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Newer antifungal agents micafungin and voriconazole for fungal infection prevention during hematopoietic cell transplantation: a meta-analysis

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Abstract. – OBJECTIVE: The new antifungal agents provide further opportunities for effective prophylaxis for fungal infections during stem cell transplantation for patients with hematologic malignancies; however, the efficacy of these antifungal prophylactic drugs has not yet been established. This study was to compare the newer antifungal agents micafungin and voriconazole for prophylaxis effects on the clinical outcomes.

MATERIALS AND METHODS: We electronically searched the database of Cochrane Central Register of Controlled Trials, Pubmed, EMbase, and relevant database articles (1996.01-2013.12). Comparative studies were carried out on proved fungal infections, mortality, and adverse effects. Meta-analysis was performed by Review Manager 5.1.6 software and the funnel plot regression was adopted to assess the publication bias.

RESULTS: We found 1508 records and 13 studies totaling 3767 patients included in analyses. Pooled comparisons of studies found that antifungal prophylaxis with the new agents does reduce the incidence of invasive fungal infections than fluconazole or itraconazole. The reduction in invasive fungal infections was achieved by using micafungin, voriconazole for antifungal prophylaxis. Using voriconazole prophylaxis can decrease the transplant mortality compared with fluconazole or itraconazole prophylaxis. Voriconazole had higher rates of liver dysfunction, lower gastrointestinal side effects over fluconazole, and lower rates of nephrotoxic effects than amphotericin B. Both micafungin and voriconazole had a significant decrease in adverse events requiring drug discontinuation compared with itraconazole.

CONCLUSIONS: This analysis indicated the 2 agents appear to be well tolerated with manageable side effects and beneficial in the prophylaxis of IFI. Further work is needed with a large scale of random controlled trials on the effect of these drugs.

Key Words:
Fungal infection, Stem cell transplant, Meta-Analysis, Outcome, Prophylaxis.

Introduction

Fungal infections are a significant cause of morbidity and mortality for neutropenic patients during hematopoietic stem transplantation (HSCT)[1-3]. The risk of fungal infection is especially increased in patients with refractory leukemia who received corticosteroids or widely used antibodies. As these infections are often difficult to diagnose and have no specific clinical features, the use of antifungal prophylaxis in these patients is popular, but the effects is uncertain. Over the past 20 years, a series of studies have evaluated the usefulness of antifungal prophylaxis agents in prophylaxis for fungal infections in these patients, he studied agents have included fluconazole[4], amphotericin B[5], and itraconazole[6,7]. Randomized trials and meta-analyses have shown reduction of the risk of invasive *Candida* infections using fluconazole and itraconazole[8,9].

In recent years, the advent of newer antifungal agents provides further opportunities for effective secondary prophylaxis. Voriconazole is an triazole agent with a broad spectrum of activity against opportunistic fungi with clinical efficacy against invasive aspergillosis[10], and has been recommended in international guidelines as primary therapy for acute invasive aspergillosis. Micafungin was launched in Japan in 2002, is a new member of the echinocandin class of antifungals effective against both *Candida* and *Aspergillus*, and preliminary clinical studies have shown good antifungal activity[11-12]. It has been approved by the US Food and Drug Administration for antifungal prophylaxis during the pre-engraftment phase in patients undergoing hematopoietic stem cell transplantation. Because amphotericin B is associated with severe renal toxicity, fluconazole has a limited spectrum of activity, the selection of an appropriate antifungal treatment is very important for HSCT patients. The two drugs, micafungin and voriconazole are

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often used for antifungal prophylaxis during this transplant[13-14,23]. However, few clinical reports have been published regarding the efficacy and safety with micafungin and voriconazole in patients with hematological diseases during HSCT. The aim of this study was to compare the newer antifungal agents micafungin and voriconazole for antifungal prophylaxis after transplantation on the clinical outcomes, i.e. the clinical proved infection, mortality, and adverse infections.

Materials and Methods

Search between 1996.01 and 2013.12 were eligible for analysis of antifungal prophylaxis and outcome for hematological patients during transplantation. We systematically reviewed all data on comparative studies of different antifungal prophylaxis.

