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Posaconazole oral suspension for secondary antifungal prophylaxis in allogeneic stem cell transplantation recipients: a retrospective study

Peipei Ye, Renzhi Pei, Youqian Hu, Dong Chen, Shuangyue Li, Junjie Cao, Fenglin Li, Mengjie Wu, Ying Fang and Ying Lu*

Abstract

Background: There is no consensus on the optimal secondary antifungal prophylaxis (SAP) regimen in patients receiving allogeneic hematopoietic stem cell transplantation (allo-HSCT). The purpose of this study was to evaluate the efficacy and safety of posaconazole oral suspension as secondary prophylaxis of invasive fungal disease (IFD) for allo-HSCT patients.

Methods: We retrospectively reviewed clinical data from prior IFD patients who received posaconazole oral suspension as systemic antifungal prophylaxis between June 2016 and January 2021 and have a follow-up period of 1 year after HSCT. The clinical outcomes of patients with a prior history of IFD ($n = 30$) and those without ($n = 93$) were compared.

Results: The 1-year cumulative incidence of prophylaxis failure was 58.3% in the group with prior history of IFD and 41.6% in the group without a prior history of IFD ($p = 0.459$). The cumulative incidence of proven, probable or possible IFD within 1 year after allo-HSCT was 23.1% in the group with prior history of IFD and 14.1% in the group without prior history of IFD ($p = 0.230$). There was no significant difference between the cumulative incidence of proven or probable IFD within 1-year after allo-HSCT in the group with a prior history of IFD and the group without ($p = 0.807$). Multivariate logistic regression revealed cytomegalovirus disease as risk factor for post-transplantation IFD occurrence in posaconazole oral suspension prophylaxis. There was not a significant difference in overall survival between the patients with IFD history and those without ($P = 0.559$).

Conclusions: Our study support that allo-HSCT recipients with a prior history of IFD and normal GI absorption can choose posaconazole oral suspension as a safe and effective SAP option.

Keywords: Secondary antifungal prophylaxis, Invasive fungal diseases, Posaconazole, Allogeneic hematopoietic stem cell transplantation

Introduction

Invasive fungal disease (IFD) is a common infectious complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1]. Especially in China, the

incidence of IFD after secondary antifungal prophylaxis (SAP) was 38.6% among patients receiving allo-HSCT [2]. In general, broad-spectrum antifungal agents such as voriconazole, itraconazole, liposomal amphotericin B, and caspofungin are effective for patients with a history of fungal infection [3]. However, due to the lack of large prospective study, there is no consensus on SAP regimen. In order to avoid prophylaxis failure, medication

*Correspondence: 814871416@qq.com

Department of Hematology, The Affiliated People's Hospital of Ningbo University, Ningbo 315101, China



that had been effective and well tolerated in initial antifungal therapy should be used for SAP [4]. However, in study done by Liu, they found no significant difference in IFD occurrence rate between such medication and other broad-spectrum medication. Therefore, using a broad-spectrum antifungal medication as SAP is feasible [3]. In addition, the opportunistic molds and yeast-like fungi (e.g. *Zygomycetes*, *Fusarium spp.* and *Candida spp.*) are gradually emerging in HSCT recipients during recent broad-spectrum antifungal treatment [5]. Therefore, SAP drug selection needs to take in account of drug resistance from such strains.

Posaconazole has become a widely accepted strategy for IFD prevention in acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) patients who undergo intensive chemotherapy and allo-HSCT recipients with graft-versus-host disease (GVHD) [6, 7]. Compared with other azole antifungals, it has strengths of broad spectrum, great potency, cost-efficiency and good long-term tolerance [6, 8–11]. However, absorption is still an important factor to consider in efficacy assessment of posaconazole.

In this retrospective study, the efficacy of posaconazole SAP therapy for IFD was assessed. In addition, we compared the clinical outcomes between allo-HSCT recipients with IFD before transplantation and those without when posaconazole was used as systemic antifungal prophylaxis.

Methods

Patients

We retrospectively analyzed the records of consecutive adult patients who underwent allogeneic HSCT and used posaconazole as systemic antifungal prophylaxis from June 2016 to January 2021 in The Affiliated People's Hospital of Ningbo University. During this period, 212 patients received allogeneic HSCT. Among the HSCT recipients, 116 (54.7%) received posaconazole oral suspension 200 mg orally three times daily and 7 (3.3%) received posaconazole oral suspension 400 mg twice daily. These 123 patients were included for our study. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of The Affiliated People's Hospital of Ningbo University. All patients have signed informed consent forms to participate in the study.

