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Original Article

Caspofungin as secondary antifungal prophylaxis and subsequent maintenance antifungal prophylaxis therapy in hematological malignancy patients

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Abstract: Aim: This study aimed to investigate the efficacy and safety of caspofungin as secondary antifungal prophylaxis (SAP) and subsequent maintenance therapy for SAP in hematological malignancy patients. Methods: Forty four patients receiving caspofungin for SAP and 43 patients not receiving any SAP agents during their subsequent chemotherapy or HSCT were reviewed retrospectively. The clinical characteristics and diagnosis were analyzed according to the diagnostic criteria for IFD. Results: The recurrence rate of IFD in 44 patients with caspofungin for SAP was 9.1% (4/44), which was much lower than that in 43 patients without SAP (9.1% vs 46.5%, P = 0.000). Patients with SAP had lower recurrent IFD-related mortality than that without SAP (12.5% vs 55.6%, P = 0.131). Among the 44 patients with SAP, caspofungin continued as maintenance antifungal prophylaxis therapy in 18 patients after neutropenia and oral medication became possible, while voriconazole in 14 patients and itraconazole in 12 patients. The recurrent IFD occurred in 2, 1, 1 patient respectively. There was no statistical difference in recurrence rates among different maintenance antifungal prophylaxis therapies (P = 0.922). No severe adverse events were observed during SAP treatment. Conclusions: Caspofungin is effective and safe to prevent IFD recurrence in hematological malignancy patients undergoing chemotherapy or HSCT. A subsequent maintenance antifungal prophylaxis therapy of oral voriconazole or itraconazole instead of caspofungin after caspofungin as SAP during neutropenia is as effective as caspofungin given constantly.

Keywords: Caspofungin, secondary antifungal prophylaxis, maintenance antifungal prophylaxis therapy, hematological malignancy

Introduction

Over the past decades, although there have been major improvements in the diagnosis and management of invasive fungal disease (IFD), it remains among the most common causes of infectious morbidity and mortality in patients with hematological malignancies, and IFD recurrence during subsequent chemotherapy or HSCT is considerable and associated with a very poor prognosis [1-5]. While considering the risk of IFD recurrence, many clinicians were reluctant to perform large-dose chemotherapy or myeblablative HSCT, which might have a major impact on the risk of leukemia relapse.

Secondary antifungal prophylaxis (SAP) is a rational strategy for patients with previous IFD. The last published European guidelines for antifungal treatment in patients with leukemia and recipients of allogeneic HSCT pointed out that SAP should be administered to these patients with previous IFD to prevent recurrence of previous IFD or onset of a new IFD during a new at-risk phase, mainly referring to a prolonged neutropenic period induced by chemotherapy or a phase of severe immunosuppression after allogeneic HSCT [6]. SAP has been proved effective in preventing IFD recurrence in patients with hematological malignancies [7-11].

However, there is no optimal SAP strategy and no specific recommendation has been made on the selection of SAP drugs. Most of them include patients with previous IFD who received

SAP with voriconazole during additional cytotoxic chemotherapy or HSCT [10, 12-14], while a few studies include patients receiving SAP with amphotericin B liposome (L-AmB) [15, 16]. However, considerable toxicity including infusion reactions and nephrotoxicity of L-AmB, liver toxicity and drug-drug interactions of triazoles sometimes limit their use for SAP especially in allo-HSCT recipients.

Caspofungin, the first antifungal drug of the novel echinocanclin class, is a broad-spectrum and less-toxic antifungal agent. It exerts its antifungal activity by inhibiting the 1,3-ß-D-glucan synthase complex, which synthesises ß-D-glucan, an essential cell wall component of Candida and Aspergillus spp [17]. The efficacy and safety of caspofungin in the first-line treatment of IFD have been demonstrated [18, 19]. The unique mechanism of action of caspofungin, its broad spectrum of activity, good safety profile, and lack of drug-drug interactions [20], make it an appealing agent for SAP. However, there are limited reports about its application as SAP to prevent IFD recurrence in hematological malignancy patients [21, 22]. There is no report about subsequent maintenance antifungal prophylaxis therapy after caspofungin as SAP. It is important for clinical practice because caspofungin presents a problem with unavailability of oral formulations which is inconvenient especially for outpatients.