Search Strategy

We performed a literature search using the databases were Pubmed (1996.01-2013.12), EMBASE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Review, IPA, DIF and the Center for International Blood and Marrow Transplant Research (CIBMTR). The search "key words" used were stem cell transplant, micafungin or voriconazole, antifungal prophylaxis, and invasive fungal infections. Our search was limited to prospective, randomized clinical trials, review articles, case reports, and abstracts reported in English language. References of retrieved articles were also checked for any relevant trials. Two reviewers (XF T, and HQ X) independently evaluated each study and abstracted the relevant information. Disagreement on the specific studies to be included in the analysis between the two reviewers was resolved through discussion. The hand search included an electronic or manual search of the table of contents as well as abstracts of conference proceedings of the various societies published in related journals. The included study characteristics (author, published year, study design, sample size, patient age, treatment regimen, diseases, source of stem cell, the number of outcome events and adverse events) were recorded into standardized abstraction data forms. The primary outcome measurements were: (i) Prevalence of invasive fungal infections (ii) all causes of mortality during the antifungal drug treatment; (iii) response to treatment; and (iv) toxicity. Secondary outcome measurements included all antifungal drug administrations during each hospital admission. Overall mortality was defined as death that occurred over the study period.

Statistical Analysis

To estimate the treatment effects, outcomes were calculated as odd ratio (OR) and their 95% confidence intervals (CI). The pooled effect estimates calculated using the Review Manager 5.1.6 statistical package and adopted funnel plot regression or Egger method[15] to assess the publication bias. The I^2 statistic was used to assess statistical heterogeneity, with $I^2 > 50\%$ considered to indicate significant result heterogeneity, that a random effects model was used to estimate the overall treatment effect under this circumstances. Publication bias assessed using a funnel plot of effect size against standard error. The possibility of publication bias was assessed using the Begg test and visual inspection of a funnel plot[15]. We also performed the Duval and Tweedie[16] nonparametric "trim and fill" procedure to assess the possible effect of publication bias in the meta-analysis, a *p*-value below 0.05 was considered statistically significant in all analyses.

Results

Trial Searches and Study Characteristics

Bibliographic search yielded 1508 articles. Of which, 1495 were excluded for irrelevant reports (n = 1185), duplicates (n = 252), review data (n = 24), absence of control group (n = 25), and absence of statistical data (n = 9), in all 13 complete data trials[17-29] totaling 3767 patients included in this meta-analyses (Figure 1), 7 studies for micafungin prophylaxis and 6 studies for voriconazole prophylaxis. The Table I described the characteristics of included studies. Patient age was from 0.6 to 86 years old and the follow-up time was from 28 days to 3 year.

Outcomes

Prevalence of Invasive Fungal Infections (IFIs)

Micafungin for Antifungal Prophylaxis

Proven infection was defined as biopsy-proven invasive or disseminated infection. As shown in Table II, only 1 study compared micafungin with placebo control[17]. The result showed that the mi-

Figure 1. Flow chart of study inclusion process.

