Beta-blocker use and hematopoietic stem cell transplant outcomes

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Introduction

- B-AR signaling impacts a wide variety of immune cell functions, including pro-inflammatory pathways [1-4], hematopoiesis [5-6], and hematopoietic reconstitution after allo-HSCT [7].
- Beta-blocker (BB) use in the setting of experimental and clinical critical illness [8, 9] and burn injury [10, 11] is associated with improved outcomes. These improvements may be due to blockade of the beta-adrenergic receptor (b-AR) and resultant anti-inflammatory effects.
- Graft versus host disease (GVHD) in allogenic hematopoietic stem cell transplant (allo-HSCT) is intricately connected to the pro-inflammatory pathway through both cytokine release and immune cell activation, leading to sustained tissue damage and inflammation [1-4].

Objectives

- We hypothesized that BB use prior to allo-HSCT may be associated with decreased GVHD and improved survival outcomes.

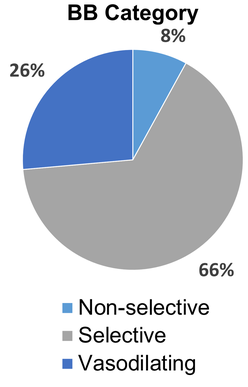
Methods

- All patients who received their first allogeneic HSCT between January 2010 and May 2020 at the Duke Adult Bone Marrow Transplant (ABMT) clinic.
- Demographic data and transplant outcomes were abstracted from the ABMT database retrospectively .
- All charts were reviewed to document BB exposure from d-100 to d-1 prior to allo-HSCT. This included BB type, BB category, duration of exposure, and clinical reason for BB use.
- Because initiation of BB during HSCT is often the result of a complication (e.g., atrial fibrillation) that could bias analysis of results, and because the primary question is GVHD prevention, we defined our BB group as those who were on a BB for at least 4 days within the 100 days before the transplant.

Table 1. Breakdown of patients who were on a BB (Yes BB, n=125) prior to allo-HSCT by BB Type and BB Category.

BB Type (Generic Name)	BB Category	N (%)
Atenolol	Selective	13 (10.4)
Carvedilol	Vasodilating	30 (24.0)
Labetalol	Vasodilating	3 (2.4)
Metoprolol	Selective	68 (54.4)
Nadolol	Non-selective	1 (0.8)
Nebivolol	Selective	1 (0.8)
Propranolol	Non-selective	7 (5.6)
Sotalol	Non-selective	1 (0.8)
Timolol	Non-selective	1 (0.8)

Figure 1. Pie chart of Yes BB group by BB Category.



Results

- Demographics recorded included Age, Sex, Race, Ethnicity, Transplant Diagnosis, Graft Source, Conditioning Regimen, GVHD Prophylaxis, HCT-CI, Weight, BMI, and Albumin. Only significant demographics were included in the table below.

Table 2. Demographics were compared between patients who were on a BB (Yes BB) (n=125) and those who were not (No BB) (n=649) prior to allo-HSCT.

Characteristic	All Patients N=774 (100%)	No BB N=649 (83.8%)	Yes BB N=125 (16.2%)	P-Value
HCT-CI (median, IQR)	3 (2 – 4)	3 (2 – 4)	4 (3 – 5)	**<.001**
Pre-Transplant Albumin (median, IQR)	3.9 (3.6 – 4.2)	4 (3.6 – 4.2)	3.8 (3.4 – 4.1)	**0.032**

- Outcomes included acute GVHD (aGVHD) occurrence and grade, chronic GVHD (cGVHD) occurrence and grade, length of stay (LOS), follow-up time, weight, BMI, albumin.

Table 3. Outcomes of patients who were not on a BB (No BB) or who were on a BB (Yes BB) prior to allo-HSCT.

