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1 **Azithromycin use and increased cancer risk among patients with bronchiolitis obliterans**
2 **after hematopoietic cell transplantation**

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33

1 **Abstract**

2 Azithromycin exposure during the early phase of allogeneic hematopoietic cell transplantation
3 (HCT) has been associated with an increased incidence of hematological relapse. We assessed
4 the impact of azithromycin exposure on the occurrence of relapse or new subsequent neoplasm
5 (SN) in patients with bronchiolitis obliterans syndrome (BOS) after HCT, who are commonly
6 treated with azithromycin alone or in combination with other agents. In a retrospective study of
7 BOS patients from two large allograft centers, the effect of azithromycin exposure on the risk of
8 relapse or SN was estimated from a Cox model with a time-dependent variable for treatment
9 initiation. The Cox model was adjusted on time-fixed covariates measured at cohort entry,
10 selected for their potential prognostic value. Similar models were used to assess the exposure
11 effect on the cause-specific hazard of relapse, SN, and death free of those events. Sensitivity
12 analyses were performed using propensity score matching. Among 316 patients, 227 (71.8%)
13 were exposed to azithromycin after BOS diagnosis. The corresponding adjusted hazard ratio in
14 patients exposed to azithromycin versus unexposed was HR = 1.51 (95% CI, 0.90 to 2.55) for
15 relapse or SN, 0.82 (95% CI, 0.37 to 1.83) for relapse, and 2.00 (95% CI, 1.01 to 3.99) for SN.
16 Patients exposed to azithromycin had a significantly lower cause-specific hazard of death free of
17 neoplasm and relapse (adjusted HR= 0.54, 95%CI, 0.34 to 0.89). In conclusion, exposure to
18 azithromycin after BOS after HCT was associated with an increased risk of SN but not relapse.

19 **Word count:** 244

20 **Key words:** pulmonary graft-versus-host disease, malignancy, relapse, hematopoietic stem cell
21 transplant, bronchiolitis obliterans

22

1 **Introduction**

2 Recently, the European Medicines Agency (EMA) and the United States Food and Drug
3 Administration (FDA) issued warnings against the long-term use of azithromycin in the setting of
4 early allogeneic hematopoietic cell transplant (HCT) for hematological malignancies [1,2]. These
5 warnings followed the results of ALLOZITHRO, a French randomized trial testing azithromycin
6 as prophylaxis against lung chronic graft-versus host disease (GVHD) i.e. bronchiolitis
7 obliterans syndrome (BOS) in recipients of allogeneic HCT [3]. The rationale for testing
8 azithromycin in this population derives from the effect of azithromycin prophylaxis in reducing
9 the incidence of BOS in lung transplant recipients [4]. ALLOZITHRO was terminated early due
10 to an unanticipated reduction in survival attributed to increased rates of hematological relapse in
11 patients who received azithromycin [3]. The mechanisms for relapse observed in the
12 ALLOZITHRO trial are under investigation. It is hypothesized that azithromycin interferes with
13 anti-tumor immune surveillance.

14 In light of these unexpected findings, the long-term use of azithromycin for the treatment
15 of BOS after HCT has been called into question. Azithromycin is frequently used alone or as
16 part of FAM (fluticasone, azithromycin, montelukast) treatment for established BOS [5,6]. In the
17 setting of HCT, BOS is usually diagnosed within the first 2 years after transplant [7] at a time
18 when the risk for hematological relapse decreases and the risk of subsequent neoplasms (SN)
19 increases [8,9].

20 The aim of this study was to determine if azithromycin treatment for BOS after allogeneic
21 HCT is associated with an increased risk of cancer, including relapse of the original malignancy
22 and SN.

