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Voriconazole in Prevention and Treatment of Febrile Neutropenia

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ABSTRACT

Invasive fungal infections are one of important complication in patients receiving chemotherapy or hematopoietic stem cell transplantation. Voriconazole is a triazole antifungal agent widely used for prophylaxis and treatment of fungal infections. It is also administered for empiric treatment of fungal infections in patients with febrile neutropenia.
Although amphotericin B preparations and fluconazole generally are used for empiric antifungal therapy and antifungal prophylaxis, but it should be noted that there are insufficient data to draw any firm conclusion about use of other new alternatives as drug of choice.
This paper will review the researches that conducted on voriconazole as an empiric antifungal therapy or antifungal prophylaxis in patients with neutropenia following chemotherapy or HSCT.

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Introduction

Antifungal agents have a number of roles such as prophylaxis, empiric treatment and treatment of proven infections in neutropenic patients. The most common cause of fungal infections in this group of patients is *Candida* species or a mold such as *Aspergillus* or *Fusarium* (1). The early diagnosis of invasive fungal infections (IFIs) is quite difficult and a delay in antifungal therapy increases mortality, therefore empirical antifungal therapy in neutropenic patients with persistent fever while receiving broad-spectrum antibiotics, has been the standard of care for many decades (1). The agents like Triazoles, echinocandins, and liposomal preparations of amphotericin B (AMB) are available for empiric antifungal therapy. Need for intravenous administration, high cost and high rates of adverse effects are our major concerns with these drugs (2).

Voriconazole (VCZ) is a triazole antifungal agent with a broad-spectrum activity against certain fungus such as *Aspergillosis*, *Candida* (including fluconazole (FCZ) resistant species), *Fusarium spp*. and *Scedosporium spp*. Therefore it is generally used for the treatment and prevention of IFIs (2,3). VCZ inhibits 14 alpha-lanosterol demethylation, which is an essential step in synthesis of ergosterol as a vital component of fungal membrane that is cytochrome P450 dependent (1). VCZ is metabolized to inactive metabolites primarily by CYP2C19 isoenzyme and minimally by CYP2C9 and CYP3A4 isoenzymes (2). Since CYP2C19 isoenzyme is the major metabolic pathway for the VCZ metabolism, its genetic polymorphism has important role on drug plasma concentrations (4).

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Table 1. Summary of studies of empiric antifungal treatment in Febrile neutropenia included voriconazole

Study (year)	Type of study	Antifungal agent	Number of Patients	Medication dose	Median duration of therapy (days)
Walsh et al (2002)	RCT	VCZ	415	6 mg/kg BD IV in day1 (LD) then 3 mg/kg BD IV or 200 mg BD PO (after at least 3 days of IV therapy)	7
		LAmB	422	3 mg/kg/d	7
Shehab et al (2007)	Retrospective cohort	VCZ	32	6 mg/kg BD IV in day1 (LD) then 3 mg/kg BD IV for 2 days, then 200 mg BD PO	10.4 (mean)
		LAmB	26	3 mg/kg/d	10.9 (mean)
Przepiorka et al (2008)	Retrospective	VCZ	27	6 mg/kg BD IV in day1 (LD) then 200 mg BD PO	11
Hideo Koh et al (2013)	Prospective Clinical trial	VCZ	103	6 mg/kg BD IV in day1 (LD) then 4 mg/kg BD IV (at least for 7 first day), then 200 mg PO BD	11
Oyake et al (2015)	RCT	VCZ	50	6 mg/kg BD IV in day1 (LD) then 4 mg/kg BD IV	9
		Micafungin	50	150 mg/day IV	12

BD: twice daily, IV: intravenous, LAmB: liposomal amphotericin B, LD: loading dose, RCT: randomized controlled trial, PO:per oral, VCZ: voriconazole.