Transplant regimens and post-transplant immunosuppression

All patients received conventional regimen such as myeloablative/reduced-intensity conditionings, and were classified based on criteria described by Giralt et al. [12]. Cyclosporine A (CsA)+mycophenolate mofetil

(MMF)+a short course of methotrexate (MTX) were administered to the patients undergoing human leukocyte antigen (HLA)-matched sibling donor (MSD) transplant for GVHD prophylaxis. After January 2019, CsA +MMF+MTX+anti-thymocyte globulin (ATG) (Thymoglobulin®, Genzyme, Cambridge, MA) were administered for 1.5 mg/kg i.v. on day-3, -2 and -1 to the MSD transplant patients whose age ≥ 45 years, and CsA +MMF+MTX+ATG (2.5 mg/kg i.v. on day-4, -3, -2 and -1) were administered to the patients undergoing haploidentical donor [13] transplants for GVHD prophylaxis, some haploidentical recipients received transplant cyclophosphamide 50 mg/kg on day+3.

Definition

IFD was classified as proven, probable, or possible infection according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSG) [14]. Suspected IFD included these proven, probable, possible IFD. Responses to treatment were classified into CR, partial response (PR), stable responses, and failure of therapy [15]. Stable IFD was defined as CR response to prior IFD at transplantations while active IFD was defined as PR or stable responses to prior IFD at transplantations [4]. Failure of antifungal prophylaxis was defined by any of following cases: changing to an alternative antifungal agent or dosing modification due to suspected IFD, gastrointestinal intolerance (GI) in patients with severe mucositis, colitis, diarrhea, nausea, or emesis, drug-drug interactions, persistent fever in an appropriate clinical context and failure to defervesce after administration of empiric antibiotics during IFD prophylaxis. The absence of suspected IFD, as well as no emerging IFD (for SAP patients specifically) without antifungal agent or dosing modification, were defined as successful cases.

Administration of prophylactic antifungal agents

Antifungal prophylaxis was started on the first day of the conditioning regimen until 90 days after transplantation in patients without IFD before transplantation. SAP was given started on the first day of the conditioning regimen until 180 days after transplantation for patients with IFD before transplantation. For patients with active IFD and received SAP for more than 180 days but never reached the eradication or stability of residual foci, the SAP will be further extended till the eradication or stability of residual foci. The antifungal prophylaxis agent was given again if patients developed chronic GVHD (cGVHD), or they were treated with long-term systemic corticosteroids. Posaconazole oral suspension (200 mg orally three times a day) was administered as primary antifungal

prophylaxis (PAP) and SAP for patients who had a history of IFD and achieved complete response (CR) after antifungal treatment before HSCT. Posaconazole oral suspension was administered at 400 mg twice daily as SAP for patients who had active IFD, then switched to 200 mg three times a day when the residual foci in the patients was eradicated. In case of antifungal prophylaxis failure, we would either change dose of posaconazole, or replace posaconazole with other broad-spectrum antifungal drugs (voriconazole, caspofungin, amphotericin B, or combination of voriconazole and caspofungin).

Efficacy evaluation

All the patients were followed up until at least 12 months after allo-HSCT. IFD was routinely monitored through clinical symptoms, chest, sinuses, and/or abdomen computed tomography test, bronchoscopy and bronchoalveolar lavage serological testing for *Aspergillus* galactomannan, (1,3)-B-D-glucan, the culture of related tissue or samples and next-generation sequencing.

Statistical analysis

Continuous variables were represented in median, and categorical variables were represented in percentages. The PAP and SAP groups were compared using the chi-square test for categorical variables and Wilcoxon rank sum test for quantitative data. The survival curves for OS was plotted using the Kaplan–Meier method. A multivariate analysis was performed using logistic regression for the occurrence of IFD. The cumulative incidences of prophylaxis failure, IFD by 1 year after allo-HSCT were calculated using Fine and Gray's model with death as a competing event. As this retrospective analysis was designed as an exploratory investigation, statistical power calculation (sample size) was not conducted. The endpoint of the last follow-up for all of the surviving patients was December, 2021. SPSS16.0 (IBM, Chicago, IL, USA) was used for the statistical analysis. The R version 3.6.0 (<http://www.r-project.org>) software was used for competing risks analysis. $P < 0.05$ was considered as statistically significant.