23

24 **Methods**

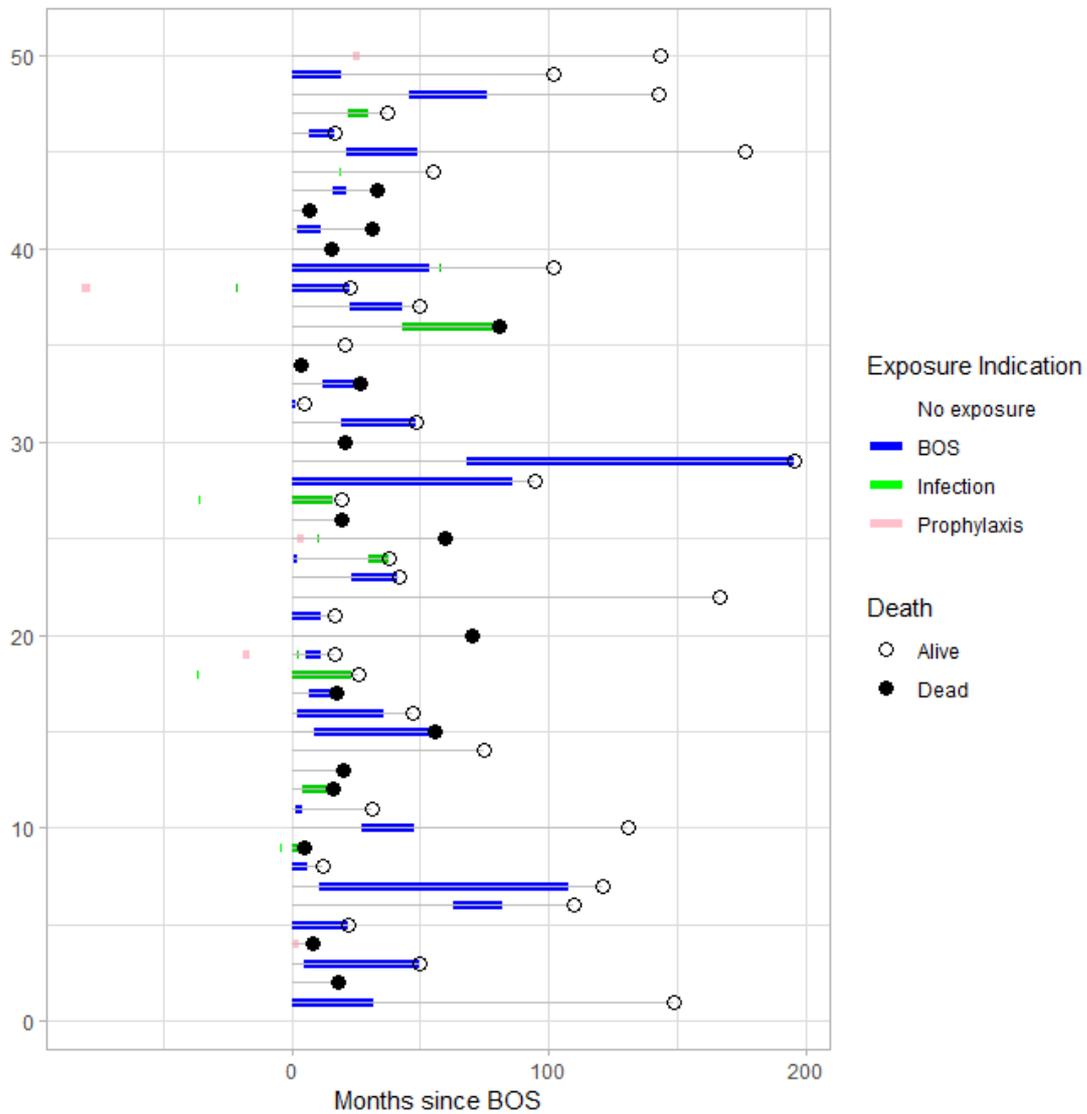
25 *Study cohort:* Patients with BOS, aged 18 and older, who survived at least 6 months
26 post-transplant, from Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care

1 Alliance in Seattle, Washington, and at the Hôpital St. Louis (SLS) in Paris, France, were
2 included. Both sites have expertise in managing post-allogeneic HCT lung complications. Any
3 patient who received an allogeneic HCT between 2000-2016 (FHCRC) or who was referred for
4 clinical care between 2000-2017 (SLS) and met criteria for BOS diagnosis were included. BOS
5 was defined by the following 2014 National Institutes of Health (NIH) spirometric criteria (forced
6 expiratory volume in 1 second (FEV1) <75%, FEV1/vital capacity (VC) <0.7, $\geq 10\%$ absolute
7 FEV1 decline compared to pretransplant baseline)[10]. Absence of a bronchodilator response
8 was not required for BOS diagnosis as this parameter was not uniformly available. Similarly,
9 chest imaging was not used to determine BOS diagnosis as high-resolution studies were not
10 available for many subjects. Chart review confirmed the absence of infectious diagnosis at the
11 time of meeting spirometric criteria for BOS. Additionally, in the SLS cohort, as previously
12 reported, BOS was also diagnosed in patients with a new-onset obstructive impairment
13 characterized by a decrease in both FEV1 and VC, a normal FEV1/VC ratio, a normal total lung
14 capacity (TLC) and elevated residual volume (RV) in the absence of alternative explanations for
15 ventilatory impairment [11,12]. Prior to undergoing HCT, all subjects from both sites signed
16 informed consent allowing the use of their clinical data for research. This study was approved by
17 the appropriate institutional review boards for FHCRC and SLS.

18 *Clinical variables:* Modified disease risk index (DRI) was used to assess disease risk at
19 the time of transplant [13]. Acute GVHD was graded from 1 to 4, according to consensus criteria
20 [14,15]. Chronic GVHD was graded according to the 2014 NIH consensus guidelines [10] if the
21 clinical data were available by chart review. Primary cause of death was determined by
22 consensus when multiple morbidities were reported (GSC and AB). Causes of death were
23 classified as respiratory (respiratory failure and respiratory infection), death related to relapse or
24 SN, transplant-related mortality, others and unknown.

25 *Azithromycin exposure:* Exposure to azithromycin was defined as the use of
26 azithromycin at any time posttransplant, including for intentional treatment of BOS or other

1 reasons, for any duration and at any dose, with the date of BOS diagnosis representing the
2 entry into the cohort. Periods of exposure were defined by courses of azithromycin intake with a
3 defined start and end date with at least one day free of intake between courses. Time-
4 dependent dynamics of azithromycin exposure are displayed with a random sample of 50
5 patients in **Figure 1** and demonstrate the following issues: (1) Azithromycin may have been
6 given before BOS diagnosis; (2) Azithromycin may have been given at BOS diagnosis; (3) In
7 some instances there is a time interval between BOS diagnosis and azithromycin intake. Each
8 observation ends with patient death or last follow-up. Clinical practice for BOS treatment
9 evolved during the study period for both cohorts; the use of azithromycin was more common in
10 the latter part of the study period.