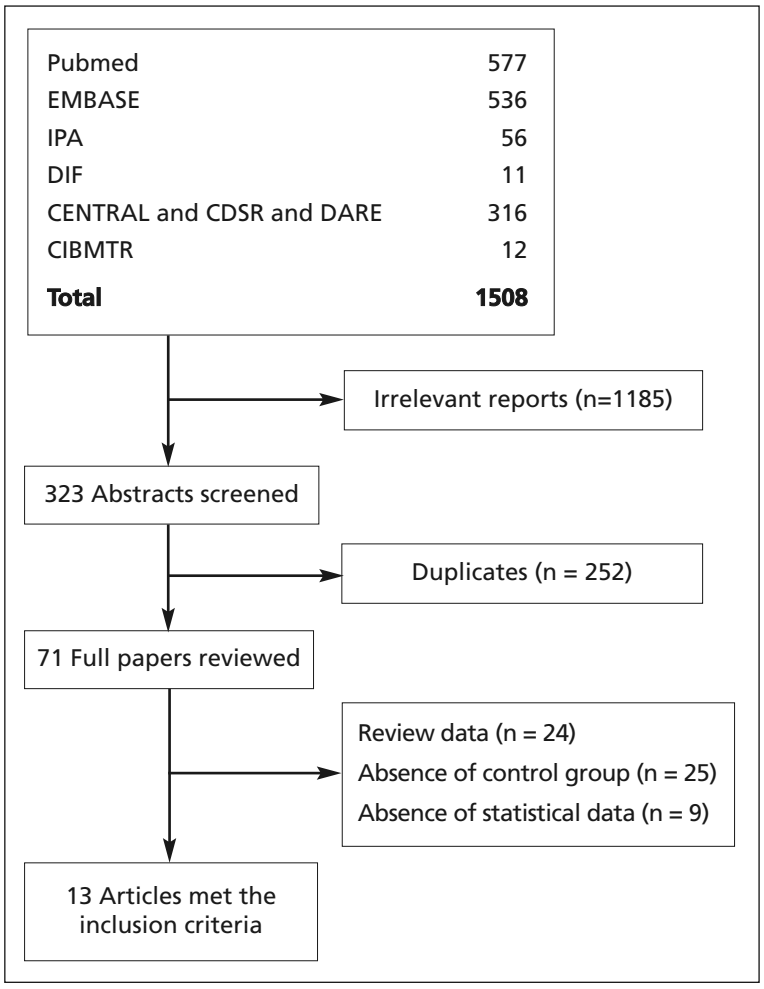

Table I. Characteristics of included studies.

Author	Pub. yr	No. patients (Tre/Con)	Design	Age (yr)	Tre	Con	Diseases	Type of Tre	Follow -up
Hirata et al[17]	2010	43/24	ROS	19-82	Mic	Pla	Hem Dis	CT, Auto, Allo	NA
Hashino et al[18]	2008	44/29	RCT	16-69	Mic	Flu	Hem Dis	Allo	49d
Hiramatsu et al[19]	2008	50/50	RCT	16-67	Mic	Flu	Hem Dis	Auto, Allo	70d
van Burik et al[20]	2004	215/621	RCT	0.6-73	Mic	Flu	Hem Dis	Auto, Allo	70d
Riedel et al[21]	2007	321/259	RCT	18-86	Vor	Flu	Hem Dis	CT, Auto, Allo	23d
Hiemenz et al[22]	2005	62/12	RCT	19-65	Mic	Flu	Hem Dis	Auto, Allo	28d
Wingard et al[23]	2010	305/295	RCT	2.7-65.7	Vor	Flu	Hem Dis	Allo	180d
Gergis et al[24]	2010	97/72	RCT	-	Vor	Flu/Itr	Hem Dis	Allo	100d
Marks et al[25]	2011	224/241	RCT	11-70	Vor	Itr	Hem Dis	Allo	360d
Kubiak et al[26]	2010	174/149	ROS	18-86	Mic	Cas	Hem Dis	Auto, Allo	63d
Huang et al[27]	2012	136/147	RCT	18-70	Mic	Itr	Hem Dis	Auto, Allo	56d
Salmeron et al[28]	2012	42/45	ROS	5-57	Vor	AmB	Hem Dis	Allo	36m
Döring et al[29]	2013	50/50	RCT	<18	Vor	Cas, Itr Itr	Hem Dis	Allo	220d

Pub. published; yr, year; Tre, treatment; Con, control; Pla, placebo; RCT, random controlled trial; ROS, retrospective observational study; Mic, micafungin; Vor, voriconazole; Cas, caspofungin; Flu, fluconazole; Itr itraconazole; AmB, amphotericin B; Hem, hematological; Dis, disease; Allo, allogeneic; Auto, autologous; SCT, stem cell transplantation; NA, not applicable.

Table II. Meta-analysis of proven infection.

Drugs	No. Studies	Patients (Yes/All)	I^2	I^2 (P Value)	OR*p* (95% CI)	*p* value
Mica vs control	1	3/43 9/24			0.13 (0.03, 0.52)	0.005
Mica vs Flu	4	23/613 25/516	0%	0.94	0.41 (0.21, 0.80)	0.009
Mica vs Casp	1	21/174 16/149			1.14 (0.57, 2.28)	0.71
Vori vs AmB	2	52/517 39/418	69%	0.07	0.91 (0.36, 2.32)	0.85
Vori vs Flu/Itra	3	10/626 21/608	0%	0.51	0.43 (0.20, 0.92)	0.03

Mica, micafungin; Vori, voriconazole; Flu, fluconazole; Itra, itraconazole; AmB, amphotericin B.

cafungin prophylaxis had significant reductions in invasive fungal infection (OR 0.13 [95% CI, 0.03-0.52], $p = 0.005$) over the placebo group.