Results

Patient characteristics

Among a total of 123 patients enrolled in the study, 30 (24.4%) had a past history of IFD received posaconazole as SAP and the remaining 93 (75.6%) patients received posaconazole as PAP. The patients had a median age of 39 years (range 14–72 years), with 70 (56.9%) males and 53 (43.1%) females. The underlying diseases were mainly AML (n=41), acute lymphoid leukemia (n=33), MDS (n=22), aplastic anemia (n=19), chronic myeloid leukemia (n=4), lymphoblastic lymphoma (n=3) and

myelofibrosis (n=1). Thirteen patients had diabetes as a complication. A hundred and three patients achieved CR and 20 patients did not the time of transplantation. 37 patients received MSD transplantation and 86 received HID transplantation. Of the 30 patients who had a history of IFD pre-transplantation, 23 patients had stable IFD and 7 patients had active IFD at the time of transplantation. Among those 30 patients, there are 5 proven IFD patients, 13 probable IFD patients and 12 possible IFD patients. We identified the pathogen in 5 proven IFD patients. Among these patients, 3 were infected by *aspergillosis* and remaining 2 were infected by *candida glabrata*. Additionally, those pathogens are theoretically sensitive to posaconazole. None of these 5 patients ever received posaconazole in their PAP treatment nor antifungal treatment. In this cohort of 123 patients, there were 21 cases (17.1%) of aGVHD (grade III-IV) and 32 (26.0%) of extensive cGVHD. Based on the patient and transplant characteristics of PAP and SAP groups in Table 1, the similar demographic and transplantation characteristics could be seen.

Antifungal prophylaxis and efficacy

Documented reason for prophylaxis failure was identified in 43.1% (50/123) cases. There were no significant differences in the incidence of IFD, gastrointestinal intolerance, persistent fever and drug-drug interaction between the groups with a past history of IFD and the groups without. (Table 2). The median duration of antifungal prophylaxis with posaconazole was 90 days (range, 9–365 days) in PAP group and 180 days (range, 15–365 days) in SAP group. The 1-year cumulative incidence of prophylaxis failure was 58.3% (95% CI, 26.5–63.6%) in group with a past history of IFD and 41.6% (95% CI, 30.3–51.2%) in the group without a past history of IFD ($p = 0.459$) (Fig. 1). The primary reason for prophylaxis failure of posaconazole intervention was GI, accounting for 50.0% (25/50) of failures. It is followed by the suspected IFD, accounting for 34.0% (17/50) of failures. Five (10.0%) patients had to discontinue posaconazole due to persistent fever. Three (6.0%) patients resulted in prophylaxis failure due to drug-drug interaction that caused hepatic toxicity, but two of them were later attributed to histologically proven GVHD.

IFD occurrence post-transplantation

Among the 93 patients who used posaconazole as PAP, eleven (11.8%) cases developed IFD, including 8 during prophylaxis period and 3 after. The IFD occurred at a median time of day + 99 after transplantation (range, day + 8 to + 262). Six (20.0%) of the 30 patients with a history of IFD developed IFD during the prophylaxis. For these patients, the IFD occurred at a median time of

Table 1 Characteristics of patients who received posaconazole oral suspension

Characteristic	PAP (n = 93)	SAP (n = 30)	P value
Previous IFD			
Proven		5 (16.7)	
Probable		13 (10.6)	
Possible		12 (9.8)	
Age at transplantation (y)			0.821
Median (range)	38 (14–72)	40 (18–68)	0.258
Gender, no. (%)			0.975
Male	53 (57.0)	17 (56.7)	
Female	40 (43.0)	13 (43.3)	
Underlying disease, no. (%)			0.067
AML	30 (32.3)	11 (36.7)	
ALL	21 (22.6)	12 (40.0)	
Other ^a	42 (45.2)	7 (23.3)	
Complication, no. (%)			0.518
Diabetes	11 (11.8)	2 (6.7)	
No diabetes	82 (88.2)	28 (93.3)	
Stage of underlying disease, no. (%)			1.0
CR	78 (83.9)	25 (83.3)	
Non-CR	15 (16.1)	5 (16.7)	
Transplant type, no. (%)			0.655
MSD	27 (29.0)	10 (33.3)	
HID	66 (71.0)	20 (66.7)	
Conditioning regimen, no. (%)			1.0
Myeloablative	81 (87.1)	26 (86.7)	
Reduced intensity	12 (12.9)	4 (13.3)	
GVHD prophylaxis, no. (%)			0.394
ATG-based	75 (80.6)	22 (73.3)	
Non-ATG based	18 (19.4)	8 (26.7)	
Acute GVHD			0.624
Grades 0–II	78 (83.9)	24 (80)	
Grades III–IV	15 (16.1)	6 (20)	
Chronic GVHD			0.388
No/limited	67 (72)	24 (80)	
Extensive	26 (28)	6 (20)	
Reduced intensity	12 (12.9)	4 (13.3)	
GVHD prophylaxis, no. (%)			0.394
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Table 1 (continued)