15 **Figure 1.** Graphical time-dependent display of 50 randomly selected patients. Each line shows one
 16 observed patient. To display the time-dependency of azithromycin treatment, time free of any
 17 azithromycin exposure is marked in grey and a time of azithromycin exposure is marked in color
 18 according to the indication. The corresponding survival event is marked with a filled circle (death) or a
 19 transparent circle (alive). BOS: bronchiolitis obliterans syndrome. For instance, patient 2 (second line at
 20 the bottom) died early free of any exposure to azithromycin. At the top (first line), patient 50 only received
 21 a short course of azithromycin for prophylaxis.

1 *Outcomes:* The primary outcome was cumulative incidence of all cancers subsequent to
2 BOS, including relapse of the original hematological disease and new SN. Secondary outcomes
3 included cumulative incidence of relapse, of SN, and of death free of relapse and SN, and
4 event-free survival (event being either relapse or SN). Data for clinical outcomes were locked on
5 November 30, 2017.

6 *Statistical methods:* To account for the time-dependent dynamics of the data, we used a
7 multi-state model with following states: BOS diagnosis, azithromycin treatment, and death (see
8 online supplement figure S1). The effect of cumulative treatment exposure on the risk of relapse
9 and/or SN after BOS diagnosis was estimated from a Cox model with time-dependent variable
10 for treatment initiation. This provides unbiased estimates of the hazard ratio allowing for control
11 of survival bias while avoiding selection bias [16,17]. The Cox model was adjusted on time-fixed
12 covariates measured at the time of transplant that were selected as potentially of prognostic
13 value: age, gender, tobacco use, total body irradiation (TBI), DRI, prior autologous HCT and
14 past exposure to azithromycin after HCT but before BOS. We also introduced chronic GVHD
15 after BOS as a time-dependent covariate. Models were finally stratified on the site to handle
16 potentially different baseline hazards.

17 Similar modeling strategies were used to assess the exposure effect on the cause-
18 specific hazard of relapse, of SN, and of death free of relapse and SN. On each end point, we
19 further tested the interaction of exposure effect according to the site using the Gail and Simon
20 test [18].

21 To account for the use of azithromycin as an intermediate event and death as a potential
22 competing event on the effect of azithromycin on the outcomes, we displayed cumulative
23 hazards [19].

24 To account for changes in clinical practices in prescribing azithromycin, sensitivity
25 analyses were performed using propensity score matching. The propensity score of
26 azithromycin administration was estimated using a multivariable logistic model, including 9

1 potential confounders for relapse or SN (namely, age, gender, DRI, prior graft, acute leukemia,
 2 myeloablative conditioning, antithymocyte globulin, chronic GVHD, and time from HCT to BOS).
 3 Estimates of propensity scores were pooled from 30 imputed datasets, obtained by multiple
 4 imputations with chained equations. Quality of the score was measured on standardized mean
 5 difference of confounders, and c-index of the model [20]. Then, 1:1 matching on the pooled
 6 propensity score was individually performed using the nearest neighbor method within a caliper
 7 of 0.20 standard deviation of the logit of the propensity score, with and without replacement [21].
 8 Estimates of azithromycin exposure used generalized linear models to handle the matching,
 9 with inverse-probability weighting and design-based standard errors.

10 Summary statistics, namely median [interquartile range, IQR] and percentage, are
 11 reported. All tests are 2-sided, with P values less than .05 considered significant. Analyses
 12 were performed on R 3.5.1 software (<https://www.R-project.org/>).

13

14 **Results**

15 *Description of the cohort.* A total of 316 patients with BOS were included in the study:
 16 185 patients from FHCRC and 131 from SLS. Baseline characteristics of the cohort are reported
 17 in **Table 1**.

18

19 **Table 1:** Characteristics of the study cohort at baseline and at BOS diagnosis according to azithromycin
 20 exposure after BOS diagnosis

	Total (n=316)	Azithromycin exposure	
		No (n=89)	Yes (n=227)
<u>Baseline characteristics at HCT</u>			
Women, n (%)	129 (40.8%)	31 (34.8%)	98 (43.1%)
Age, median (IQR), y	48.6 [33.6-58.6]	47.9 [36-59]	48.7 [33-57.6]
Diagnosis, n (%)			
Acute leukemia	140 (44.3%)	35 (39.3%)	105 (33.5%)
Chronic myeloid leukemia	32 (10.1%)	12 (13.5%)	20 (8.8%)
Other myeloproliferative disorders	8 (2.5%)	3 (3.4%)	5 (2.2%)