Another key point to remember is about VCZ plasma concentrations. As drug concentrations more than 5–5.5 mg/L are associated with drug- related adverse events and concentrations more than 1–2 mg/L are associated with optimal efficacy (5). There are developing evidences that support the use of therapeutic drug monitoring for VCZ in the majority of patients (6). It should be noted that, hepatotoxicity, visual changes, photosensitivity and hallucination are the most common drug-related adverse events in patients receiving VCZ (7).

Febrile neutropenia is one of the most common complications among patients with hematologic malignancies undergoing chemotherapy or hematopoietic stem cell transplant (HSCT) (8). Empiric antifungal treatment should be initiated immediately in high risk patients with persistent or recurrent fever after 4-7 days of broad-spectrum antibiotic therapy. Immediate administration of appropriate antifungal agent is associated with favorable outcome and reduces the morbidity and mortality in neutropenic patients with persistent fever (8, 11). The possible empiric antifungal options in these patients for presumed IFI are AMB preparations, Itraconazole (ITZ), VCZ or Caspofungin (9). Antifungal prophylaxis is recommended in intermediate and high risk patients with neutropenia following chemotherapy or HSCT to reduce the incidence of fungal infections (10). Agents like FCZ, ITZ, VCZ, posaconazole and caspofungin have been considered as antifungal options for prophylaxis in these patients (8). Although AMB preparations and FCZ generally are used for empiric antifungal therapy and antifungal prophylaxis, but it should be noted that there are insufficient data to draw any firm conclusion about use of other new alternatives as drug of choice (8, 9).

This paper will review the researches that conducted on VCZ as an empiric antifungal therapy or antifungal prophylaxis in patients with neutropenia following chemotherapy or HSCT.

Methods

Our search was performed in the 3 following electronic databases: Medline, Scopus and Cochrane Database of Systematic Reviews. We searched all the literatures which published upon January 2016 investigating VCZ for prophylaxis or treatment of febrile neutropenia. We also investigated through the list of references included in the studies.

The keywords that we used as search terms were "Voriconazole," Vfend," "neutropenia," "febrile neutropenia," "treatment," and "prophylaxis," .

Irrelevant articles (basic experimental studies, non-English language reports and studies that did not include clinical end-point assessments, non-full text articles and case reports) were excluded. A total of 9 relevant human

Table 2. Summary of studies outcome based on the criteria of five-part composite endpoint.

Study (year)	Antifungal agent	Percentage of Patients					
		Success rate	Breakthrough fungal infections	Premature discontinuation of therapy due to toxicity or lack of efficacy	Fever resolution during neutropenia	7 days survival after voriconazole discontinuation	Successful treatment of baseline fungal infections
Walsh et al (2002)	VCZ	26	1.9	9.9	32.5	92	46.2
Walsh et al (2002)	LAmB	30.6	5	6.6	36.5	94.1	66.7
Shehab et al (2007)	VCZ	41	12	37.5	59	100	Patients didn't have baseline fungal infections
Shehab et al (2007)	LAmB	27	12	11.5	54	77	Patients didn't have baseline fungal infections
Hideo Koh etal (2013)	VCZ	31.1	0	16.5	32	95.1	NA
Oyake et al. (2015)	VCZ	NA	13.3	56	62.2	100	Patients didn't have baseline fungal infections
Oyake et al. (2015)	Micafungin	NA	4.1	24	65.3	98	Patients didn't have baseline fungal infections

LAmB: liposomal amphotericin B, NA: no data, VCZ: voriconazole.

studies up to the date of publication were included.

Results

We extracted 9 relevant published studies about VCZ for prophylaxis or treatment of febrile neutropenia. Five studies included VCZ for treatment of febrile neutropenia and four studies included VCZ as prophylaxis in neutropenia.

