CORRESPONDENCE

Outcomes of toxoplasmosis after allogeneic hematopoietic stem cell transplantation and the role of antimicrobial prophylaxis

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Toxoplasma gondii is an opportunistic infection in allogeneic hematopoietic stem cell transplant (allo-HCT) recipients and could lead to life-threatening complications such as pneumonia, meningoencephalitis, or disseminated disease with mortality rate of up to 60% [1, 2]. Toxoplasmosis usually occurs secondary to reactivation of latent *Toxoplasma* infection rather than through new encounter [3, 4]. The risk factors of *Toxoplasma* reactivation include *Toxoplasma*-seropositive allo-HCT recipients, seronegative donors, conditioning regimens containing anti-thymocyte globulin and myeloablative chemotherapy, umbilical cord blood or unrelated donor grafts, graft-versus-host disease (GVHD), immunosuppressive treatment, and lack of *Toxoplasma* antimicrobial prophylaxis [5–8].

The incidence of *Toxoplasma* reactivation after allo-HCT ranges between 0.3% and 8% in North America to around 11.6% in endemic European countries [2, 5, 8–10]. Allo-HCT recipients can develop either *Toxoplasma* infection, an asymptomatic parasitemia defined by positive *Toxoplasma* PCR test in blood only (with or without fever); or *Toxoplasma* disease which is a constellation of clinical and radiological evidence of end-organ damage along with positive *Toxoplasma* PCR in blood or in other body fluids or positive histopathological examination [2, 6, 11]. In this study, we aimed to describe the real-world experience of monitoring *Toxoplasma* PCR in blood of *Toxoplasma*-seropositive patients following allo-HCT, and to evaluate the risk factors associated with *Toxoplasma* reactivation.

We conducted a single-center retrospective study of all *Toxoplasma gondii*-seropositive recipients of allo-HCT performed between January 2012 through June 2021. The study was approved by the institutional review board, and a waiver of informed consent was granted. According to our institutional HCT guidelines for *Toxoplasma*-seropositive recipients, a weekly surveillance PCR in the blood is recommended following transplant and until at least day +180 post HCT or longer when clinically indicated, along with Trimethoprim-Sulfamethoxazole (TMP-SMX, 800 mg–160 mg one tablet daily) as a preferred agent for anti-*Toxoplasma* prophylaxis to be started after neutrophil and platelet engraftment and continued for six months posttransplant or for the duration of their immunosuppressive treatment. *Toxoplasma*-seropositive recipients underwent *Toxoplasma* PCR blood monitoring at least once weekly with a limit of detection of 376 copies/ml for our test.

We assessed the incidence of *Toxoplasma* reactivation (infection or disease) and the effects of anti-*Toxoplasma* prophylactic agents (TMP-SMX 800mg-160mg, atovaquone, or dapsone) on survival. We also evaluated risk factors for *Toxoplasma* reactivation. We compared allo-HCT recipients who had *Toxoplasma* reactivation to those who did not. We assessed the effects of demographics, underlying comorbidities, treatment modalities, GVHD treatment on outcomes. We also evaluated factors that impacted non-relapse mortality (NRM), progression-free survival (PFS) and overall survival (OS) in the study population.