Four clinical trials compared the IFIs between micafungin and fluconazole for antifungal prophylaxis and the detail is shown in Figure 2.

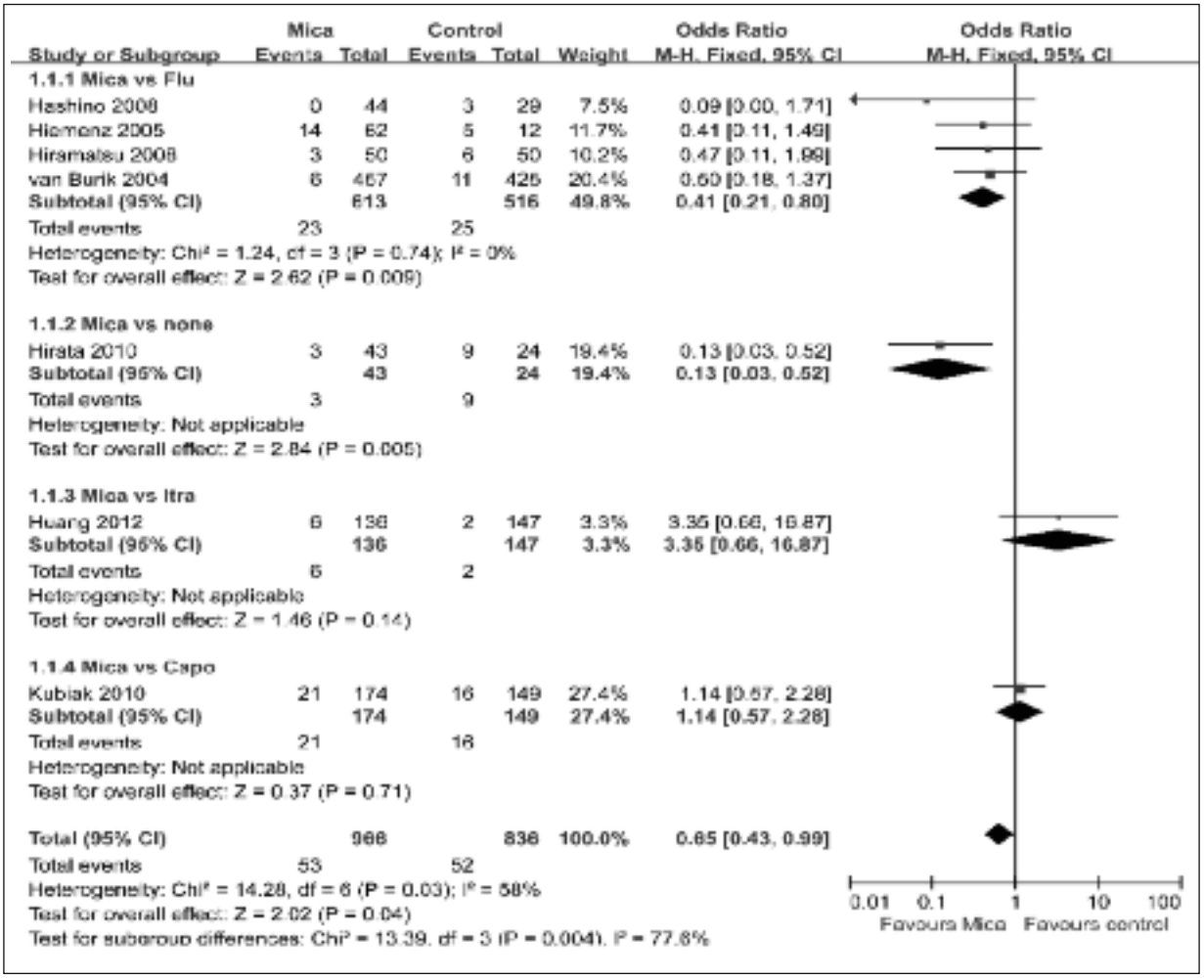

Figure 2. Micafungin and other antifungal prophylaxis on prevalence of invasive fungal infections. Mic, micafungin; Capo, caspofungin; Flu, fluconazole; Itra, itraconazole;