Myelodysplastic disorders	52 (16.4%)	20 (22.5%)	32 (36.6%)
Lymphoid malignancies	73 (23.1%)	16 (18%)	57 (25.11%)
Others	11 (3.5%)	3 (3.4%)	8 (3.5%)
Disease risk index at HCT, n (%)			
Low	47 (14.9%)	18 (21.7%)	29 (13.3%)
Intermediate	176 (55.7%)	43 (51.8%)	133 (61%)
High	68 (21.5%)	19 (22.9%)	49 (22.5%)
NA	25 (7.9%)	9 (10.1%)	16 (7%)
History of smoking, n (%)	122 (38.6%)	45 (51.1%)	77 (33.9%)
History of solid cancer prior to HCT, n (%)	31 (9.8%)	4 (4.5%)	27 (11.9%)
Prior autologous HCT, n (%)	96 (30.4%)	19 (21.3%)	77 (33.9%)
Donor type, n (%)			
Related	138 (43.7%)	42 (47.2%)	96 (42.3%)
Haploidentical	5 (1.6%)	2 (2.2%)	3 (1.3%)
Unrelated HLA-match [#]	130 (41.1%)	32 (36%)	98 (43%)
Unrelated HLA-mismatch ^{##}	36 (11.4%)	9 (10.1%)	27 (11.9%)
Donor/recipient sex, n, (%) [*]			
Male/male	91 (29.5%)	28 (32.9%)	63 (28.3%)
Male/female	57 (18.5%)	16 (18.8%)	41 (18.4%)
Female/male	92 (29.9%)	27 (31.8%)	65 (29.1%)
Female/female	68 (22.1%)	14 (16.5%)	54 (24.2%)
Source of stem cells graft, n (%)			
Peripheral blood	273 (86.4%)	74 (83.1%)	199 (87.7%)
Bone marrow	36 (11.4%)	11 (12.4%)	25 (11%)
Cord blood	7 (2.2%)	4 (4.5%)	3 (1.3%)
Conditioning regimen, n (%)			
Myeloablative	180 (57%)	47 (52.8%)	133 (58.6%)
Nonmyeloablative	136 (43%)	42 (47.2%)	94 (41.4%)
TBI	159 (50.3%)	33 (37.1%)	126 (55.5%)
Dose, median (IQR), Grays	2 (2-12)	2 (2-12)	2 (2-12)
Antithymocyte globulin ^{###}	39 (12.3%)	14 (15.7%)	25 (11.0%)
Lung function			
FEV1 (% predicted), median (IQR),	92.8 [82.8-100.2]	91.1 [83.1-97.9]	92.9 [82.7-100.7]
FVC (% predicted), median (IQR)	95.1 [85.9-105.6]	92.0 [83.9-103.7]	96.2 [86.5-106.0]
<u>Characteristics at BOS diagnosis</u>			
Months from HCT, median (IQR),	16.8 [10.8-30.6]	13.9 [10.7-24.5]	18.1 [11-33.5]
Chronic GVHD			
Before BOS	273 (86.4%)	76 (85.4%)	197 (86.8%)
At or after BOS, n (%)	33 (10%)	10 (11%)	23 (10%)
Grade max			
Mild	25 (7.9%)	13 (14.8%)	12 (5.4%)
Moderate	117 (37%)	33 (37.5%)	84 (37.8%)
Severe	161 (50.9%)	39 (44.3%)	122 (54.9%)
Death free of chronic GVHD	5 (1.6%)	2 (2.2%)	3 (1.3%)
Absence of chronic GVHD	5 (1.6%)	1 (1.1%)	4 (1.8%)
Lung function			

FEV1 (% predicted), median (IQR),	55.9 [42.9-65.5]	60.4 [51.1-68.8]	53.2 [40.4-63.7]
FVC (% predicted), median (IQR)	71.9 [64.0-83.5]	72.9 [65.5-83.6]	71.3 [63-83.5]
FEV1/FVC, median (IQR)	0.63 [0.51-0.69]	0.67 [0.60-0.73]	0.61 [0.48-0.67]
RV (% predicted), median (IQR)	131.7 [103.0-161.3]	134.8 [113.9-161.1]	130.8 [100.8-161.3]
Treatments for BOS†, n (%)			
Azithromycin	197 (62%)	0 (0%)	197 (87%)‡
Systemic steroids	105 (33%)	16 (18%)	89 (39%)
ICS/LABA	153 (48%)	44 (49%)	109 (48%)
ICS without LABA	154 (49%)	18 (20%)	98 (43%)
Montelukast	146 (46%)	7 (8%)	139 (62%)

- 1
- 2 *Excluding cord blood recipients, and 1 missing value for a recipient of a peripheral blood stem cell graft
- 3 †Treatments administered for BOS at the time of diagnosis or thereafter; of the 227 patients who received
- 4 azithromycin after the diagnosis of BOS, 197 received it specifically for the treatment of BOS and 30 for
- 5 another indication (antimicrobial prophylaxis or treatment of an infection)
- 6 ‡ A total of 95 patients (30%) received the azithromycin in the FAM regimen (fluticasone, azithromycin,
- 7 montelukast).
- 8 #: 74 patients minimal 8/8 HLA-match and 56 patients 10/10 HLA-match
- 9 ##: 34 patients 7/8 HLA-match and 2 patients 9/10 HLA-match
- 10 ###: no patients had HCT with ex vivo depletion of donor T-cells
- 11 IQR: interquartile range; HCT: hematopoietic cell transplant; FEV1: forced expiratory volume in 1 second;
- 12 FVC: forced vital capacity; GVHD: graft-versus-host disease; ICS/LABA: inhaled corticosteroids/long-
- 13 acting beta-agonist; ICS: inhaled corticosteroids; HLA: human leukocyte antigen; NA: not available

14

15 The median time to BOS diagnosis after HCT was 16.8 months [IQR 10.8 to 30.6]. The

16 description of the patients according to the transplant center (FHCRC vs. SLS) is reported in the

17 online supplement, (Table S1, Figure S2, Figure S3).

18 *Azithromycin exposure.* Overall, 237 patients (75%) received azithromycin during their

19 follow-up for one to 3 courses. Characteristics of both azithromycin-exposed and unexposed

20 cohorts are summarized in **Table 1**. The description of azithromycin exposure any time after

21 HCT is summarized in **Table 2**. The median length of exposure to azithromycin after BOS

22 diagnosis was 16 months [IQR 7 to 36].