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PAP primary antifungal prophylaxis, SAP secondary antifungal prophylaxis, IFD Invasive fungal diseases, AML acute myeloid leukemia, ALL acute lymphoid leukemia, Other^a: myelodysplastic syndrome in 22 patients, aplastic anemia in 19 patients, chronic myeloid leukemia in 4 patients, lymphoblastic lymphoma in 3 patients and myelofibrosis in 1 patient. CR complete responses, MSD HLA-matched sibling donor, HID haploidentical donor, GVHD graft-versus-host disease, ATG antithymocyte globulin

Table 2 Reason for failure of antifungal prophylaxis with posaconazole oral suspension

	PAP (n = 93)	SAP (n = 30)	P
Suspected IFD	11 (11.8)	6 (20.0)	0.259
Proven IFD	3 (3.2)	0 (0)	
Probable IFD	5 (5.4)	3 (10)	
Possible IFD	3 (3.2)	3 (10)	
Gastrointestinal intolerance	20 (21.5)	5 (16.7)	0.567
Persistent fever	3 (3.2)	2 (6.7)	0.595
Drug–drug interaction	2 (2.2)	1 (3.3)	1.0

PAP primary antifungal prophylaxis, SAP secondary antifungal prophylaxis, IFD Invasive fungal diseases. Suspected IFD: it includes proven/probable/possible IFDs.

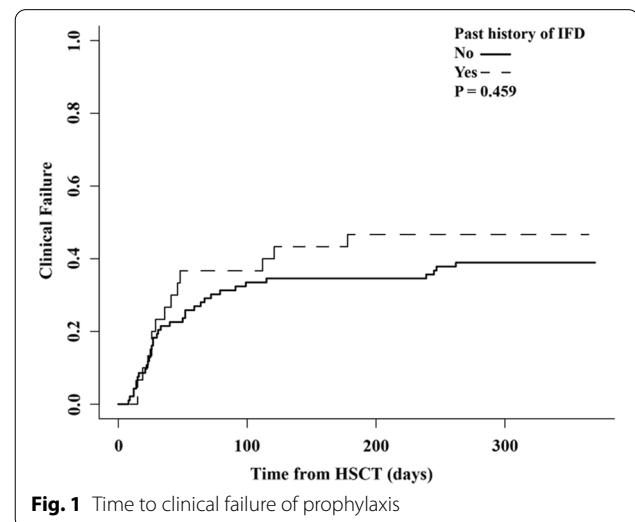


Fig. 1 Time to clinical failure of prophylaxis

day + 27.5 after transplantation (range, day + 15 to + 178). Two and one patient developed *aspergillosis* and *Candida spp* infection in PAP group, respectively. There were no

cases of proven IFD in SAP group. Eight and 6 patients developed probable and possible IFD within 1-year after allo-HSCT, respectively. The 1-year cumulative incidence of proven, probable or possible IFD was 14.1% (95% CI, 6.0%-21.5%) in the patients without a history of IFD and 23.1% (95% CI, 5.1%-37.7%) in the group with a past history of IFD ($p=0.230$, Fig. 2). The cumulative incidence of proven or probable IFD within 1-year after allo-HSCT was 10.3% (95% CI, 3.3%-16.7%) in the group without a history of IFD and 12.0% (95% CI, 0.0%-23.9%) in the group with a past history of IFD. No significant difference between those two groups was observed ($p=0.807$).

Treatment and outcome of post-transplantation IFD

Seventeen patients who developed IFD during our study received salvage therapy. Of these, eight (47.1%) patients were treated with voriconazole, 2 (11.8%) patients with caspofungin, 5 (29.4%) patients with voriconazole and caspofungin combination therapy, 1 (5.9%) patient with L-AmB and 1 (5.9%) patient with dose adjustment on posaconazole. After salvage therapy, There are 2 (11.8%) patients died of IFD, 11 (64.7%) patients achieved CR and 4 (23.5%) patients achieved PR. One (9.1%) death happened in PAP group while 1 (16.7%) happened in the SAP group.

Risk factors for IFD

The potential risk factors for post-transplantation IFD are presented in Table 3. Having cytomegalovirus (CMV) disease post-transplantation preceding IFD [hazard ratio (HR), 12.591; 95% CI 2.571 to 61.659; $p=0.002$] was identified as a strong risk factor for post-transplantation IFD based on both univariate and multivariate analysis.