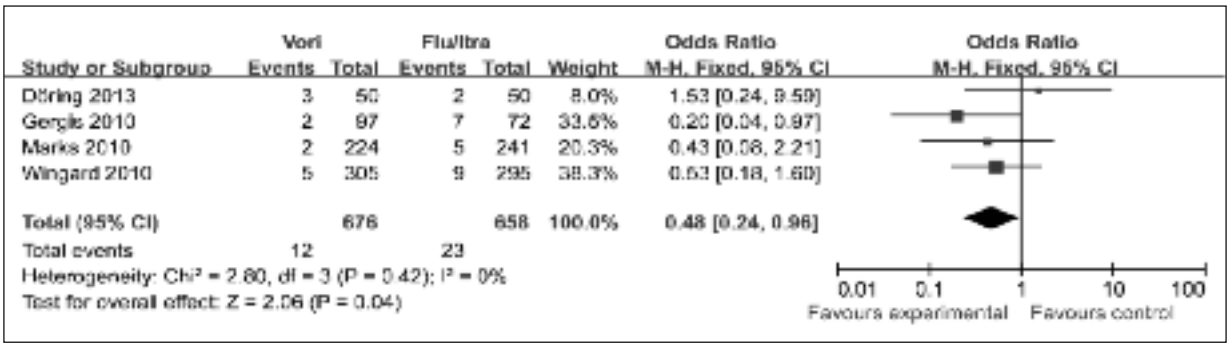

Figure 3. Voriconazole and fluconazole for antifungal prophylaxis on prevalence of invasive fungal infections.

All of the studies showed a non-significant effect in the rate of IFIs; however, the pooled result indicated that the IFIs was significantly lower in micafungin group than that in fluconazol group (3.75% *vs* 4.84%, OR 0.41 [95% CI, 0.21-0.80], $p = 0.009$). This means micafungin for antifungal prophylaxis during SCT can significantly reduced the occurrence of proven invasive fungal infections over fluconazole by about one-half. There was no evidence of heterogeneity or inconsistency among these studies for the IFIs outcome ($I^2 = 0\%$; $p = 0.74$), indicating that the trials were similar and the fixed-effects model was used to estimate the overall treatment effect. No difference found in *IFIs* between micafungin and itraconazole or caspofungin for antifungal prophylaxis (Figure 2).

Voriconazole for Antifungal Prophylaxis

As shown in Figure 3, the proven invasive fungal infections occurred during the phase in 12 of the 676 patients (1.78%) in the voriconazole group and in 23 of 658 patients (3.45%) in the fluconazole or itraconazole group (OR 0.48 [95% CI, 0.24-0.96], $p = 0.04$), which indicated that voriconazole prophylaxis led a lower risk of fungal infections than fluconazole or itraconazole. In the same, patients with micafungin or voriconazole for antifungal prophylaxis had lower risk of IFIs than that with fluconazole or itraconazole ($p = 0.009$ and $p = 0.03$ respectively, shown in Table II). No difference found in *IFIs* between or micafungin and capofungin or voriconazole and AMB for antifungal prophylaxis ($p = 0.71$ and $p = 0.85$ respectively).

Mortality from Proven Invasive Fungal Infections

Mortality from any cause was extracted from all trials and the result was showed in Table III. The fatality rate occurred with voriconazole prophylaxis was significantly lower than that with fluconazole or itraconazole prophylaxis (OR 0.76 [95% CI, 0.58-1.00], $p = 0.05$), which corresponded to nearly 25% reduction. The difference between micafungin *vs* fluconazole or micafungin vs caspofungin was not statistically significant.

Adverse Reactions

As shown in Table IV, a total of 55 voriconazole-treated patients and 21 micafungin-treated patients experienced liver dysfunction. Voriconazole group had higher rates of liver dysfunction

Table III. Meta-analysis of mortality.

Drugs	No. Studies	Patients (Yes/All)	I^2	I^2 (P Value)	ORp (95% CI)	p value
Mica vs control	1	0/43 4/24			0.05 (0.00, 1.02)	0. 05
Mica vs Flu	4	28/581 31/548	0%	0.88	0.79 (0.46, 1.36)	0.39
Mica vs Casp	1	13/174 12/149			0.92 (0.41, 2.09)	0.85
Vori vs Flu/Itra	5	113/718 141/703	61%	0.04	0.76 (0.58, 1.00)	0.05

Mica, micafungin; Casp, caspofungin; Flu, fluconazole; Itra, itraconazole.

