060	0.19 (0.03–1.37)	0.099
Overall survival	1.14 (0.59–2.19)	0.70	1.10 (0.42–2.85)	0.85
Relapse-free survival	1.14 (0.64–2.06)	0.65	1.57 (0.66–3.76)	0.31
Relapse	0.90 (0.40–2.01)	0.79	1.88 (0.64–5.55)	0.25
Non-relapse mortality	1.56 (0.63–3.84)	0.34	1.41 (0.32–6.20)	0.65

GVHD, graft-versus-host disease. HLA indicates human leukocyte antigens. HCT-CI, hematopoietic cell transplantation comorbidity index. aHR, adjusted hazard regression. CI, confidence interval.

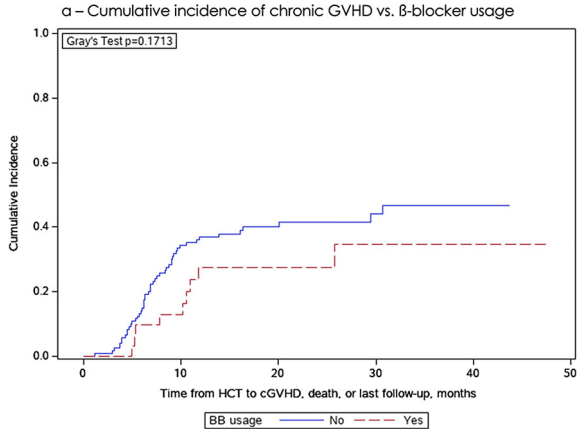

Fig. 1a. Cumulative incidence of chronicGVHD vs.ß-Blocker usage.

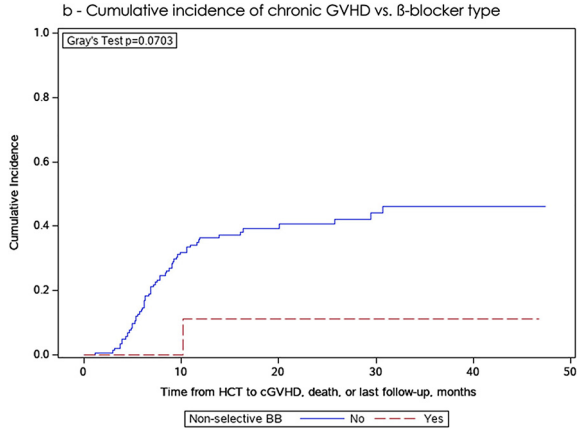

Fig. 1b. Cumulative incidence of chronicGVHD vs.ß-Blocker usage.

developing cGVHD, with a greater reduction for those exposed to a non-selective vs. selective ß-blocker. Due to the smaller sample size and lower than expected incidence of ß-blocker use in this cohort, these relationships just missed reaching statistical significance. Furthermore, there was no evidence of harm from ß-blocker use in this population as indicated by the non-significant differences in OS, RFS, incidence of relapse, and NRM. These data provide preliminary evidence to support the potential for ß-blocker use as a safe prophylactic adjunct in the prevention of cGVHD and preservation of GVT and warrant future investigation.

GVHD involves the release of pro-inflammatory cytokines that lead to the activation of donor T-cells against self-antigens, eventually leading to end organ damage. In addition to acute inflammation, cGVHD involves chronic inflammation, dysregulated immunity, and scar tissue formation. Increased physiological stress is associated with increased ß-AR activation [21,27–29] as well as depression, hematological disease, and HCT. Depression also involves pro-inflammatory signaling that is associated with increased morbidity and mortality [34]. These overlaps in signaling pathways represent one potential biobehavioral mechanism by which patients with depression who undergo allo-HCT are at risk for increased incidence of aGVHD [35]. ß-blockers have anti-inflammatory properties; they have been demonstrated to improve OS in solid organ cancers [32–36] that involve inflammation and improve OS and inflammatory markers in multiple myeloma [37,38].

