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Azithromycin may increase hematologic relapse rates in matched unrelated donor hematopoietic cell transplant recipients who receive anti-thymocyte globulin, but not in most other recipients

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Chronic GVHD (cGVHD) of the lung after hematopoietic cell transplant (HCT) typically manifests as bronchiolitis obliterans syndrome (BOS), and is associated with high mortality (1). Azithromycin is a macrolide antibiotic with anti-inflammatory properties that improves pulmonary outcomes after lung transplantation (2). Treatment with a combination of fluticasone, azithromycin, and montelukast (FAM) can reduce the rate of pulmonary impairment in HCT recipients with BOS (3). However, pulmonary impairment after a diagnosis of BOS is often irreversible, highlighting the need to treat BOS early in its course (4). A randomized controlled trial of prophylactic azithromycin given at the time of pre-HCT conditioning was terminated prematurely due to lower airflow decline-free survival rates in those receiving azithromycin (5). Post-hoc analyses revealed a 70% increase in the incidence of hematologic relapse at 2 years in the azithromycin arm. This resulted in a warning by the Food and Drug Administration for the long-term use of prophylactic azithromycin to prevent BOS in HCT recipients. Because azithromycin for the treatment of BOS is typically given later in the course of HCT rather than at the time of conditioning, and because hematologic relapse rates generally decline after one year post-HCT (6), the

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concern for relapse may not apply to many HCT recipients receiving azithromycin for the treatment of BOS. We conducted a retrospective chart review of allogeneic HCT recipients. We hypothesized that azithromycin given later in the course of HCT, primarily for the treatment of BOS, would not be associated with higher rates of hematologic relapse.

We collected data on all patients at least 18 years of age undergoing first allogeneic HCT at our institution between February 1999 and March 2018 who developed pulmonary impairment, defined as declines in forced expiratory volume in 1 second (FEV_1) of 10% or in mid-expiratory flow rates of 25%, relative to pre-HCT values (7), a population we theorized would be most likely to receive extended courses of azithromycin treatment. It is our institutional policy to administer anti-thymocyte globulin (ATG) to unrelated donor and cord blood transplants, but not to matched related donor (MRD) transplants. All patients received calcineurin-based post-HCT immunosuppression as cGVHD prophylaxis. Haploidentical transplants received post-HCT cyclophosphamide. Our institutional review board approved the study (PA17–0732) with a waiver of informed consent.

We defined exposure to azithromycin as at least two continuous weeks of azithromycin therapy for BOS, treatment of infections such as mycobacterium avium intracellulare (MAI), or long-term infection prophylaxis. BOS was defined by National Institutes of Health criteria (8). Exposure to azithromycin was identified by review of patient charts and pharmacy databases. Hematologic relapse was defined as morphological or cytological evidence of malignancy in the bone marrow or peripheral blood as recommended by the Center for International Blood and Marrow Transplant Research (CIBMTR) (9). Conditioning intensity was defined according to CIBMTR (10).

Our primary endpoint was the rate of malignancy relapse according to exposure to azithromycin. The cumulative incidence of relapse since HCT was estimated by considering death before relapse as a competing risk. Patient characteristics were evaluated using chi-square or Fisher’s exact test for categorical variables, and Wilcoxon’s rank-sum test for continuous variables. Predictors of relapse were evaluated in univariate and multivariate analyses using Fine and Gray competing risks regression analysis. Exposure to azithromycin, the presence of cGVHD, and the initiation of oral steroids were treated as time-dependent covariates. In addition, the potential varying effect of azithromycin exposure over time was accounted for. Backward elimination was used to select variables with $p<0.05$ to be retained in the final multivariate model. We tested for interactions between time-dependent azithromycin exposure and other covariates and adjusted the multivariate model accordingly. Statistical significance was set at the 0.05 level. Statistical analyses were performed using primarily STATA 14.0 (StataCorp, Statistical Software Release 14, College Station, TX).