23

1 **Table 2:** Description of azithromycin exposure any time after HCT for 237 patients*

Number of azithromycin exposures per patient [†]	N (%)
1	165 (52.2%)
2	60 (19%)
3	12 (3.8%)
Characteristics of 1st exposure	
Duration (days, median, IQR)	230 [7;847]
Before BOS	66 (20.9%)
At or after BOS	167 (52.9%)
Both before and after BOS	4 (1.3%)
Characteristics of 2nd exposure	
Duration (days, median, IQR)	244.5 [90;884.8]
Before BOS	7 (2.2%)
At or after BOS	64 (20.2%)
Both before and after BOS	1 (0.32%)
Characteristics of 3rd exposure	
Duration (days, median, IQR)	191.5 [69.2;783.2]
Before BOS	0 (0%)
At or after BOS	12 (3.8%)
Both before and after BOS	0 (0%)

2 * 10 patients received azithromycin only before BOS for a median time of 7 days among the 237 patients
 3 who received azithromycin during the study period; † a single exposure of azithromycin was defined by
 4 azithromycin intake with a start and end date; the minimum duration of the 1st exposure after BOS was 7
 5 days. A subsequent azithromycin exposure was considered if there was at least one day free of intake
 6 between two courses of azithromycin.

7 BOS: bronchiolitis obliterans syndrome; IQR: interquartile range

8

9 *Cancer outcomes.* The median time of follow-up after BOS was 41 months [IQR 17 to

10 95]. There were 53 (16.8%) patients who relapsed; 30 relapses were documented after BOS

11 **(Table 3).**

12

13 **Table 3:** Type of hematological relapses and subsequent neoplasms after BOS diagnosis according to
 14 prior exposure to azithromycin

	Azithromycin exposure	
	No n=89	Yes n=227
Hematological relapses type after BOS, n (%)	10 (11%)	20 (9%)

Acute leukemia	3	5
Chronic myeloid leukemia	1	2
Lymphoid malignancies	4	8
Myelodysplastic disorders	2	5
Others	0	0
Subsequent neoplasms*, n (%)	8 (9%)	35 (15%) 33 after azithromycin†
<u>Types</u>		
Squamous cell carcinoma	3 (37.5%)	21 (60%)
Adenocarcinoma	2 (25%)	8 (22.9%)
Verrucous carcinoma	1 (12.5%)	0
Carcinoma NOS	0 (0%)	2 (5.7%)
Bowen's disease	0 (0%)	2 (5.7%)
Malignant melanoma	0 (0%)	2 (5.7%)
Lymphoma	1 (12.5%)	0
Mast cell leukemia	1 (12.5%)	0
<u>Anatomic Site</u>		
Breast	0 (0%)	3 (10.7%)
Gut	1 (16.7%)	3 (10.7%)
Skin	2 (33.3%)	14 (50%)†
Oral cavity	1 (16.7%)	7 (20%)
Pancreas	1 (16.7%)	0
Penis	0 (0%)	1 (3.6%)†
Prostate	1 (16.7%)	3 (10.7%)
Uterus	0 (0%)	2 (5.7%)
Blood	1 (12.5%)	0 (0%)
Lung	1 (16.7%)	1 (3.6%)
Brain	0 (0%)	1 (3.6%)

1 *Basal cell carcinomas excluded; † 2 malignancies occurred after BOS but before azithromycin onset,
2 including 1 malignant melanoma of the upper extremity and 1 squamous cell carcinoma of the penis.
3 BOS: bronchiolitis obliterans syndrome; NOS: not other specified

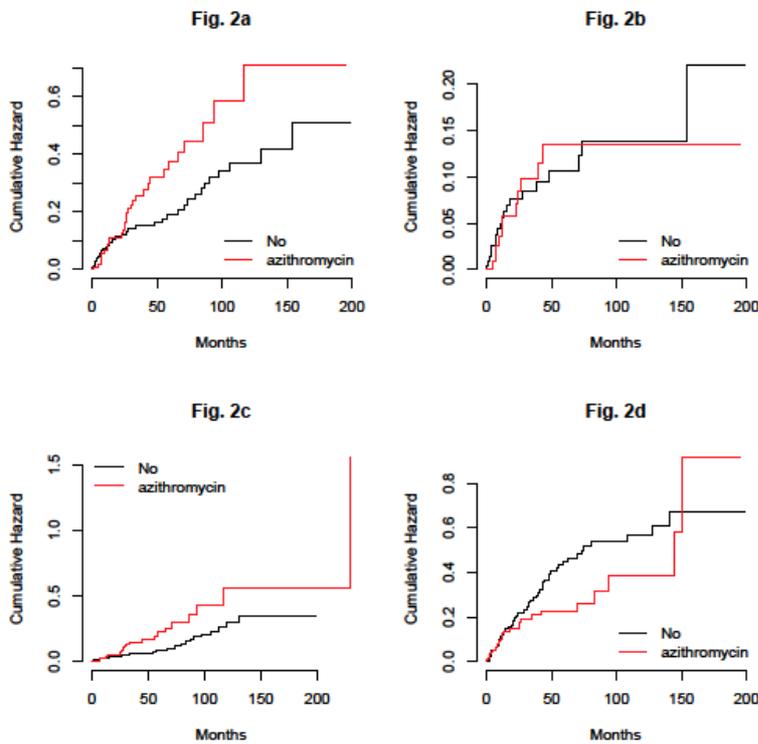
4

5 Median time from first azithromycin exposure after BOS to relapse was 15.6 months
6 [IQR 8.5-36.3]; from transplant to relapse was 41.8 months [IQR 23.1-60.0]. Excluding basal cell
7 carcinomas, 43 (13.6%) patients developed a SN after BOS, including 10 patients who did not
8 receive azithromycin prior to the diagnosis of SN, and 33 in patients previously exposed to
9 azithromycin. Among these 43 patients with SN after BOS, 18 developed more than one
10 subsequent malignancy, including only 2/10 free of any azithromycin exposure and 16/33 after
11 azithromycin exposure (p=0.15). The median time of developing a SN after azithromycin