We identified a total of 3051 consecutive patients who received an allogeneic HCT between January 2012 through June 2021. Of the total cohort, 2681 patients had negative IgG serology to *Toxoplasma gondii* (seronegative group), whereas 370 patients (12%) had positive *Toxoplasma* IgG serology (seropositive group). The final analysis included 314 seropositive patients; 22 (7%) had positive *Toxoplasma* reactivation (infection or disease) and 292 (93%) did not have reactivation (Fig. 1a). Sixty-four percent of the patients were male with a median age of 57 years (range, 5–77 years) and 66% were Caucasian. Majority of patients had myeloid neoplasms (72%), and about half went to transplant in first complete remission (56%) and using nonmyeloablative preparative regimen (67%). Most patients (88%) were not exposed to cats. Fifty-one percent of the *Toxoplasma*-seropositive patients did not receive any active antimicrobial prophylaxis against *Toxoplasma*, and pentamidine was only used for prophylaxis against *Pneumocystis jirovecii*. While 29% received TMP-SMX, 17% received Atovaquone, and 4% received Dapsone when TMP-SMX was not an option. Twenty patients (91%) with toxoplasma reactivation had not received antimicrobial prophylaxis with anti-*Toxoplasma* activity while two patients (9%) had reactivation on atovaquone. With the exception of antimicrobial prophylaxis against *Toxoplasma gondii*, there were no significant differences in baseline patients' characteristics between the seropositive group without *Toxoplasma* reactivation and the group with reactivation. A summary of patients in the seropositive group and their clinical characteristics is shown in (Supplementary Table 1). A statistically significant higher percentage of the *Toxoplasma* reactivation patients did not receive antimicrobial prophylaxis (91% vs 48%; $p < 0.001$). *Toxoplasma* disease was seen in 16 patients (73%) while *Toxoplasma* infection was identified only in six patients (27%). The median time from the transplant to *Toxoplasma* disease diagnosis was 37.5 days (range, 15–202) and the initial positive *Toxoplasma* PCR in blood was frequently concurrent with end organ disease in 16 patients. Features of *Toxoplasma* infection and disease are outlined in Table 1.

Summaries of PFS, OS, and NRM are outlined in Supplementary Table 2. The median PFS was significantly shorter in the group who did not receive antimicrobial prophylaxis (9.4 months) compared to those who received prophylaxis either with TMP-SMX (63.3 months) or atovaquone (42.8 months; $p = 0.004$). Similarly, the median OS was significantly shorter in the group

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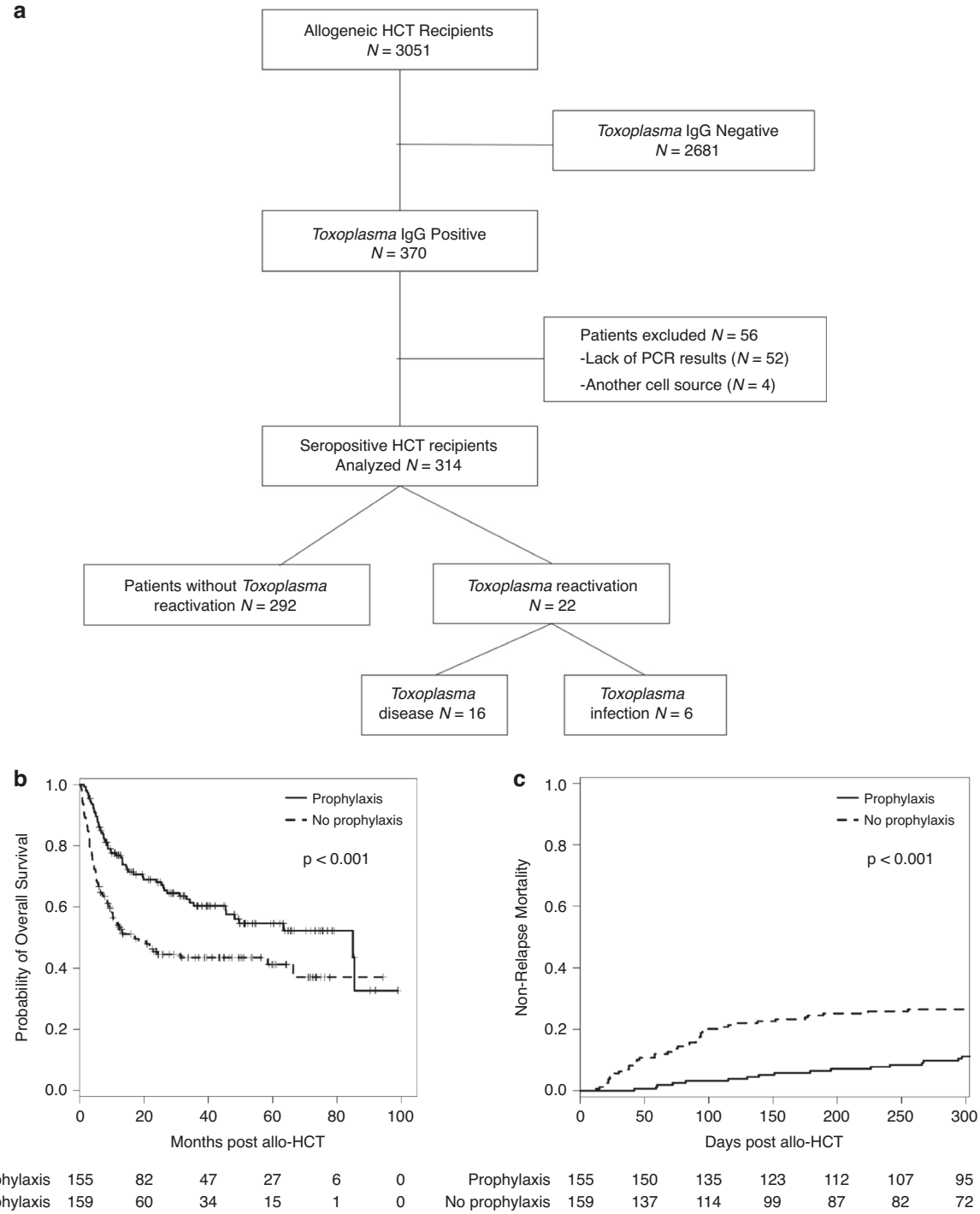