Table 1 describes the characteristics of the study cohort (n=1382). 127 patients developed BOS. 117 patients were exposed to azithromycin for at least two consecutive weeks (median: 366 days, n=78 for BOS, n=39 for infection), at a median of 545 days post-HCT. A total of 440 patients experienced relapse of their malignancy, including 13 HCT recipients exposed to azithromycin. The majority of relapses (n=420) occurred within 5 years post-

HCT (median 9 months). The 5-year cumulative incidence of hematologic relapse after transplant was 32%.

In univariate analyses, the use of azithromycin, considered as a time-dependent covariate, was not associated with an increased rate of hematologic relapse (hazard ratio [HR] 1.3, 95% CI 0.6–2.9, p=0.5). Indication for azithromycin (HR=0.8, 95% CI 0.2–2.3, p=0.6) and exposure to oral steroids (HR=0.8, 95% CI 0.6–1.1, p=0.1) were not associated with the relapse rate. Development of cGVHD (HR=0.7, 95% CI 0.6–0.9, p=0.01) was associated with a lower rate of relapse, and a diagnosis of acute lymphoblastic leukemia (HR=1.4, 95% CI 1.1–1.8, p=0.02), active disease at the time of transplant (HR=1.7, 95% CI 1.4–2.1, p<0.001), and non-myeloablative conditioning (HR=1.3, 95% CI 1.0–1.5, p=0.02) were associated with higher rates of relapse. Testing for interaction effects revealed a significant interaction between azithromycin exposure and donor type and preparative regimen (p=0.035).

Azithromycin exposure was associated with a higher rate of relapse in matched unrelated donor (MUD) HCT recipients who received ATG (MUD/ATG) as part of conditioning (n=423, HR=3.8, 95% CI 1.1–13, p=0.04), but not in the remaining recipients (n=959, HR=0.6, 95% CI 0.2–1.6, p=0.3). This trend persisted, but did not reach significance in multivariate analyses (HR 2.4, 95% CI 0.8–6.8, p=0.1, Table 2). Independently, exposure to azithromycin (HR=0.8, 95% CI 0.3–1.9, p=0.7) and MUD/ATG (HR=0.9, 95% CI 0.7–1.1, p=0.3) were not associated with increased rates of relapse.

In this study, we found that prolonged azithromycin treatment did not increase risk of relapse in most HCT recipients, but potentially increased risk for relapse in MUD/ATG recipients. While our findings require validation in external cohorts, these results suggest caution should be applied when initiating extended courses of azithromycin in MUD/ATG recipients. Effective treatment of BOS requires prompt initiation of treatment, but Bergeron et al found that azithromycin was potentially harmful if given prophylactically (5). In a subsequent study of 316 HCT recipients with BOS, Cheng et al discovered no increase in relapse with azithromycin exposure, but found an increase in subsequent neoplasms in those who had received azithromycin (11). ATG utilization was lower than in our study (12% vs. 38%), and therefore any potential subgroup analyses examining relapse in MUD/ATG recipients would likely lack statistical power.

This is a large, comprehensive analysis of consecutive first allogeneic HCT recipients who were exposed to azithromycin to treat BOS or infection. However, the proportion of patients who received azithromycin and the number of relapses after azithromycin exposure were small, and the association between azithromycin and relapse among MUD-HCT recipients who received ATG needs to be evaluated in other cohorts. In addition, we did not examine whether azithromycin increases the risk for secondary cancers as recently reported by Cheng et al (11).

In conclusion, in a large retrospective cohort of first allogeneic HCT recipients with pulmonary impairment, we found that azithromycin did not increase the risk of relapse in most HCT recipients. However, we found a potential increase in relapse risk with

azithromycin exposure in MUD-HCT recipients who received ATG for in preparative regimens, and azithromycin should potentially be avoided in this subpopulation.

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Abbreviations

ATG	anti-thymocyte globulin
BOS	bronchiolitis obliterans syndrome
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
FAM	fluticasone, azithromycin, and montelukast
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
cGVHD	chronic graft-versus-host disease
HCT	hematopoietic cell transplantation
HR	hazard ratio
MAI	mycobacterium avium intracellulare

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Table 1.