1 exposure was 43.5 months [IQR 8.5-36.3]. Median time from transplant to SN was 81 months
2 [IQR 44.7-117.5]. Twenty-four (56%) of SN were of squamous cell histology (Table 3). The type
3 of hematological relapse and SN according to sites are reported in the online supplement Table
4 S2, as well as details on the duration of follow-up in each group of patients (Table S3). There
5 was no evidence of any difference in relapses/SN according to the association with fluticasone
6 and montelukast ($p=0.42$ by the exact Fisher test).

7 The cumulative hazards for relapse or SN are displayed in **Figure 2**.

8



9

10 **Figure 2.** Cumulative hazard of relapse and/or subsequent neoplasm, either overall (Fig. 2a), or for
11 relapse (Fig. 2b) and subsequent neoplasm (Fig. 2c), separately, and death free of relapse and
12 subsequent neoplasm (Fig. 2d). Cumulative hazard can be interpreted as the probability of failure at time
13 t given survival until time t . Note that when the cumulative hazard function is a straight line (such as in
14 Fig.2a, for the non-exposed group), the underlying hazard function is constant over time.

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The corresponding unadjusted hazard ratio (azithromycin-exposed vs. unexposed) are 1.49 (95%-CI, 0.91 to 2.44) for relapse or SN, 0.90 (95%-CI, 0.42 to 1.93) for relapse, and 1.88 (95%-CI, 1.00 to 3.51) for SN. The effect of azithromycin exposure on hazard of malignancy was confirmed in adjusted multivariate models (HR 2.00 [95%CI, 1.01 to 3.99, p=0.048], **Table 4**), adjusting for factors associated with the occurrence of relapse or SN or both after BOS on univariable analyses (see online supplement Table S4). Further adjusting on year of allograft, indication for the graft (distinguishing AML from other diagnoses), TBI dose, the use of a myeloablative regimen, and antithymocyte globulin did not modify these findings (see online supplement Table S5).

Table 4: Estimation of azithromycin effect using multivariable time-dependent Cox models

	Relapse or subsequent neoplasm		Relapse		Subsequent neoplasm	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
AZM exposure	1.51 (0.90 to 2.55)	0.12	0.82 (0.37 to 1.83)	0.63	2.00 (1.01 to 3.99)	0.048
TBI	1.17 (0.62 to 2.23)	0.62	0.55 (0.22 to 1.40)	0.21	1.96 (0.90 to 4.27)	0.091
DRI	1.64 (1.20 to 2.24)	0.002	2.07 (1.35 to 3.16)	0.0008	1.53 (1.02 to 2.29)	0.038
cGVHD-t	0.86 (0.34 to 2.15)	0.74	1.28 (0.37 to 4.41)	0.69	0.65 (0.18 to 2.37)	0.52
Age	1.00 (0.98 to 1.02)	0.91	0.99 (0.96 to 1.02)	0.40	1.02 (0.99 to 1.04)	0.14
Sex/Male	1.07 (0.64 to 1.79)	0.79	1.06 (0.46 to 2.46)	0.89	0.94 (0.50 to 1.77)	0.86
History of smoking	1.28 (0.74 to 2.23)	0.38	1.45 (0.64 to 3.33)	0.38	1.08 (0.55 to 2.13)	0.82
Prior autologous HCT	1.99 (1.03 to 3.87)	0.041	4.24 (1.61 to 11.1)	0.003	1.37 (0.68 to 2.77)	0.38
AZM exposure before BOS	0.59 (0.30 to 1.17)	0.13	0.85 (0.31 to 2.36)	0.76	0.53 (0.23 to 1.22)	0.14

1 HR: Hazard ratio; CI: confidence interval; TBI: Total body irradiation; ATG: antithymocyte globulin; DRI:
2 disease risk index; cGVHD-t: time dependent occurrence of chronic graft-versus-host-disease; HCT:
3 Hematopoietic cell transplantation; AZM: azithromycin; BOS: bronchiolitis obliterans syndrome; HR:
4 hazard ratio; CI: confidence interval

5

6 Sensitivity analysis considering only extensive chronic GVHD rather than overall chronic
7 GVHD and adding time from HCT to BOS diagnosis in the adjusted multivariate models
8 confirmed the azithromycin exposure effect on the occurrence of SN (HR 2.03, 95%CI 1.01 to
9 4.08, $p=0.047$) (see online supplement Table S6). There was no effect of cumulative months of
10 exposure to azithromycin before the occurrence of relapse or SN; restriction of azithromycin
11 exposure to greater than 7 days, or greater than 28 days (adjusted HR=2.05, 95%CI, 1.01 to
12 4.19, $P=.047$) did not modify the hazard of malignancy in exposed patients compared to
13 unexposed, likely due to the duration of exposure of at least 7 months in 75% of the exposed
14 patients.