Fig. 1 Study design and outcomes. a Consort diagram of the study population. **b** Overall survival stratified by anti-*toxoplasma* prophylaxis. **c** Non-relapse mortality (in days) stratified by anti-*toxoplasma* prophylaxis.

who did not receive antimicrobial prophylaxis compared to those who did receive prophylaxis (17.2 months vs. 84.9 months; $p < 0.001$) (Fig. 1b, c). *Toxoplasma* reactivation was associated with worse OS on univariate and multivariable analyses (HR [95% CI]: 1.86 [1.07–3.24]; $p = 0.029$) and NRM (HR, [95% CI]: 2.32 [1.06-5.09]; $p = 0.035$) (Supplementary Tables 2, 3).

The current study represents a large single-center cohort of *Toxoplasma*-seropositive patients experiencing *Toxoplasma* reactivation following allo-HCT. It showed a notable decrease in NRM at Day +100 post allo-HCT in patients receiving antimicrobial prophylaxis. We have found that reactivation occurred early post-transplant (approximately 1 month) suggesting that early application of prophylactic medication is needed in all *Toxoplasma*-seropositive recipients.

A multicenter study evaluated the clinical characteristics of toxoplasmosis in solid organ transplant and HCT recipients, described 8 patients with toxoplasmosis post allo-HCT with a median time to *Toxoplasma* reactivation of 57 days (IQR, 47–213 days) [12]. Meers and colleagues reported a study with 182 *Toxoplasma*-seropositive patients receiving allo-HCT where 17

Table 1. Characteristics of *Toxoplasma* reactivation, infection and disease.

PT no	Age at SCT/ sex	Underlying disease	Donor type	CR at time of SCT	Engrafted	Day of engraftment	Onset after HCT, days	Prophylaxis at onset of Toxo	Infection or disease	Diagnosis	Treatment, duration	Outcomes at 24 weeks of Toxo diagnosis	Died of Toxo at last follow-up
1	61/F	AML	Haplo SCT (daughter, HPC-M)	MRD +	Yes	Day +20	28	No	Probable pulmonary and CNS diseases plus septic shock	PCR positive in blood AMS GGOs on CT chest Pressors	TMP-SMX (2 days)	Died	yes
2	75/ M	MDS	MUD	yes	Yes	Day +19	43 (after 2nd)	No	Probable pulmonary disease	PCR positive in blood GGOs on CT chest	PMN–SDZ (3 days) then TMP-SMX (43 days)	Alive	No (died of disease)
3	52/ M	DLBCL	MUD	yes	Yes	Day+12	27	No	Probable pulmonary disease and septic shock	PCR positive in blood GGOs on CT chest Pressors	Clinda-PMN (22 days) then TMP-SMX (20 days)	Died	yes
4	39/ M	gamma-delta T-cell lymphoma	Haplo SCT (mother)	yes	Yes	Day +13	202	Yes*	Probable pulmonary, CNS, and ocular diseases	PCR positive in blood GGOs on CT chest Multiple brain lesions on MRI Retinitis on eye exam	Clinda-PMN (26 days) then TMP-SMX (36 days)	Died	yes
5	63/ M	myelofibrosis	MUD	no	Yes	Day+15	36	No	Probable pulmonary and CNS diseases	PCR positive in blood and CSF Leptomeningeal enhancement on MRI	TMP-SMX (1 day)	Died	yes
6	57/ M	MDS/MPN	MUD	no	Yes	Day +27	75	No	Probable pulmonary and CNS diseases	PCR positive in blood GGOs on CT chest Focal area of cortical necrosis on MRI	TMP-SMX (11 days) then Clinda-PMN (12 days)	Died	yes
7	51/ M	Follicular lymphoma	MUD	yes	Yes	Day +6	151	No	Probable CNS and ocular diseases	PCR positive in CSF Multiple brain enhancing lesions on MRI Papilledema and infiltrative optic neuropathy	TMP-SMX (103 days)	Alive	alive
8	40/ M	DLBCL	MUD	yes	Yes	Day +17	40	No	Probable pulmonary disease	PCR positive in blood GGOs on CT chest	TMP-SMX (67 days)	Alive	alive