The associations between ß-adrenergic signaling and GVHD and GVT are nuanced and depend on receptor type, cell type and origin (host vs. donor), and tissue type (e.g. bone marrow microenvironment) as proposed by Wang et al. [29]. This may explain this study's lack of effect of ß-blockers on the incidence of aGVHD while still demonstrating improvement in the cause-specific hazard and incidence of cGVHD. With regard to cell type and origin, Mohammadpour et al. demonstrated that the blockade of murine host $ß_2$ adrenergic signaling enhanced GVT without increasing GVHD through the involvement of host DCs and host CD8 + T-cells, but exacerbated GVHD through the likely involvement of host CD4 + T-cells [29,30]. In support of this, Leigh et al. demonstrated that $ß_2$

Table 3. Comparison of cumulative incidences and ß-blocker groups. GVHD, graft-versus-host disease.

Outcomes	ß-blocker	No ß-blocker	P-value	Non-selective ß-blocker	Selective or no ß-blocker	P-value
Cumulative Incidence of grade II-IV aGVHD at Day 100	22.6%	20.0%	0.539	11.1%	21.1%	0.841
Cumulative Incidence of grade III-IV aGVHD at Day 100	3.2%	8.3%	0.984	0.0%	7.7%	0.399
Cumulative Incidence of cGVHD at 1-year	27.6%	37%	0.171	11.1%	36.5%	0.070

adrenergic signaling in murine host T-cells is essential for inhibiting GVHD [29,36]. It is also known that the development of aGVHD - and to a certain degree, cGVHD - involves the co-activation of donor T-cells [37,39]. Since $ß_2$ adrenergic signaling may enhance host CD4 + and CD8 + T-cell activity, which play different roles in the development of GVHD and GVT, and, with T-cells in general playing a more prominent role in the development of aGVHD, it is reasonable then that ß-blocker use may not necessarily improve incidence of aGVHD but still reduce the incidence of cGVHD whose pathophysiology involves many more factors and is not as well defined. Also, it is possible that ß-blockers may improve GVT since there was no significant increase in relapse or decrease in RFS, though further investigation is warranted.

The reduction in cGVHD without reduction in aGVHD could also be explained by the differential roles of ß-blockers in the bone marrow microenvironment. $ß_2$ and $ß_3$ adrenergic signaling regulates the bone marrow microenvironment and promotes hematopoietic stem cell (HSC) proliferation and mobilization that is critical to the development of both GVHD and GVT [29]. The majority of ß-blockers in the study have limited affinity for $ß_3$ receptors compared to $ß_1$ and $ß_2$. $ß_3$ adrenergic signaling may have a more prominent role in HSC proliferation while $ß_2$ signaling may be more involved in HSC mobilization [29]. It is unknown whether proliferation or mobilization or their specific underlying mechanisms play a differential role in the development of acute vs. chronic GVHD. Further studies are needed to differentiate the roles of various ß-adrenergic signaling pathways to better understand these relationships.

These data add to the growing literature with regard not only to the safety, but potential efficacy, for ß-blockers to improve HCT outcomes. In a recent randomized control trial of propranolol among multiple myeloma patients undergoing autologous HCT, tolerance was good with an adherence rate of 94% [31]. In the same cohort, propranolol reduced expression of the conserved transcriptional response to adversity gene expression profile [28], a marker of SNS activity and inflammation associated with worse outcomes following HCT [15,38]. Propranolol was also associated with reduced infection rates and accelerated engraftment in this cohort [28].

There are several limitations to the current study. Most notably, the study was powered with the assumption that one-third of patients would be on ß-blockers based on incidence in other populations [27]. However, the current cohort is composed of one-fourth of individuals on ß-blocker therapy; thus, power was lower than initially planned for. Therefore, it is possible that the current near-significant findings between ß-blocker use and cGVHD represent slight underpowering and not a true lack of association. Another limitation is the retrospective nature of this study; future research utilizing a randomized controlled trial is needed to confirm the associations observed here.

Data from the current study suggest a reduction in the risk of developing cGVHD for patients on a non-selective ß-blocker during the time of HCT, without any negative impact on survival or relapse. ß-blockers may be a safe and efficacious peri-HCT adjunct in the prevention of cGVHD and preservation of GVT and warrant additional investigation prior to implementation as standard of care.

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