In this article, we retrospectively analyzed the medical records of 44 hematological malignancy patients who received caspofungin for SAP and 43 patients without SAP during their successive chemotherapy or HSCT in our hospital between Jan 2008 and Jun 2013, and evaluated efficacy and safety of caspofungin as SAP. We also assessed the efficacy of different subsequent antifungal maintenance prophylaxis therapies after neutropenia.

Patients and methods

Patients group

Among 164 hematological malignancy patients with previous IFD (proven and probable) receiving further chemotherapy and/or HSCT in our hospital between Jan 2008 and Jun 2013, 44 patients who were administered caspofungin for SAP and 43 patients who did not receive any SAP agents were enrolled in this study. The other 77 patients were not included in our study because they received other SAP drugs. All the patients were followed up until at least 180 days after chemotherapy or HSCT. The study protocol was approved by the author's institutional ethics committee, namely the Ethics Committee of General Hospital of Chinese People's Liberation Army, and was conducted in accordance with the Declaration of Helsinki. We then retrospectively viewed the charts, electronic medical records, and laboratory records of these patients.

IFD was diagnosed on the basis of the revised 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) criteria [23, 24].

The stage of underlying diseases was categorized. Low-risk stage was defined as first complete remission of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) or non-Hodgkin's lymphoma (NHL), hypoplastic myelodysplastic syndrome (MDS) (refractory anemia or refractory anemia with ringed sideroblasts), first chronic phase of chronic myeloid leukemia (CML). High-risk stage was defined as those that were not included into the low-risk stage.

Management of underlying diseases

All the hematological malignancy diseases were managed according to NCCN guidelines. Patients with chemotherapy received standard chemotherapy for their hematological malignancies. Patients submitted to autologous HSCT or allogeneic HSCT received traditional conditioning regimen; and prophylaxis for graft-versus-host-disease (GVHD) included cyclosporine, mycophenolate mofetil and short-course methotrexate.

SAP strategy

SAP started on the first day of conditioning or about two days before chemotherapy, and covered the duration of neutropenia and terminated till neutrophil recovery or discontinuation of immunosuppressions or failure of SAP. The maintenance antifungal prophylaxis therapy was defined as the antifungal prophylaxis therapy after neutropenia and oral medication became possible. In patients with chemothera-

Table 1. Diagnostic criteria and results for 87 patients with previous IFD

Diagnostic criteria	IFD category				Total (%) n = 87
	Proven (%)		Probable (%)		
	IPA n = 4	IC n = 2	IPA n = 61	IC n = 20	
Host factors					
Neutropenia (> 10 days)	4 (100)	2 (100)	23 (37.7)	10 (50)	39 (44.8)
T > 38°C With Prolonged neutropenia	4 (100)	2 (100)	23 (37.7)	6 (30)	35 (40.2)
Immunosuppressant	3 (75)	1 (50)	30 (49.2)	15 (75)	49 (56.3)
Previous IFD	4 (100)	2 (100)	61 (100)	20 (100)	87 (100)
With AIDS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
GVHD	1 (25)	1 (50)	13 (21.3)	5 (25)	20 (23.0)
Corticosteroids[#]	3 (75)	1 (50)	26 (42.6)	9 (45)	39 (44.8)
Clinical criteria					
Halo sign	3 (75)	2 (100)	45 (73.8)	16 (80)	66 (75.9)
Air-crescent sign	2 (50)	0 (0)	10 (16.4)	4 (20)	16 (18.4)
Cavity	1 (25)	0 (0)	6 (9.8)	3 (15)	10 (11.5)
Symptoms of LRI	3 (75)	2 (100)	31 (50.8)	12 (60)	48 (55.2)
Permanent fever	2 (50)	1 (50)	32 (52.5)	14 (70)	49 (56.3)
Mycological criteria					
Positive sputum microscopy	0 (0)	/	23 (37.7)	/	23 (26.4)
Positive sputum culture	1 (25)		20 (32.8)		21 (24.1)
G test positive	1 (25)	0 (0)	11 (18.0)	6 (30)	18 (20.7)
qPCR [30][*]	4 (100)		16 (88.9)		20 (90.9)
Positive blood culture	0 (0)	2 (100)	0 (0)		2 (2.3)
No bacterial positive	0 (0)	0 (0)	15 (24.6)	8 (40)	23 (26.4)
Histology					
Biopsy specimen of the lung	4 (100)	1 (50)	0 (0)	0 (0)	5 (5.7)