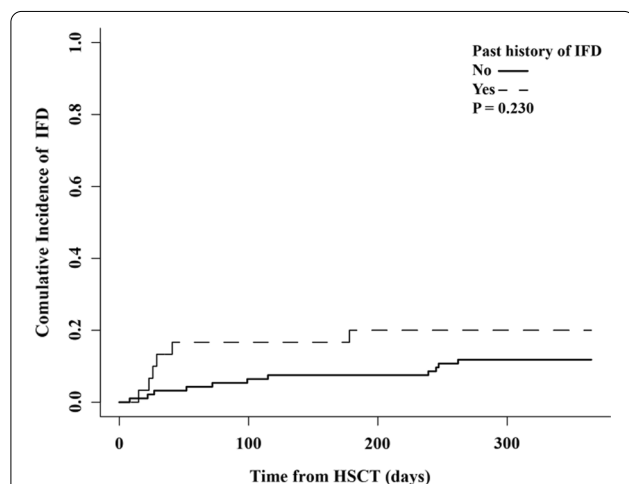


Fig. 2 Cumulative incidence of invasive fungal diseases during the study

Survival

With a median follow-up of 685 days (range 8–2005 days) post-transplantation, there were 26 deaths, the causes of which included relapse (10 cases), infections (6 cases including 2 fungal and 1 bacterial infection, 1 caused by CMV encephalitis, 1 by pneumocystis carinii and 1 by adenovirus encephalitis), GVHD (5 cases), thrombotic microangiopathy (4 cases) and hematencephalon (1 case). The 2-year OS after allo-HSCT was $74.9\% \pm 4.0\%$. No significant differences of 2-year OS were seen between PAP group and SAP group ($76.9\% \pm 4.5\%$ versus $68.1\% \pm 8.9\%$, $p=0.559$; Fig. 3). In the multivariable analysis, aGVHD III-IV (HR, 5.582; 95% CI, 2.297 to 13.565; $p=0.001$) and relapse of underlying primary diseases (HR, 3.736; 95% CI, 1.599 to 8.731; $P=0.002$) were risk factors that significantly associated with poor OS (Table 4).

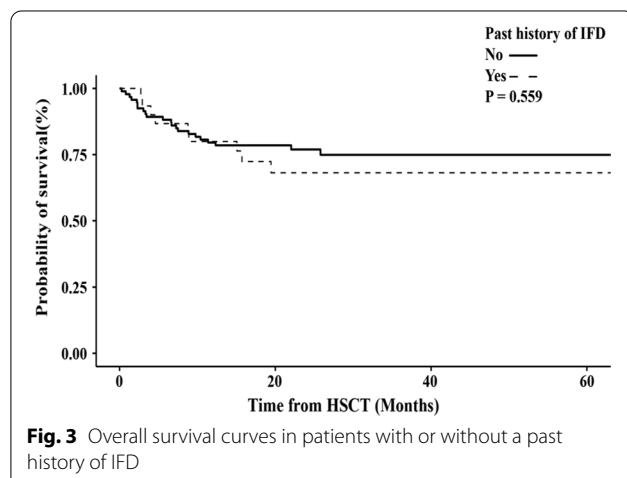
Discussion

To our knowledge, this is the first report to evaluate the efficacy and safety of secondary prophylaxis with posaconazole in patients undergoing allo-HSCT. The number of observed prophylaxis failure (43.1%) during the study was high comparing to previous reports (33%) [9]. However, previous report mainly focused on PAP in recipients of intensive chemotherapy with a short follow-up phase [9]. Our study had found some risk factors for prophylaxis failure such as more GI events during conditioning regimens, use of corticosteroid and immunosuppressant, GVHD, CMV infections, extended follow-up time and so on. In patients with IFD history undergoing allo-HSCT, 2 retrospective studies had demonstrated the incidence of IFD was 42.9% with itraconazole as SAP agent, 31.3% with voriconazole as SAP agent, 0% to 55.5% with L-AmB as SAP agent and 13.8% to 16.7% with caspofungin as SAP agent. Our results showed a relatively low rate of the 1-year incidence of IFD (23.1%) in allo-HSCT recipients who received posaconazole as second prophylactic. It is suggested that posaconazole is relatively effective. A major cause of prophylaxis failure, accounting for nearly half of cases, was GI intolerance. Posaconazole was stopped in only three patients with abnormal liver function tests, while two of them were later found to be related to liver GVHD based on biopsy. Therefore, posaconazole is suggested to be safe and suitable for long-term treatment. The most common cause for posaconazole discontinuation was intolerance and clinician concern for absorption that occurred much earlier than discontinuations for suspected IFD, which was in line with recent reports [16]. Overall, posaconazole appears to be safe and effective in protecting such patients without severe mucositis, colitis, diarrhea, nausea, or emesis from recurring or new systemic fungal disease.