Table 1. continued

PT no	Age at SCT/ sex	Underlying disease	Donor type	CR at time of SCT	Engrafted	Day of engraftment	Onset after HCT, days	Prophylaxis at onset of Toxo	Infection or disease	Diagnosis	Treatment, duration	Outcomes at 24 weeks of Toxo diagnosis	Died of Toxo at last follow-up
9	64/F	AML	MUD	no	Yes	Day +17	32	No	Probable pulmonary disease	PCR positive in blood Bilateral nodular opacities on CT chest	TMP-SMX (40 days)	Alive	alive
10	69/ M	AML	MRD	yes	Yes	Day +19	40	No	Probable CNS disease	PCR positive in blood Brain ring-enhancing lesions on MRI	PMN–SDZ (5 days) then TMP-SMX (19 days)	Alive	No (died of disease)
11	60/F	Hodgkin lymphoma	Double cord	yes	Yes	Day +12	34	No	Probable pulmonary and CNS diseases plus septic shock	PCR positive in blood and CSF Respiratory failure Multiple brain enhancing lesions on MRI Pressors	TMP-SMX (29 days)	Died	yes
12	62/F	MPN	MUD	no	Yes	Day +21	34	No	Probable pulmonary disease	PCR positive in blood Bilateral lung nodules on CT chest	PMN–SDZ (9 days) then Clinda-PMN (30 days)	Died	yes
13	54/ M	MDS	MRD	no	Yes	Day +15	103	No	Probable CNS disease	PCR positive CSF Multiple ring-enhancing lesions on MRI	PMN–SDZ (10 days) then TMP-SMX (7 days) then Clinda-PMN (71 days)	Alive	Alive
14	22/ M	ALL	Haplo SCT	yes	Yes	Day +12	39	No	Probable pulmonary and CNS diseases	PCR positive in blood GGOs and nodules on CT chest AMS and Multiple areas of FLAIR abnormality on MRI	Clinda-PMN (78 days)	Alive	No (died of disease)
15	27/ M	AML	MUD	yes	Yes	Day +12	19	No	Probable pulmonary and CNS diseases	PCR positive in blood and CSF GGOs /nodules on CT chest Brain enhancing lesions on MRI	Clinda-PMN (16 days) then TMP-SMX (89 days) then Clinda-ATV (11 days)	Alive	No (died of disease)