Footnotes: IFD, invasive fungal diseases; IPA, invasive pulmonary aspergillosis; IC invasive candida; AIDS, acquired immune deficiency syndrome; GVHD, graft versus host disease; LRI, lower respiratory infections; qPCR, real-time qualitative polymerase chain reaction. [#]Corticosteroid was defined as 1 mg/kg or 2 mg/kg for more than 3 weeks for the treatment of acute lymphoblastic leukemia or for the management of GVHD before IFD. [*]Four proven IPA patients and 18 probable IPA patients were included in a qPCR diagnostic study, while 4 (4/4, 100%) and 16 (16/18,88.9%) were qPCR positive respectively.

py or auto-HSCT, the maintenance antifungal prophylaxis therapy terminated till neutrophil recovery, while there were other immunosuppressive conditions, such as prophylaxis or treatment for GVHD in allo-HSCT recipients, the maintenance antifungal prophylaxis therapy terminated till discontinuation of immunosuppressions or failure of SAP.

So, 44 patients were divided into three groups by different treatment. Eighteen patients received caspofungin with a loading dose of 70 mg on the first day, followed by maintenance doses of 50 mg daily intravenously till the end of SAP. Fourteen patients received caspofungin 70 mg on the first day and 50 mg daily intravenously since the second day till oral medication became possible after neutropenia then received voriconazole orally with a loading dose of 400 mg every 12 h (for two doses) followed by maintenance doses of 200 mg every 12 h. Twelve patients received caspofungin 70 mg on the first day and 50 mg daily intravenously since the second day till oral medication became possible after neutropenia, then received itraconazole with a loading dose of 200 mg, every 12 h (for three doses) intravenously, followed by maintenance doses of 200 mg every 12 h orally.

Assessment of SAP efficacy

Success of SAP was defined as the absence of documented IFD recurrence and the absence of a new IFD. Failure of SAP was defined as recurrence of previous IFD or occurrence of a new IFD. In this study, we didn't indentify whether it is IFD recurrence or occurrence of a new

Table 2. Characteristics of patients in SAP group of caspofungin and non-SAP group