Table 3 Univariate and multivariate analysis of risk factors for IFD

Risk factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Patient age (years)				
< 50 versus \geq 50	0.947 (0.307–2.920)	0.925		
Gender				
Female versus male	0.503 (0.166–1.529)	0.226		
Underlying disease, no. (%)				
AML	1.0			
ALL	0.737 (0.216–2.509)	0.625		
Other ^a	0.367 (0.102–1.321)	0.125		
Stage of underlying disease				
CR versus Non-CR	0.611 (0.129–2.896)	0.534		
Diabetes				
Yes versus no	2.057(0.504–8.399)	0.315		
Transplant type				
MSD vs HID	0.543 (0.146–2.025)	0.363		
Conditioning regimen				
Reduced intensity vs Myeloablative	0.0 (0.0)	0.998		
GVHD prophylaxis				
ATG-based vs no ATG-based	0.851 (0.253–2.869)	0.795		
History of IFD pre-transplant				
No versus yes	0.537 (0.180–1.602)	0.265		
CMV DNA				
Negative versus positive	0.711 (0.245–2.067)	0.531		
CMV disease				
Yes versus no	14.306 (3.033–67.481)	0.001	12.591(2.571–61.650)	0.002
Acute GVHD				
Grades III–IV versus Grades 0–II	3.309 (1.064–10.393)	0.039	2.770 (0.801–9.579)	0.107
Chronic GVHD				
Extensive versus no/limited	1.678 (0.565–4.985)	0.351		

IFD Invasive fungal diseases, AML acute myeloid leukemia, ALL acute lymphoid leukemia, Other^a: myelodysplastic syndrome in 22 patients, aplastic anemia in 19 patients, chronic myeloid leukemia in 4 patients, lymphoblastic lymphoma in 3 patients and myelofibrosis in 1 patient. CR complete responses, MSD HLA-matched sibling donor, HID haploidentical donor, GVHD graft-versus-host disease, ATG antithymocyte globulin



To identify the relevant risk factors of taking posaconazole orally as anti-fungal prophylaxis therapy in patients post allo-HSCT, further studies are required. CMV organ disease have been found as risk factor for IFD relapse for allo-HSCT[17]. In this retrospective study, patients with CMV organ disease also had higher incidence of IFD than those without CMV organ disease during posaconazole prophylaxis. This might be attributed to local and systemic immunosuppression induction by CMV organ disease, use of glucocorticoids, prolonged lymphopenia, GVHD and ganciclovir treatment of CMV complicated by neutropenia [17–19]. Therefore, intensification of antifungal prophylaxis and strict monitoring by radiological, serological method and molecular diagnostic should be considered for these patients [20]. However, the result should be

Table 4 Risk factors for overall survival

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Patient age (years)				
< 50 versus \geq 50	0.687 (0.329–1.435)	0.318		
Stage of underlying disease				
NR versus CR	2.374 (1.090–5.167)	0.029	1.430 (0.541–3.778)	0.470
Transplant type				
MSD vs HID	0.876 (0.392–1.959)	0.747		
Conditioning regimen				
Reduced intensity vs Myeloablative	1.441 (0.553–3.759)	0.455		
History of IFD pre-transplant				
No versus yes	0.794 (0.366–1.724)	0.560		
CMV disease				
Yes versus no	1.663 (0.505–5.481)	0.403		
Acute GVHD				
Grades III–IV versus Grades 0–II	7.851 (3.785–16.284)	0.001	5.582 (2.297–13.565)	0.001
Chronic GVHD				
Extensive versus no/limited	0.347 (0.121–0.994)	0.049	0.421 (0.141–1.258)	0.121
Post-transplantation IFD				
Yes versus no	2.082 (0.897–4.836)	0.088	1.035 (0.357–3.007)	0.949
Relapse of underlying primary diseases				
Yes versus no	6.928 (3.391–14.157)	0.001	3.736 (1.599–8.731)	0.002

NR no response, CR complete responses, MSD HLA-matched sibling donor, HID haploidentical donor, IFD invasive fungal diseases, GVHD graft-versus-host disease

interpreted carefully due to low amount of events in the proportional hazard model to cause inconclusive result.