15 There was no evidence of any azithromycin exposure by site interaction (FHCRC or
16 SLS) on adjusted estimates, with p -values of Gail and Simon interaction tests ($p=0.38$ for
17 relapse or malignancy; $p=0.18$ for relapse; $p=0.78$ for subsequent malignancy) (see online
18 supplement Figure S4 and Figure S5). That is, the effect of azithromycin appeared to be the
19 same for patients treated at FHCRC and those treated at SLS.

20 *Survival outcomes.* Since death is a competing event for SN or relapse, the effect of
21 azithromycin exposure after BOS on deaths free of relapse and/or SN were examined. One
22 hundred and twenty (38%) subjects had died as of last follow-up including 32 patients who died
23 of relapse and 7 of cancer (**Table 5**).

24

25 **Table 5:** Causes of death

Primary cause of death (n=120)	N (%)
Respiratory causes	54 (45%)
Respiratory failure*	37 (30.8%)
Respiratory infection	17 (14.2%)

Relapse/SN causes	32 (26.7%)
Relapse	25 (20.8%)
SN	7 (5.8%)
Transplant-related mortality	8 (6.7%)
Others	12 (10%)
Unknown cause	14 (11.7%)

1

2 *6 patients died of multiple causes after lung transplantation; SN: subsequent neoplasm

3 Besides relapse, respiratory causes (n=54, 45%) were the most common primary
4 causes of death. Regarding the effect of azithromycin exposure, the hazard of death free of
5 malignancy and relapse was not modified, either unadjusted or adjusted for prognostic
6 variables, compared to unexposed patients (HR=0.69, 95%CI, 0.42 to 1.12, P= .13; HR=0.71,
7 95%CI, 0.43 to 1.19, P=0.19, respectively). Patients exposed to azithromycin had a significantly
8 decreased cause-specific hazard of death free of malignancy (adjusted HR= 0.54, 95%CI, 0.34
9 to 0.89, P= .014; Figure 2d) while their cause-specific hazard of death free of relapse was not
10 significantly decreased (adjusted HR=0.62, 95%CI, 0.38 to 1.03, P= .06). Cause-specific hazard
11 of death from all respiratory causes was similar in both groups of patients (HR=1.01, 95%CI,
12 0.68 to 1.51, P= .96), as well as that of death from respiratory failure (HR= 1.13, 95%CI, 0.68 to
13 1.86, P= .64) and from respiratory infection (HR=0.84, 95%CI, 0.43 to 1.64, P= .61).

14 *Sensitivity Analyses.* A propensity score for receiving azithromycin was estimated; this
15 differed between exposed and unexposed patients as measured by the c-index of the model (at
16 0.66) and the standardized mean differences (SMD) of the potential confounders across the
17 treatment groups with an average value at 0.17. Of the 227 patients who received azithromycin,
18 76 (33%) could be matched without replacement, up to 225 (99%) were matched when
19 replacement was allowed. Balance was improved with an average SMD and c-index at 0.076
20 and 0.499, respectively without replacement, and at 0.10 and 0.504 with replacement.
21 Estimates of exposure effects confirmed previous results, with an increased risk of SN (although
22 based on the sample of 76 treated and 76 untreated this was not statistically significant), and no
23 increased risk of relapse (**Table 6**).

1

2 **Table 6:** Estimation of azithromycin (AZM) effect using matched samples on propensity score to receive
3 azithromycin

AZM exposure	Relapse or subsequent neoplasm		Relapse		Subsequent neoplasm	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
With replacement	1.21 (0.77-1.91)	0.42	0.78 (0.42-1.43)	0.43	2.25 (1.19-4.25)	0.013
Without replacement	2.12 (0.67-3.07)	0.36	0.88 (0.30-2.58)	0.81	2.21 (0.78-6.32)	0.14

4 OR: odd ratio; CI: confidence interval

5

6 Discussion

7 In this analysis of a large multi-site cohort of patients with BOS after HCT, exposure to
8 azithromycin after BOS diagnosis was associated with an increased risk of developing a SN but
9 not with risk for relapse of the original malignancy. These results were independent of chronic
10 GVHD status and were further confirmed for each site independently. In the ALLOZITHRO trial,
11 azithromycin was given early posttransplant when the risk of relapse is inherently high. In the
12 current study, azithromycin was given many months to years after HCT for established BOS
13 when the risk of relapse diminishes and the risk of SN increases in association with chronic
14 GVHD and prolonged immunosuppressive treatment [22]. In this context, an increase in relapse
15 associated with azithromycin would have required a much larger cohort for analysis, but an
16 increased risk of SN associated with azithromycin is consistent with the natural history of long-
17 term survivors. Thus, these results constitute a second signal suggesting the potential
18 association of azithromycin with cancer in allogeneic HCT.

19 Antibiotic use has previously been associated with various cancers [23]. Azithromycin
20 may directly interfere with antitumor immune-surveillance through an inhibitory effect on various
21 cell types, including lymphocytes, dendritic cells and natural killer cells in a dose-dependent way
22 [24-26]. Long-term, low-dose azithromycin was shown to be associated with downregulation of

1 genes regulating antigen presentation, interferon and T-cell responses, and numerous
2 inflammatory pathways in patients with neutrophilic chronic obstructive pulmonary disease [27].
3 There is growing evidence that antibiotics may alter immune functions that are important for
4 surveillance and control of malignancy through the modification of gut microbiota [28] which
5 composition was shown to be associated with tumorigenesis [29,30]. In the specific setting of
6 HCT, alterations in gut microbiota within the first month following HCT was associated with both
7 incidence and severity of GVHD and hematological relapse [31,32]. These data may explain the
8 increase of relapse found in the ALLOZITHRO trial where patients received azithromycin prior to
9 and during engraftment, which is an immunologically vulnerable period for the control of the
10 hematological malignancy [33,34]. Similar mechanisms may be involved in the development of
11 SN associated with azithromycin exposure later in the course of survivorship.