Characteristics	SAP (n, %)	N- SAP (n, %)	*P* value
Gender			0.337
Male	26 (59.1)	21 (48.8)	
Female	18 (40.9)	22 (51.2)	
Age (years old)			0.090
< 40	24 (54.5)	31 (72.1)	
≥ 40	20 (45.5)	12 (27.9)	
Underlying disease			0.739
Acute leukemia	38 (86.4)	39 (90.7)	
Others	6 (13.6)	4 (9.3)	
Disease stage			0.239
Low-risk stage	28 (63.6)	22 (51.2)	
High-risk stage	16 (36.4)	21 (48.8)	
Disease treatment			0.014
Chemotherapy or Auto-HSCT	15 (34.1)	26 (60.5)	
Allo-HSCT	29 (65.9)	17 (39.5)	
Use of corticosteroid*			0.901
Yes	19 (43.2)	18 (41.9)	
No	25 (56.8)	25 (58.1)	
Duration of neutropenia			0.599
< 14 d	29 (65.9)	26 (60.5)	
≥ 14 d	15 (34.1)	17 (39.5)	
Conditioning regimens			0.505
With TBI	7 (24.1)	6 (35.3)	
Without TBI	22 (75.9)	11 (64.7)	
Conditioning regimen			0.936
With ATG	15 (51.7)	9 (52.9)	
Without ATG	14 (48.3)	8 (47.1)	
Acute GVHD			1.000
Presence	8 (27.6)	5 (29.4)	
Absence	21 (72.4)	12 (70.6)	
Chronic GVHD			0.956
Presence	10 (34.5)	6 (35.3)	
Absence	19 (65.5)	11 (64.7)	
CMV DNAemia [31]			0.708
Presence	17 (58.6)	9 (52.9)	
Absence	12 (41.4)	8 (47.1)	
Diagnosis of previous IFD			0.202
Proven	5 (11.4)	1 (2.3)	
Probable	39 (88.6)	42 (97.7)	

Footnotes: HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host-disease; CMV, cytomegalovirus; TBI, total body irradiation; allo-HSCT, allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous hematopoietic stem cell transplantation. *Use of corticosteroid was defined as 1 mg/kg or 2 mg/kg for more than 3 weeks for the treatment of acute lymphoblastic leukemia or for the management of GVHD before IFD.

IFD, because there were no records about this.

Management of SAP toxicity

During the period of SAP, adverse events of SAP drugs were monitored by daily clinical examination and routine biological tests including blood routine, biochemistry about three times a week during hospitalization, and once a week for outpatients. For allo-HSCT recipients, levels of cyclosporine were monitored during cyclosporine medication.

Statistical analysis

Demographics and characteristics were summarized using descriptive statistics. Categorical data were compared between groups by chi-square tests or Fisher's exact test. Analyses were performed with SPSS software version 19.0 (IBM, USA). Two-tailed *P* values < 0.05 were considered statistically significant.

Results

Demographics and clinical characteristics

All the 87 patients suffered a previous pulmonary IFD. Among them, proven and probable IFD were diagnosed in 6 and 81 patients, respectively. Four of 6 proven cases were diagnosed Aspergillus infection and 2 were Candida infection. Four patients with invasive pulmonary Aspergillus (IPA) infection were diagnosed by biopsy specimen of the lung, while 2 patients with invasive Candida (IC) infection by blood culture. All of the IPA were caused by A. fumigatus. One of the proven IC was caused by C. albicans, while the other by C. glabrata. Sixty one of 81 patients were diagnosed with probable IPA infection and twenty with probable IC infection. Diagnostic criteria and results for the 87 patients were shown in **Table 1**.

The characteristics of patients in SAP group of caspofungin and non-SAP group are shown in **Table 2**. Patients admitted to allo-HSCT were more likely to have received caspofungin for SAP (P = 0.014).

Table 3. Drugs of maintenance antifungal prophylaxis therapy, and recurrence rate

SAP agent	Maintenance antifungal prophylaxis therapy	No of patients	Recurrence rate of IFD	P
Caspofungin	Caspofungin	18	11.1% (2/18)	0.922
	Voriconazole	14	7.1% (1/14)	
	Itraconazole	12	8.3% (1/12)	

Footnotes: SAP, secondary antifungal prophylaxis; IFD, invasive fungal disease.