Characteristics of the study cohort

Variable	Overall	(%)	Azithromycin exposure		p-value
	N=1382		Yes N=117 n (%)	No N=1265 n (%)	
Year of HCT					<0.001
Earlier than 2000	59	4	1 (1)	58 (5)	
2001–2005	219	16	3 (3)	216 (17)	
2006–2010	417	30	32 (27)	385 (30)	
2011–2015	552	40	67 (57)	485 (38)	
2015–2018	135	10	14 (12)	121 (10)	
Underlying malignancy					0.6
AML/MDS	677	49	61 (52)	616 (49)	
ALL	168	12	15 (13)	153 (12)	
NHL	237	17	18 (15)	219 (17)	
HL	57	4	2 (2)	55 (4)	
CLL	108	8	7 (6)	101 (8)	
CML	103	7	12 (10)	91 (7)	
MM	32	2	2 (2)	30 (2)	
Age at transplant (years), median (range)	52 (18–76)		54 (19–75)	52 (18–76)	0.1
≤40	366	26	25 (21)	341 (27)	
41–50	276	20	23 (20)	253 (20)	
51–60	433	31	37 (32)	396 (31)	
>60	307	22	32 (27)	275 (22)	
Remission status at HCT					0.1
Complete remission	611	44	61 (52)	550 (43)	
No complete remission	771	56	56 (48)	715 (57)	
Cell source					0.04
Peripheral blood	911	66	89 (76)	822 (65)	
Cord blood	83	6	7 (6)	76 (6)	
Bone marrow	388	28	21 (18)	367 (29)	
Donor type					0.5
MUD + ATG	423	31	34 (29)	389 (31)	
MUD - ATG	177	13	17 (15)	160 (13)	
MRD + ATG	21	2	0	21 (2)	
MRD – ATG	596	43	53 (45)	542 (43)	
Cord blood + ATG	69	5	7 (6)	62 (5)	
Cord blood - ATG	14	1	0	14 (1)	
Mismatch Related/Unrelated + ATG	7	1	2 (2)	5 (1)	
Mismatch Related/Unrelated - ATG	76	5	4 (3)	72 (6)	

Variable	Overall	(%)	Azithromycin exposure		p-value
	N=1382		Yes N=117 n (%)	No N=1265 n (%)	
Preparative regimen					0.9
None	862	62	74 (63)	788 (62)	
ATG	520	38	43 (37)	477 (38)	
Conditioning regimen					
Myeloablative	969	70	95 (81)	874 (69)	0.01
Non-myeloablative	413	30	22 (19)	391 (31)	
cGVHD status					
Positive	681	49%	93 (79%)	588 (46%)	
Negative	701	51%	24 (20%)	677 (53%)	<0.001
Duration of azithromycin therapy (days), median (interquartile range)	384 (154, 966)			N/A	
≤150			29 (25%)		
151–366			28 (24%)		
367–1096			34 (29%)		
>1096			26 (22%)		

* CMV seropositivity data were unavailable for one patient in this study.

Abbreviations: CNI, calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolate mofetil; CMV, cytomegalovirus; MRD, matched related donor; HLA, human leukocyte antigen; MUD, matched unrelated donor; ATG: anti-thymocyte globulin ATG: anti-thymocyte globulin

Table 2.

Multivariate predictors of hematologic relapse within 5 years of HCT

Variable	Multivariate HR (95% CI)	p-value
Azithromycin exposure (time varying) / MUD + ATG		
No / No	1.0	
Yes / No	0.8 (0.3–1.9)	0.7
No / Yes	0.9 (0.7–1.1)	0.3
Yes/ Yes	2.4 (0.8–6.8)	0.1
cGVHD status (time-varying)	**0.7 (0.6–0.9)**	**0.01**
Underlying malignancy		
All other diagnoses	1.0	
ALL	**1.7 (1.3–2.3)**	**<0.001**
Remission status at HCT		
Complete remission	1.0	
No complete remission	**1.9 (1.6–2.4)**	**<0.001**

Abbreviations: HCT, hematopoietic cell transplant; HR, hazard ratio; CI, confidence interval; MUD, matched unrelated donor; ATG: anti-thymocyte globulin; ALL, acute lymphoblastic leukemia