Voriconazole in treatment of fungal infections

In 2002, Walsh et al., in one open-labeled, prospective, randomized, international, multicenter, comparative trial on 837 patients with febrile neutropenia indicated that not only VCZ wasn't inferior to liposomal AMB as an empiric antifungal agent, but also breakthrough fungal infections, infusion related reactions and nephrotoxicity were lower among patients who received VCZ. The overall success rate in VCZ group was 26% and 30.6% in liposomal AMB group. Breakthrough fungal infections (P:0.02), duration of hospitalization in high risk patients (P:0.03), infusion-related reactions (P<0.01) and nephrotoxicity (P<0.001) were lower in patients who received VCZ but there were more episodes of hallucinations (P<0.001) and visual changes (P<0.001) in VCZ group. There weren't significant differences in hepatotoxicity and overall mortality between two groups (12).

In 2007, Shehab et al., in their Retrospective, cohort study on 55 febrile neutropenic patients demonstrated that empiric VCZ therapy was as effective as liposomal AMB with lower incidence of adverse effects. Survival within 7 days after the end of therapy was higher (P:0.006) in patients treated with VCZ. Resolution of fever (P:0.8) and breakthrough IFIs (P>0.99) were similar between two groups. The incidence of elevated serum creatinine concentration (more than 1.5 fold from baseline at the end of therapy) and electrolyte abnormalities (Hypokalemia or hypomagnesaemia) were significantly higher in patients undergoing treatment with liposomal AMB (P:0.02 and P:0.01, respectively). However, Visual disturbances (P:0.2), elevated liver function tests (P>0.999) and discontinuation of therapy due to lack of efficacy (P:0.4) were observed more in VCZ group, but it wasn't statistically significant. In this study, they switched to liposomal AMB after 72 hours of treatment with VCZ for patients who had persistent fever (13).

In 2008, Przepiorka et al., showed that oral VCZ is a safe and effective empiric antifungal agent in patients with uncomplicated febrile neutropenia. In this retrospective study on 31 episodes of uncomplicated fever and neutropenia in 27 patients with hematologic malignancies, treated with oral VCZ, patients were followed for at least 3 months. Neither of the patients in this study had the signs of IFI on chest radiographs or computed tomographic scans, and nor had the criteria for definite or probable IFI.

The median duration of fever after initiation of VCZ was 4 days (range 0–32 days). In this study 3 months survival rate was 81%. While according to previous studies (5, 9) the median success rate for parenteral drugs was 48%, but the success rate with oral VCZ was 55% in this study. Based on the results of this study, toxicity and premature discontinuation rate were lower with oral VCZ than with ITZ and posaconazole, making it the best option among oral antifungals. There was no patient who discontinuing the antifungal agent due to toxicity or lack of efficacy (14).

In 2013, Hideo Koh et al., demonstrated that empirical VCZ therapy is safe and effective in febrile neutropenic patients with hematologic malignancy or HSCT. In this open label, prospective, multicenter clinical trial on 103 patients, intravenous VCZ was administrated at least for 7 days in patients with persistent febrile neutropenia after 3 days of broad-spectrum antbiotic therapy. Then, Intravenous VCZ was switched to oral form. Clinical efficacy (defined as fever resolution and 7 days survival after VCZ discontinuation), treatment success (defined as achievement to all criteria of the composite endpoint), the resolution of fever during neutropenia and breakthrough fungal infection were observed in 68.9 %, 31.1%, 32% and 0% of patients, respectively. In seven patients treated with oral VCZ from the beginning of therapy for some reasons, clinical efficacy (57.1%) and treatment success (14.3%) were lower and the article doesn't support the use of oral therapy except in cases of severe renal dysfunction. Empiric antifungal therapy with VCZ was discontinued because of toxicity (abnormal vision and liver toxicity) and lack of efficacy in 9.7% and 5.8% of patients, respectively (15).

In 2015, Oyake et al., in an open-label, prospective, randomized, multicenter, comparative trial demonstrated that although VCZ was as effective as micafungin in patients with febrile neutropenia, but in tolerability, VCZ was inferior to micafungin. This study was conducted on 100 patients with persistent febrile neutropenia who were treated empirically with broad spectrum antibiotics for 4-7 days. Breakthrough fungal infection (P:0.1), Survival for more than seven days after treatment (P:0.3), fever resolution during neutropenia (P:0.9) and discontinuation of antifungal drug because of poor efficacy (P:0.6) did not differ significantly between two groups. Premature discontinuation of antifungal agent due to toxicity was observed more (P: 0.007) in

VCZ group (16).