Efficacy of caspofungin on prophylaxis of IFD recurrence

All patients were followed up for 180 days after chemotherapy or HSCT. In 44 patients receiving caspofungin for SAP, the overall recurrence rate of IFD was 9.1% (4/44), with 0% in patients with chemotherapy or auto-HSCT and 13.8% (4/29) in allo-HSCT recipients; while in 43 patients without SAP, the overall recurrence rate was 46.5% (20/43): 38.5% (10/26) in patients with chemotherapy or auto-HSCT and 58.8% (10/17) in allo-HSCT recipients. The total recurrence rate between these two groups was statistically different (P = 0.000). Further stratified analysis indicated that either for patients receiving allo-HSCT or receiving chemotherapy/auto-HSCT, there was also statistical difference in the recurrence rates between these two groups (P = 0.001, 0.007 respectively).

Efficacy of different regimens of maintenance antifungal prophylaxis therapy

After neutropenia and oral medication becoming possible, caspofungin continued as SAP in 18 patients, while voriconazole and itraconazole were used as maintenance antifungal prophylaxis therapy in 14 and 12 patients. The recurrent IFD occurred in 2, 1, 1 patient respectively. There was no statistical difference in recurrence rates among different maintenance antifungal prophylaxis therapies (P = 0.922) (**Table 3**).

Safety of SAP

During caspofungin administration, no severe caspofungin-related adverse events were observed and level of cyclosporine was stable (200-400 ng/ml) in allo-HSCT recipients. Although there was some injury of hepatic and renal function during maintenance antifungal prophylaxis therapy with voriconazole or itraconazole, it did not affect the SAP treatment due to the use of ancillary drugs.

Characteristics of patients with IFD recurrence

After a follow-up period of 180 days, IFD recurrence occurred in 4 patients with SAP (9.1%) and 20 patients without SAP (46.5%). Among these 24 patients, 10 were male and 14 were female. The underlying diseases were AML (n = 15), ALL (n = 7), and CML (n = 2). Ten patients were receiving chemotherapy or autogeneic HSCT and 14 patients were undergoing allogeneic HSCT. All the 24 patients were diagnosed as probable IFD, 4 probable IPA in SAP group and 16 probable IPA and 4 probable IC in non-SAP group. In SAP group, all of the 4 recurrent IFD were allo-HSCT recipients, and three of the 14 allo-HSCT recipients (21.4%) conditioning with ATG had a recurrence of IFD compared with one of the 15 patients (6.7%) without ATG (P = 0.330).

Patient outcome

At the end of follow-up, 17 patients had died: 8 patients were in the group of receiving SAP and 9 patients were in the non-SAP group. Patients with SAP had less recurrent IFD-related mortality than that without SAP (12.5% (1/8) vs 55.6% (5/9)). However, IFD-related mortality between these two groups was not statistically different (P = 0.131).

Discussion

The results of this study showed that caspofungin is effective to prevent IFD recurrence in hematological malignancy patients undergoing chemotherapy or HSCT. Caspofungin is safe without severe toxicity and drug-drug interactions. A subsequent therapy of oral voriconazole or itraconazole as maintenance antifungal prophylaxis therapy after using caspofungin as SAP during neutropenia is as effective and safe as caspofungin given constantly for SAP.

In recent years, several studies have evaluated the role of SAP in prevention of second episodes of IFD in patients with hematological malignancy, and there is a practical consensus for giving SAP to patients who are going to experience a new prolonged neutropenic phase or

transplant [5, 7, 8, 25-27]. Our present study found that the IFD recurrence rate in patients receiving SAP was significantly decreased compared with that in patients not receiving SAP (9.1% vs 46.5%, P = 0.000), and that patients with SAP had lower recurrent IFD-related mortality than that without SAP (12.5% vs 55.6%), although there was no statistical difference (P = 0.131). Our study further proved the necessity and efficacy of SAP.