Table IV. Meta-analysis of adverse reactions.

Adverse reactions	Drugs	No. Studies	Patients (Yes/All)	I^2	I^2 (p value)	OR (95% CI)	*p* value
Liver function	Mica	3	12/521	0%	0.64	0.93 (0.42, 2.04)	0.86
	vs Flu		13/538				
	Mica	1	9/137	-	-	1.41 (0.51, 3.89)	0.51
	vs Itra		7/147				
	Vori	1	26/80	-	-	1.79 (1.01, 3.16)	0.05
	vs Flu		46/217				
	Vori	1	29/224	-	-	2.84 (1.41, 5.71)	0.003
	vs Itra		12/241				
Renal Function	Mica	1	6/96	-	-	1.11 (0.34, 3.59)	0.86
	vs Flu		5/81				
	Mica	1	6/137	-	-	6.69 (0.79, 56.28)	0.08
	vs Itra		1/147				
	Vori	1	26/80	-	-	1.79 (1.01, 3.16)	0.05
	vs Flu		46/217				
	Vori	1	31/321	-	-	0.17 (0.11, 0.27)	$<$0.0001
	vs AmB		99/259				
Rash	Mica	2	3/469	0%	0.98	2.11 (0.31, 14.56)	0.45
	vs Flu		1/486				
	Mica	1	39/149	-	-	1.11 (0.67, 1.84)	0.67
	vs Casp		42/174				
GI	Vori	2	35/274	14%	0.25	0.25 (0.16, 0.38)	$<$0.0001
	vs Itra		106/291				
	Mica	1	0/137				
	vs Itra		12/147	-	-	0.04 (0.00, 0.67)	0.03
Fever	Mica	1	13/425	-	-	2.37 (0.89, 6.30)	0.08
	vs Flu		6/457				
	Mica	1	23/137	-	-	1.29 (0.47, 1.28)	0.44
	vs Itra		20/147				

Mica, micafungin; Vori, voriconazole; Casp, caspofungin; Flu, fluconazole; Itra, itraconazole; AmB, amphotericin B; GI, gastrointestinal reactions.

over fluconazole and itraconazole treated group ($p = 0.05$ and $p = 0.003$ respectively), no difference between micafungin and fluconazole for antifungal prophylaxis. Moreover, both the voriconazole and micafungin group had lower risk of gastrointestinal side effects than itraconazole (OR = 0.25 and OR = 0.04 respectively). As respected, hypokalemia, and renal-related adverse events were more common in the amphotericin B group than voriconazole group. More patients in the amphotericin B group had nephrotoxic effects (24.8 percent, vs. 9.7 percent in the voriconazole group). The prevalence of other adverse events such as fever and rash between micafungin and fluconazole was similar.

Adverse Events Requiring Discontinuation

A significant decrease in adverse events requiring discontinuation was observed in the micafungin and voriconazole prophylaxis group compared with the itraconazole group (OR = 0.03 and OR = 0.43 respectively; Table V). No difference was found between micafungin and fluconazole or other antifungal agents. The reasons for interrupting voriconazole treatment mainly included abnormal liver function parameters, for interrupting micafungin treatment mainly included fever and treatment-related gastrointestinal side effects, the most often reported reason for drug discontinuation in itraconazole was gastrointestinal side effects (nausea, vomiting and diarrhea).

Discussion

As early diagnosis of IFIs is difficult and the treatment is challenging, the antifungal prevention is important for HSC patients[30]. The goal of primary antifungal prophylaxis is to prevent morbidity and mortality from IFIs. Risk factors for fungal infection in allogeneic HSCT recipients include bowel mucosal damage from cytotoxic chemotherapy, neutropenia, use of central intra-

Table V. Meta-analysis of adverse reactions to stop use.