It has been demonstrated that prophylaxis with posaconazole is associated with an increased efficacy of IFD prevention and an improved survival comparing to fluconazole or itraconazole prophylaxis in acute leukemia or MDS patients undergoing intensive chemotherapy [6]. Furthermore, safety and efficacy were recently assessed on a phase 3, randomized controlled, non-inferiority trial, and suggested that posaconazole had similar all-cause mortality and better tolerability than voriconazole for primary treatment in participants with invasive aspergillosis, including the patients undergoing allo-HSCT [21]. These results were similar to ours and confirmed that PAP of posaconazole was effective and safe in patients undergoing allo-HSCT. It is theoretically feasible to select the agent that had been effective, broad-spectrum and well tolerated in primary antifungal therapy for SAP. In our study, the 2-year overall survival rate of the 30 patients with IFD history was $68.1\% \pm 8.9\%$ which was not significantly different than patients without a history of IFD before transplantation. The majority of deaths were caused by primary disease relapse and III–IV GVHD. This indicates that posaconazole prophylaxis can be used safely for allo-HSCT patients with a history of IFD. In addition, it is important to note that early

diagnosis and prompt antifungal therapy are all critical to patient outcomes.

Our study have several limitations. First, our study is single-centered study with small sample size, which means the findings of our study may not be generalized. Second, posaconazole was switched to other antifungal agents in approximately one-fifth of patients long before discontinuations for suspected IFD. Therefore, a small portion of our results did not reflect only the effect of posaconazole prophylaxis, but also multitude of challenges in clinical practice and in a real-world in this complex patient population. Therefore, for those patients with more complex variables should be considered. Finally, routine therapeutic drug monitoring for posaconazole was not carried out in clinical practice in this study. In the literature, the plasma concentration of posaconazole was related to the incidence of IFD [22]. This potential posaconazole serum concentration differences would make data analysis more difficult and complex, but will be considered in the future study.

Conclusion

In summary, our study support that allo-HSCT patients without impaired GI absorption and with a prior history of IFD can choose posaconazole as prophylactic option. Our study showed posaconazole is well-tolerated over a prolonged period of time. The availability of oral

posaconazole makes the agent convenient for outpatient use, for example, in patients with cGVHD or taking long-term systemic immunosuppressant. Given the limitations we mentioned above, further investigation in prospective randomized large trials is required.

Abbreviations

allo-HSCT: Allogeneic hematopoietic stem cell transplantation; AML: Acute myeloid leukemia; ATG: Anti-thymocyte globulin; CMV: Cytomegalovirus; CR: Complete response; CsA: Cyclosporine A; GI: Gastrointestinal intolerance; GVHD: Graft-versus-host disease; HID: Haploidentical donor; HLA: Human leukocyte antigen; IFD: Invasive fungal disease; MDS: Myelodysplastic syndromes; MMF: Mycophenolate mofetil; MSD: Matched sibling donor; MTX: Methotrexate; PAP: Primary antifungal prophylaxis; PR: Partial response; SAP: Secondary antifungal prophylaxis.

Acknowledgements

We would like to thank all authors of our department for their excellent work and all patients. We also would like to thank Shanghai Tissuebank Diagnostics Co., Ltd. for valuable assistance in proof reading and revision for the manuscript.

Author contributions

PY, YL conceived and designed the study, analyzed the data, interpreted the results, and wrote up the draft manuscript. YL, RP, YH, DC, SL, JC and FL, contributed to the analysis of the data, interpretation of the results and critically reviewing the manuscript. YL, MW and YF involved in the manuscript review and editing. All authors read and approved the final manuscript.

Funding

This work was supported by medical and health science and technology program of Zhejiang province (2020KY912) and Ningbo medical science and technology project (2020Y45).

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. The data are not publicly available due to containing information that could compromise the privacy of research participants.

Declarations

Ethics approval and consent to participate

This study was approved by the local Ethic Committee (The Affiliated People's Hospital of Ningbo University, Ningbo, China) in 2016. This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was provided by patients or by their legal representatives. All methods in this study were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Written informed consent was obtained from the patient. All authors gave their consent for publication of this manuscript.

Competing interests

The authors declare that they have no competing interests.