However, despise the widespread use of SAP, there are no standard prophylactic strategy, including optimal agents for SAP. Caspofungin has been widely used in the first-line treatment of IFD and proved to be effective and safe [18, 19]. Consequently, several studies have evaluated the efficacy of caspofungin as SAP in patients with hematological malignancies. In a retrospective published study performed by Vehreschild JJ et al in 448 patients with an underlying hematological malignancy and a previous IFD, a total of 75 patients were evaluated, including 28 receiving caspofungin and 47 receiving itraconazole for SAP. There was no difference in the occurrence of IFD recurrence between both groups (32.1% vs 31.9%). Patients with uncontrolled first IFD, uncontrolled underlying disease or in those receiving allo-HSCT were more likely to have received caspofungin prophylaxis [22]. De Fabritiis P et al [21] reported an 11.1% incidence of IFD recurrence in 18 patients submitted to allogeneic HSCT receiving caspofungin for SAP. In present study, we found an overall 9.1% incidence of IFD recurrence in patients with caspofungin for SAP, with 0% in patients with chemotherapy or auto-HSCT and 13.8% in allo-HSCT recipients. The incidence of IFD recurrence under SAP of caspofungin varied in different regions and centers [21, 22, 28]. It was difficult to compare them because the group of patients was heterogeneous, with different underlying diseases, different characteristics of previous IFD, different intensity of subsequent therapies, and so on.

So far, to our knowledge, no report has made the comparison between caspofungin given constantly for SAP and oral voriconazole or itraconazole as alternative drugs for subsequent antifungal maintenance prophylaxis therapy after caspofungin as SAP during neutropenia. In our study, we performed a statistical analysis on the differences in recurrence rates relative to different strategies of maintenance therapy for SAP. There was no statistical significant difference (11.1% vs 7.1% vs 8.3%, P = 0.922) (**Table 3**). We also found that oral voriconazole or itraconazole as maintenance antifungal prophylaxis therapy was well tolerated. This study, for the first time, demonstrates that a subsequent antifungal prophylaxis therapy by oral voriconazole or itraconazole after caspofungin as SAP during neutropenia is as effective and safe as caspofungin given constantly throughout the course of SAP. It indicates the possibility of switching from intravenous to oral therapy, which will take many benefits for patients by reducing the need for prolonged hospitalization and daily intravenous therapy, reducing the total costs, and so on. These are important for patients because of quality of life improved and costs reduced.

Previous studies have identified several risk factors associated with the recurrence of IFD under SAP, such as characteristics of prior IFD, status of underlying hematological disease, duration of primary antifungal therapy, duration of neutropenia, time interval from the diagnosis of IFD to transplantation or chemotherapy, acute GVHD, use of corticosteroid, and so on [1, 2, 4, 8, 28]. In our study, we didn't perform an assessment on risk factors for IFD recurrence due to our relatively small sample. However, we found recurrent IFD more frequently occurred in patients undergoing allo-HSCT than in patients undergoing chemotherapy or auto-HSCT either for patients with SAP or without SAP. The probable cause is that allo-HSCT recipients have prolonged neutropenia and receive high-dose corticosteroid and long-term immunosuppressions to prevent or treat GVHD [29]. We also found that patients with SAP conditioning with ATG had higher IFD recurrent rate than that without ATG (21.4% vs 6.7%), although there was no statistical difference (P = 0.330). The use of ATG to allo-HSCT recipients might increase the risk of IFD by increasing a phase of severe immunosuppression.

Our study has several limitations: its uncontrolled and retrospective nature, its small sample and lack of species identification when diagnosing a recurrent IFD, which might affect the evaluation of SAP efficacy, because a recurrence of IFD may be an entirely new IFD and these two types can be difficult to differentiate.

In conclusion, the results of our retrospective study indicate caspofungin is effective and safe to prevent IFD recurrence in hematological malignancy patients undergoing chemotherapy or HSCT. A subsequent maintenance antifungal prophylaxis therapy of oral voriconazole or itraconazole after caspofungin as SAP during neutropenia is as effective and safe as caspofungin given constantly. Sequential prophylaxis therapy with intravenous caspofungin followed by oral voriconazole or itraconazole may be an optimal approach for SAP.

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Disclosure of conflict of interest

None.

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