Voriconazole as Prophylaxis in patient with febrile neutropenia

In 2007, the Riedel et al., in a retrospective, observational cohort study on 370 patients with chemotherapy induced neutropenia suggested that prophylaxis with azoles (VCZ in high risk patients and FCZ in low risk patients) is preferred over conventional AMB. This conclusion was based on both the lower incidence of mild to moderate (P<0.0001) and severe renal dysfunction (P<0.001) in patients treated with azoles compared with conventional AMB and the availability of oral dosage forms of azoles. However, cost and incidence of severe hepatic toxicity (P:0.05) were higher in VCZ prophylaxis group compared with amphotericin or FCZ group. The incidence of breakthrough *Aspergillus* infection didn't differ significantly between azoles and AMB group (17).

In 2010, Wingard et al., in one randomized, double-blind, multicenter trial on 600 post allogeneic HSCT patients demonstrated that prophylaxis with VCZ resulted in overall survival similar to that of FCZ. In this study, 305 patients received VCZ and 295 patients received FCZ from days 0 to 100 or 180 (in higher risk patients) post transplantation as an antifungal prophylaxis agent. The incidence of invasive fungal disease in VCZ group at 18 months was 7.3% and 11.2% in FCZ group (P:0.12), and at 12 month was 12.7% and 13.7% respectively (P:0.6). The incidence of invasive *aspergillus* infection was greater significantly in FCZ group (P:0.09). There were not any significant differences in fungal-free survival and overall survival between two groups at 6 and 12 months. Drug toxicity profile was also similar between two groups (18).

In 2011, Marks et al., in a prospective, randomized, open-label, multicenter trial showed that prophylaxis with VCZ was superior to ITZ in patients undergoing allogeneic HSCT. In this study, 234 patients received VCZ and 255 patients received ITZ from days 1 to 100 or 180 (in higher risk patients for IFIs) post transplantation. Success of antifungal prophylaxis in this trial at day 100 was 54% and 39.8% (P<0.01) and at day 180 was 48.7% and 33.2 % (P = 0.0002) in VCZ group and ITZ group, respectively. More patients also tolerated VCZ for rather than 100 days (53.6% vs. 39%, P<0.01). Adverse gastrointestinal reactions were detected more in ITZ group, but the incidence of hepatotoxicity and visual abnormality were higher significantly in VCZ group. There weren't any significant differences between two groups in survival and incidence of IFI (19).

In 2014, in a single-center cohort study, Ting-Chi Yeh et al., administered Ciprofloxacin and VCZ in patients with childhood ALL and AML who were receiving intensive chemotherapy and compared the outcomes parameters in prophylaxis period with pre-prophylaxis period. Ciprofloxacin and VCZ were administrated when patients became neutropenic. This prophylaxis regimen significantly reduced total episodes of IFIs in induction, consolidation and re-induction regimen (P<0.01) and febrile neutropenia episodes (P<0.01) in neutropenic patients with ALL. Total episodes of blood stream infections in induction, post remission high-dose and post remission modest-dose (P<0.01), total episodes of IFIs

Table 3. Summary of studies of antifungal prophylaxis in neutropenia included voriconazole.