Received: 10 February 2022 Accepted: 29 April 2022

Published online: 15 May 2022

References

- Wang L, Wang Y, Hu J, Sun Y, Huang H, Chen J, et al. Clinical risk score for invasive fungal diseases in patients with hematological malignancies undergoing chemotherapy: China Assessment of Antifungal Therapy in Hematological Diseases (CAESAR) study. *Front Med*. 2019;13(3):365–77.
- Gao L, Sun Y, Meng F, Han M, Huang H, Wu D, et al. Antifungal prophylaxis of patients undergoing allogeneic hematopoietic stem cell transplantation in China: a multicenter prospective observational study. *J Hematol Oncol*. 2016;9(1):97.
- Liu M, Li Y, Zhang Y, Zhao X, Zhai B, Zhang Q, et al. Secondary antifungal prophylaxis in hematological malignancy patients with previous invasive fungal disease: a retrospective analysis. *PLoS ONE*. 2014;9(12): e115461.
- Liu Q, Lin R, Sun J, Xiao Y, Nie D, Zhang Y, et al. Antifungal agents for secondary prophylaxis based on response to initial antifungal therapy in allogeneic hematopoietic stem cell transplant recipients with prior pulmonary aspergillosis. *Biol Blood Marrow Transplant*. 2014;20(8):1198–203.
- Richardson M, Lass-Flörl C. Changing epidemiology of systemic fungal infections. *Clin Microbiol Infect*. 2008;14(Suppl 4):5–24.
- Cornely OA, Maertens J, Winston DJ. Posaconazole vs fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356(4):348–59.
- Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007;356(4):335–47.
- Chan TS, Marcella SW, Gill H, Hwang YY, Kwong YL. Posaconazole vs fluconazole or itraconazole for prevention of invasive fungal diseases in patients with acute myeloid leukemia or myelodysplastic syndrome: a cost-effectiveness analysis in an Asian teaching hospital. *J Med Econ*. 2016;19(1):77–83.
- Copley MS, Waldron M, Athans V, Welch SC, Brizendine KD, Cober E, et al. Itraconazole vs posaconazole for antifungal prophylaxis in patients with acute myeloid leukemia undergoing intensive chemotherapy: a retrospective study. *Int J Antimicrob Agents*. 2020;55(3): 105886.
- Tang L, Yang XF, Qiao M, Zhang L, Tang XW, Qiu HY, et al. Posaconazole vs voriconazole in the prevention of invasive fungal diseases in patients with hematological malignancies: a retrospective study. *J Mycol Med*. 2018;28(2):379–83.
- O'Sullivan AK, Weinstein MC, Pandya A, Thompson D, Langston AA, Perfect JR, et al. Cost-effectiveness of posaconazole versus fluconazole for prevention of invasive fungal infections in US patients with graft-versus-host disease. *Am J Health Syst Pharm*. 2012;69(2):149–56.
- Giralt S, Ballen K, Rizzo D, Bacigalupo A, Horowitz M, Pasquini M, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant*. 2009;15(3):367–9.
- Wilkinson AN, Chang K, Kuns RD, Henden AS, Minnie SA, Ensby KS, et al. IL-6 dysregulation originates in dendritic cells and mediates graft-versus-host disease via classical signaling. *Blood*. 2019;134(23):2092–106.
- De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46(12):1813–21.
- Cornely OA, Maertens J, Bresnik M, Ebrahimi R, Ullmann AJ, Bouza E, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis*. 2007;44(10):1289–97.
- Guarascio AJ, Slain D. Review of the new delayed-release oral tablet and intravenous dosage forms of posaconazole. *Pharmacotherapy*. 2015;35(2):208–19.
- Kontoyiannis PP-ARCD. How I transplant a patient with a history of invasive fungal disease. *Blood*. 2020;136(24):2741–53.
- Martino R, Parody R, Fukuda T, Maertens J, Theunissen K, Ho A, et al. Impact of the intensity of the pretransplantation conditioning regimen in patients with prior invasive aspergillosis undergoing allogeneic hematopoietic stem cell transplantation: a retrospective survey of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Blood*. 2006;108(9):2928–36.
- Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. *Clin Infect Dis*. 2008;47(8):1041–50.

20. Kidd SE, Chen SC, Meyer W, Halliday CL. A new age in molecular diagnostics for invasive fungal disease: are we ready? *Front Microbiol.* 2019;10:2903.
21. Maertens JA, Rahav G, Lee DG, Ponce-de-Leon A, Ramirez Sanchez IC, Klimko N, et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. *Lancet.* 2021;397(10273):499–509.
22. Li W, Xia F, Zhou H, Qiu H, Wu D, Ma X, et al. Efficacy of posaconazole prophylaxis for fungal disease in hematology patients treated with chemotherapy and transplantation: an open-label, prospective, observational study. *Front Microbiol.* 2020;11:349.

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