Outcomes	All Patients N=774 (100%)	No BB N=649 (83.8%)	Yes BB N=125 (16.2%)	P-Value
Acute GVHD Occurrence, n (%)	498 (64.3%)	429 (66.1%)	69 (55.2%)	**0.020**
Acute GVHD Grade (None vs Low vs High), n (%)				**0.064**
0	276 (35.7%)	220 (33.9%)	56 (44.8%)	
1	107 (13.8%)	93 (14.3%)	14 (11.2%)	
2+	391 (50.5%)	336 (51.8%)	55 (44%)	
Acute GVHD Grade (None/Low vs High), n (%)				**0.112**
0-1	383 (49.5%)	313 (48.2%)	70 (56%)	
2+	391 (50.5%)	336 (51.8%)	55 (44%)	
Chronic GVHD Occurrence, n (%)	341 (44.1%)	280 (43.1%)	61 (48.8%)	**0.243**
Chronic GVHD Grade, n (%)				**0.348**
No GVHD	433 (55.9%)	369 (56.9%)	64 (51.2%)	
Mild-Moderate	81 (10.5%)	64 (9.9%)	17 (13.6%)	
Severe	260 (33.6%)	216 (33.3%)	44 (35.2%)	
Length Of Stay in days (median, IQR)	88 (76 – 98)	87 (76 – 97)	90 (77 – 103)	**0.903**
Follow-Up Time in months (median, IQR)	14.03 (5.8 – 47.38)	14.23 (5.8 – 47.74)	13.77 (5.8 – 37.51)	**0.998**
Post-Transplant Weight in lbs (median, IQR)	170 (144 – 197)	162 (142 – 205)	172 (144 – 196)	**0.552**
Post-Transplant BMI in kg/m2 (median, IQR)	25.69 (22.57 – 29.1)	25.74 (22.54 – 29.1)	25.08 (22.65 – 29.9)	**0.467**
Post-Transplant Albumin (median, IQR)	3.8 (3.5 – 4.2)	3.9 (3.5 – 4.2)	3.7 (3.35 – 4)	**0.005**
Change in Albumin (Post-Pre) (median, IQR)	0 (-0.4 - 0.3)	0 (-0.4 - 0.3)	-0.1 (-0.5 - 0.15)	**0.213**

- We performed multivariate analysis (MVA) to further examine associations between BB use and other co-variates on aGVHD after allo-HSCT.
- Albumin at d+90 was excluded from MVA to avoid post-hoc confounding since aGVHD commonly occurs before d+90.
- All co-variates, including BB use, was **not** significant on MVA (**p=0.249**).
- Additionally, we subdivided the Yes BB group by BB Category (Figure 1) . The same outcomes were analyzed.

Table 4. Outcomes of patients who were on a BB prior to allo-HSCT by BB Category.

Outcomes	All Patients N=125 (100%)	Non-selective N=10 (8%)	Vasodilating N=33 (26.4%)	Selective N=82 (65.6%)	P-Value
Acute GvHD Occurrence, n (%)	69 (55.2%)	7 (70%)	14 (42.4%)	48 (58.5%)	**0.180**
Length Of Stay in days (median, IQR)	90 (77 – 103)	97 (82 – 104)	85 (67 – 90)	92 (79 – 112)	**0.013**

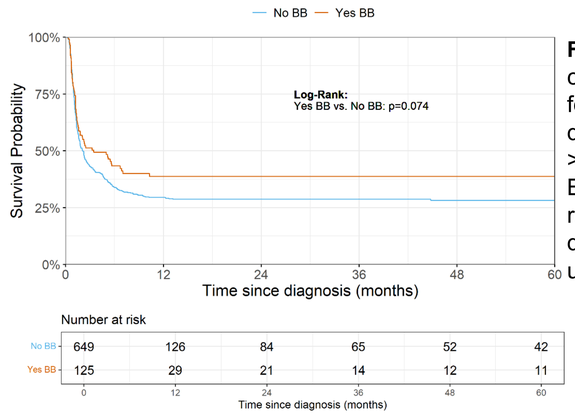


Figure 2. Kaplan-Meier curve of aGVHD-free rate for treatment groups defined by exposure to BB >4 days prior to HSCT. No BB = blue and Yes BB = red. Overall group differences were evaluated using log-rank tests.

Conclusions

- We are hesitant to fully support a role for BBs as a prophylactic intervention to prevent aGVHD since MVA was non-significant (**p=0.249**).
- Use of a vasodilating BB was associated with reduced LOS compared to non-selective BB and selective BB (**p=0.013**). Further research is necessary to substantiate these preliminary findings.
- The lack of statistically significant in survival outcomes suggest neither benefit nor harm from BBs, consistent with current data on their pharmacological safety (**all p>0.05**).

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