Study (year)	Type of study	Antifungal agent	No. of Patients	Underlying disease	Medication dose (mg/day)	Authors' Conclusions
Riedel et al (2007)	Cohort	Voriconazole (In high risk patients)	84	Hematologic malignancy undergoing chemotherapy or HSCT	200 mg BD per day (PO)	prophylaxis with Azoles is preferred over conventional amphotericin B. (because of lower incidence of renal toxicity and availability of oral dosage)
		Fluconazole (In low risk patients)	237		400 mg/day (PO)	
		conventional amphotericin B	259		0.3 to 0.7 mg/kg/ day IV	
Wingard et al (2010)	Randomized trial	Voriconazole	305	Hematologic malignancy following Allo-HSCT	200 mg BD per day (PO)	Although overall survival and the incidence of invasive fungal disease didn't differ between two groups, but the incidence of invasive Aspergillus infection was greater significantly in fluconazole group.
		Fluconazole	294		400 mg/day (PO)	
Marks et al (2011)	Randomized trial	Voriconazole	234	Hematologic malignancy following Allo-HSCT	200 mg BD per day (PO)	Prophylaxis with voriconazole was superior to itraconazole. (voriconazole was more tolerable than Itraconazole)
		Itraconazole	255		200 mg BD per day (PO)	
Ting-Chi Yeh et al (2014)	Cohort	Voriconazole	109 (number of Courses of Voricoazole)	AML undergoing chemotherapy	4 mg/kg BD (PO)	Prophylaxis with voriconazole (concomitant use of ciprofloxacin) reduced the rate of severe infections, episodes of febrile neutropenia and mortality

AML: acute myeloblastic leukemia, BD: twice daily, HSCT: hematopoietic stem cell transplant IV: intravenous, LD: loading dose, PO: per oral.

in induction, consolidation and re-induction regimens (P<0.01) were significantly reduced in prophylaxis period compared with pre-prophylaxis period. Prophylaxis also reduced the episodes of blood stream infections (P:0.02) and the length of ICU stay (P:0.01) in patients with ALL and febrile neutropenia (P:0.01) and death (P:0.03) in patients with AML. According to the result of this study breakthrough fungal infections with FCZ prophylaxis occurred but VCZ demonstrated more effectiveness in preventing IFI in patients after HSCT (20).

Discussion

IFI is one of the most important complications in neutropenic patients following chemotherapy or HSCT. According to ASCO guideline, empiric antifungal therapy should be initiated 4 to 7 days after administration of broad-spectrum antibiotics in patients with persistent neutropenia and fever (9), because early and appropriate treatment of IFIs can decrease mortality in this population and quick diagnosis of IFI is difficult (21). Lipid formulation of AMB, VCZ and caspofungin are acceptable antifungal agents for empiric therapy (8).

The available evidences seem to suggest that VCZ is a proper option for empiric treatment of febrile neutropenia. Efficacy, tolerability and cost are three important aspects for selection of appropriate antifungal agent in patients with neutropenia and persistent fever. In accomplished studies, efficacy and safety of VCZ was comparable with liposomal AMB and micafungin. Efficacy was evaluated in 4 of 5 accessible studies based on five criteria of the composite endpoint (Table 4).

Przepiorka et al., didn't use five criteria of the composite endpoint for evaluation of efficacy. In this study, treatment success with oral VCZ was defined as fever resolution without any antibiotic change and without the incidence of new fungal infection. They also assessed 3-month survival and premature antifungal discontinuation and compared the results with previous studies that were done on different antifungal agents. Treatment success with oral VCZ was more than median treatment success rate obtained from previous studies by various antifungal agents. Adverse effects and premature antifungal discontinuation were lower in comparison with different antifungal agents in other studies. Although they concluded that oral VCZ is cost-effective and safe, but It is important to note that the number of the patients was low (27 patients) and the study was not done as randomized clinical trial.

Walsh et al., in 2002 compared VCZ with liposomal AMB as an empiric antifungal agent in persistently neutropenic patients. Although they did not prove that VCZ isn't non-inferior to liposomal AMB, but they reported significantly lower incidence of breakthrough fungal infections, infusion-related reactions and nephrotoxicity in the

Table 4. Five criteria of the composite endpoint.