Table 1. continued

PT no	Age at SCT/ sex	Underlying disease	Donor type	CR at time of SCT	Engrafted	Day of engraftment	Onset after HCT, days	Prophylaxis at onset of Toxo	Infection or disease	Diagnosis	Treatment, duration	Outcomes at 24 weeks of Toxo diagnosis	Died of Toxo at last follow-up
16	2 SCT 51/F 52/F	FLT3 + AML	#1 – MRD #2 – MRD Same donor	Yes yes	Yes	Day +11	15	No	Probable pulmonary and CNS diseases	PCR positive in blood and CSF Patchy opacities on CT chest Brain enhancing lesions on MRI	TMP-SMX (25 days)	Died	yes
17	40/F	ALL	Double cord	Yes	Yes	Day +23	26	Yes*	Infection	PCR positive in blood	Clinda-AZT-ATV (49 days) then Clinda-ATV (34 days)	Alive	Alive
18	64/ M	AML	MRD	yes	Yes	Day +13	30	No	Infection	PCR positive in blood	TMP-SMX~ (35 days)	Alive	Alive
19	58/ M	AML	MRD	MRD +	Yes	Day +15	48	No	Infection	PCR positive in blood	TMP-SMX~ (43 days)	Alive	No (died of disease)
20	44/ M	ALL	MRD	yes	Yes	Day +9	37	No	Infection	PCR positive in blood	None	Alive	No (GVHD)
21	27/ M	AML	MUD	yes	Yes	Day +13	32	No	Infection	PCR positive in blood	None	Died^	No (died of disease)
22	34/ M	Hodgkin lymphoma	MRD	yes	Yes	Day +10	55	No	Infection	PCR positive in blood	Clinda-PMN (11 days)	Died	No (GVHD)

*Atovaquone was used as prophylaxis in both patients. ~ TMP/SMX treatment dose. ^Cause of death was not related to toxoplasmosis.

ALL acute lymphoblastic leukemia, *AML* acute myeloblastic leukemia, *ATV* atovaquone, *AZT* Azithromycin, *Clinda* Clindamycin, *CR* conditioning regimen, *CNS* central nervous system, *CSF* cerebrospinal fluid, *CT* computed tomography, *DLBCL* diffuse large B cell lymphoma, *F* female, *GGOs* ground glass opacities, *GVHD* graft versus host disease, *HCT* hematopoietic cell transplantation, *M* male, *MDS/MPN* myelodysplastic syndrome/Myeloproliferative neoplasm, *MRD* matched related donor, *MRI* magnetic resonance imaging, *MUD* matched unrelated donor, *No* number, *PMN–SDZ* pyrimethamine–sulfadiazine, *TMP–SMX* trimethoprim–sulfamethoxazole, *PCR* polymerase chain reaction, *PT* patient.

patients (9.3%) developed *Toxoplasma* reactivation. The median time of *Toxoplasma* disease was 63 days (range, 27–139 days) and was 67 days (range, 25-166 days) for *Toxoplasma* infection [8]. However, in our cohort, the median time of *Toxoplasma* disease was shorter, 37.5 days (range, 15–202 days).

In addition, our study demonstrated a significant decrease in NRM, improvement in OS, and longer PFS with the use of antimicrobial prophylaxis, primarily with TMP-SMX. However, there are several limitations regarding the use of TMP-SMX during the pre-engraftment period as it may affect the bone marrow recovery and toxicities. A preemptive approach of implementation of blood PCR surveillance has been adopted in many cancer centers to detect early infection but unfortunately, the concomitance of positive surveillance *Toxoplasma* PCR and end organ disease has been increasingly reported [2, 6, 13]. This study, similar to others, highlights the importance of considering early initiation of anti-*Toxoplasma* prophylaxis which may prevent the occurrence of *Toxoplasma* infection and disease following allo-HCT and potentially lower NRM and improve survival.

Understanding the risk of toxoplasmosis in seropositive HCT recipients will help clinicians to optimize the preventive measures and management. Although, the exact duration of continuing prophylaxis or weekly *Toxoplasma* PCR monitoring while on TMP-SMX is not well known, it is clear that prophylaxis should start early post-transplant and likely needs to be continued while patients are receiving immunosuppressive agents. Moreover, our study suggests that prophylaxis with TMP-SMX reduces non-relapse mortality and improves survival and should be standard practice for all *Toxoplasma* seropositive patients.

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AUTHOR CONTRIBUTIONS

Conceptualization: AEM, TA, ES, VM, SA. Data gathering: AEM and TA. Formal analysis: DM. Writing of the original draft: AEM, TA, SA. Review and editing of the final draft: JR, MD, AO, SS, GA, BO, RM, IK, QB, NS, SC, GR, FM, CH, DM, PK, KR, YN, PA, AA, MF, MQ, UP, RC.

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ADDITIONAL INFORMATION

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