12 Long-term immunosuppressive treatments are known to be associated with the
13 development of SN. Unfortunately, because of the retrospective design of our study, which
14 included a long period of patient follow-up, complete data on immunosuppressive therapy for
15 GVHD was not available. However, when taking into account in the statistical model the severity
16 of GVHD, a reflection of the intensity of immunosuppressive treatment, the effect of
17 azithromycin on SN persists. We could not identify whether patients with cancer predisposition
18 syndromes were included in our cohort of patients. Notably, however, the association of
19 azithromycin with SN also persists when adjusted for DRI, which likely reflects a predisposition
20 to SN.

21 Patients who received azithromycin developed more SN but very few died of their SN.
22 Most SN in azithromycin-exposed patients after BOS belonged to an intermediate prognostic
23 group of malignancies [35]. We postulate that the duration of follow-up after cancer diagnosis
24 may not have been long enough to assess the effect of the malignancy on mortality.

25 The paradoxical finding of more SN but decreased cause-specific hazard of death free of
26 malignancy with azithromycin exposure may result from attenuating the progression of BOS, or

1 by reducing the number of respiratory exacerbations related to the underlying obstructive lung
2 disease. A steroid-sparing effect of azithromycin [5] may reduce infections or other life-limiting
3 complications related to chronic corticosteroid use. Similarly, a recent retrospective analysis
4 demonstrated a survival benefit of extracorporeal photopheresis in patients with BOS after HCT
5 in the absence of an impact on FEV1 [36]. Our retrospective data did not allow for a full
6 exploration of these hypotheses, as some long-term survivors are managed outside of the
7 transplant center for non-malignancy related concerns and intercurrent infectious events are not
8 comprehensively captured. Furthermore, the full effect of azithromycin on the respiratory
9 function of patients with BOS was beyond the scope of our current analysis.

10 In addition to the limitations noted above, this study is limited by the retrospective
11 design. However, a retrospective cohort analysis is the only way to address the serious
12 concerns about azithromycin arising from the ALLOZITHRO trial and the EMA and FDA
13 warnings in a timely fashion. This study represents the largest cohort of BOS patients analyzed
14 to date, although the overall cohort remains relatively small due to the rarity of this complication.
15 The study was designed to look specifically at azithromycin exposure after any designation of
16 BOS. Despite differences in clinical practice between FHCRC and SLS, the effect of
17 azithromycin was similar at each site, which further adds to the strength of our analysis. The era
18 of transplant experienced by the study subjects span two decades, during which time transplant
19 practices and indications have changed, although we did standardize disease risk and GVHD
20 grading as much as possible. Significantly, the results were not modified when the year of
21 transplant is included in the models. Nevertheless, as with any predictive analysis from
22 observational cohort data, residual unobserved confounders (for instance in the reasons for
23 administering azithromycin) cannot be excluded in our study.

24 We also recognized the potential for immortal time bias in our cohort, in which the
25 exposed group may have an inherent survival bias, when comparing the effect of azithromycin
26 with varying exposures over time. To address this bias, we utilized a cohort design with time-

1 dependent Cox models in which the estimated hazard ratio represents the adjusted incidence
2 rate ratio. This approach compares the risk of an event between exposed and non-exposed
3 patients at each event time, and re-evaluates to which risk group each person belonged based
4 on whether there had been an exposure by that time, and tends to result in estimates with lower
5 bias and greater precision compared with a nested case–control design [16,17]. Given the
6 potential confounding by indication due to observational data, causal inference methods based
7 on propensity score matching were further used as sensitivity analyses. This confirmed an
8 increased occurrence of SN in the azithromycin group; note that it was no longer statistically
9 significant when replacement was not allowed, likely due to a lack of power given the limited
10 sample size.

11 In the light of these results, a careful assessment of the potential risks and benefits
12 should be performed for each patient with BOS to determine whether azithromycin treatment
13 should be prescribed. The increased risk of SN must be weighed against the potential benefit of
14 chronic exposure. Azithromycin has been generally considered by most practitioners to be safe
15 and is in widespread use for respiratory infections and various chronic respiratory diseases. In
16 the setting of HCT, although azithromycin has become standard of care for BOS treatment at
17 many centers, robust data supporting its efficacy in ameliorating lung dysfunction are lacking.
18 As in other chronic lung diseases, long-term use may reduce infectious morbidity, however this
19 has never been demonstrated in BOS after HCT. In addition to known cardiovascular and
20 hearing loss side effects, concerns regarding antibiotic resistance and changes in microbiome
21 diversity related to chronic azithromycin use and its consequences have emerged [37].
22 Additional studies are needed both to determine whether azithromycin is beneficial for patients
23 with BOS after HCT and to elucidate the underlying mechanisms of azithromycin-associated
24 cancers.

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19

20 **Supplementary data:** Supplementary data related to this article can be found online
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