• Fever resolution during neutropenia
• No breakthrough fungal infection
• Premature discontinuation of therapy due to toxicity or lack of efficacy
• 7 days survival after voriconazole discontinuation
• Successful treatment of baseline fungal infections

VCZ treated patients. However outcomes about fever resolution, 7 days survival and premature discontinuation of therapy and successful treatment of baseline fungal infections were better in liposomal AMB group. After subgroup analysis, they found that high risk patients treated with VCZ had better outcome in comparison with liposomal AMB and concluded that high risk patients for IFIs should receive VCZ.

In one retrospective study conducted by Shehab et al., efficacy of VCZ was not inferior to liposomal AMB. Although VCZ was superior to liposomal AMB in success rate and in all criteria of the composite endpoint, but the significant difference only in survival rate was found. They didn't assess successful treatment of baseline fungal infections because patients with documented baseline fungal infections were excluded. Furthermore, they found that adverse effects and costs were lower in VCZ group. Although the type of study design was observational and retrospective, that is considered inferior to prospective study, but two groups were well balanced. In one prospective study conducted by hideo Koh et al., in Japan in persistently neutropenic patients, success rate with VCZ as an empiric antifungal agent was superior to VCZ or liposomal AMB in Walsh et al., clinical trial. Similarly, all components of composite endpoint (except fever resolution) favored VCZ when compared with liposomal AMB in Walsh et al., study.

Oyake et al., compared VCZ with micafungine for empiric treatment of febrile neutropenia. Although clinical efficacy based on five criteria of the composite endpoint outlined by Walsh et al., were similar between two treatment groups, but there were more adverse effects and premature drug discontinuations in VCZ group. The limitation of this study was the small number of patients that were recruited (50 patients in each group).

Based on current studies, VCZ is an effective antifungal agent for fungal infection prophylaxis in patients with neutropenia. Riedel et al., demonstrated that VCZ reduced the incidence of breakthrough fungal infections similar to conventional AMB in high risk hematology/oncology patients with lower episodes of renal dysfunctions. In comparison with FCZ that was used in low risk patients, the incidence of breakthrough fungal infection was lower in high risk patients who received VCZ. All episodes of breakthrough *candida* infections and most episodes of severe breakthrough *Aspergillus* infections happened in low risk patients who received FCZ. Wingard et al., also found that prophylaxis with VCZ reduced the incidence of *Aspergillus* infections compared with FCZ in patients undergoing HSCT. It is important to note that overall survival didn't differ between VCZ and FCZ or ITZ patients in post HSCT. However, VCZ prevented better from IFI and the incidence of *Zygomycetes* infections didn't differ significantly between patients who received VCZ or FCZ as an antifungal prophylaxis.

It was demonstrated that VCZ is more effective than ITZ, another anti-mold agent. Because of higher incidence of gastrointestinal toxicity, patients treated with ITZ were not able to continue prophylaxis period as much as patients received VCZ. Although the incidence of hepatotoxicity and visual abnormalities were higher in VCZ group, but VCZ patients tolerated the prophylaxis for longer period of time. Riedel et al., demonstrated that although prophylaxis with VCZ was a successful strategy in neutropenic patients, but the rate of severe hepatotoxicity was greater compared with patients treated with FCZ or conventional AMB. On the other hand, Wingard et al., demonstrated that drug toxicity profile didn't differ between FCZ group and VCZ group. It was shown that conventional AMB caused more episodes of renal dysfunctions compared with VCZ or FCZ as a prophylaxis antifungal agent.

Conclusion

This study demonstrates that voriconazole can be an appropriate agent for prophylaxis and empirical therapy in neutropenic patients with persistent fever. Its use may preserve renal function and has fewer acute infusion-related toxic effects while its efficacy is not inferior to liposomal AMB and the oral dosage form is also available.

We should consider that the limitation of VCZ as the primary antifungal agent is the potential for serious cytochrome P450-based drug-drug interactions, the development of infections from Zygomycetes species, the need for therapeutic drug monitoring and possibility of hepatotoxicity.

Further research, including randomized controlled trial comparing the efficacy of voriconazole versus amphotericin B and echinocandins is needed.

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