Drugs	No. Studies	Patients (Yes/All)	I^2	I^2 (P Value)	ORp (95% CI)	p value
Mica vs control	1	3/43 0/24			4.23 (0.21, 85.51)	0.35
Mica+Flu vs Flu	2	24/411 18/336	0%	0.94	1.16 (0.62, 2.17)	0.64
Mica vs Flu	2	74/507 83/475	58%	0.12	0.81 (0.17, 1.14)	0.22
Mica vs Itra	1	1/137 29/147			0.03 (0.00, 0.22)	$<$0.001
Mica vs Casp	1	2/174 3/149			0.57 (0.09, 3.43)	0.54
Vori vs Itra	1	31/224 66/241			0.43 (0.27, 0.68)	$<$0.001

Mica, micafungin; Casp, caspofungin; Flu, fluconazole; Itra, itraconazole.

venous catheters and immunosuppressive therapy for graft-versus-host disease (GVHD). Moreover, single trials for antifungal prophylaxis sometimes do not achieve an adequate statistical power to detect a statistically significant difference which can be overcome by meta-analysis. Meta-analysis has been shown its validity in combining data from many trials for clinical requirements[31]. In this meta-analysis, we have included data from 13 randomized clinical trials evaluating the effect of antifungal prophylaxis in 3767 patients undergoing hematological stem cell transplantation. Our analysis indicated that use of primary antifungal prophylaxis in the highest risk patients is benefit for preventing morbidity and mortality due to IFIs. The results indicated that using micafungin, and voriconazole for antifungal prophylaxis significantly reduced the prevalence of proven invasive fungal infections over fluconazole, and itraconazole, and voriconazole prophylaxis also reduced the mortality from IFIs with less renal-related adverse events or gastrointestinal side effects than amphotericin B or itraconazole.

For many years, fluconazole has been the antifungal drug of choice for primary prophylaxis in HSCT recipients[32]. It has activity against yeasts (e.g., *Candida* sp.), but not against *Aspergillus* species and other molds which led to an unacceptable increase in infections from filamentous fungi and resistant yeasts during HSCT[33]. Fluconazole also can penetrate the central nervous system (CNS) and eye, making it a valuable drug for maintenance therapy for meningitis and endophthalmitis[34]. Licensed mold-active azoles include itraconazole, voriconazole and posaconazole. They have a broad spectrum of antifungal activity that includes *Candida* sp., *Aspergillus* sp. and rarer molds. The poor oral bioavailability of itraconazole and drug interaction profile made it a less desirable agent for prophylaxis in HSCT recipients, although It has been proved itraconazole for prophylactic use was as effective as fluconazole or even better[35]. Voriconazole has activity against *Candida* and *Aspergillus* species and is available orally and intravenously. Voriconazole has also been evaluated for prophylaxis in allo-HSCT recipients in a large randomized trial that published in "Blood" journal[23]. In this study, six hundred patients were randomized to test voriconazole superiority in the primary endpoint of failure-free survival (FFS). The findings suggested that voriconazole failed to meet superiority in the failure-free survival FFS endpoint, but there were trends to fewer IFIs, specifically invasive aspergillosis, in the voriconazole treated group. Treatment with either itraconazole or voriconazole may be hampered by drug-related toxicity, significant drug interactions, or other pharmacokinetic obstacles. All azoles can cause hepatotoxicity, usually reversible hyperbilirubinemia or liver enzyme abnormalities. Abdominal adverse effects include anorexia, nausea, vomiting, diarrhea, or abdominal pain. Voriconazole had higher rate of liver and renal dysfunction over fluconazole-treated patients. A significant decrease in adverse events requiring discontinuation was observed in the voriconazole prophylaxis group compared with the itraconazole group[25]. Despite the higher prevalence of treatment-related hepatic adverse events reported with voriconazole, patients were

able to continue voriconazole for longer periods than itraconazole which led higher prevalence of gastrointestinal side effects including nausea, vomiting and diarrhoea.

The echinocandins are fungicidal against *Candida* species including the azole-resistant isolates by damage the fungal cell wall synthesis. Representatives of the echinocandins include caspofungin, micafungin, and anidulafungin[36], of which caspofungin has been licensed in the United States and the European Union since 2001 for second-line treatment of invasive aspergillosis in patients who are refractory to or intolerant of other agents[37]. The use of micafungin was not associated with nephrotoxicity or infusion-related reactions that commonly observed in patients receiving amphotericin B. Our analysis showed decreased rates of fungal infection during transplantation with micafungin compared with fluconazole. In addition, both caspofungin and voriconazole have a better safety profile than both azoles and polyenes. Thus, for empirical treatment of candidemia, echinocandins may be considered as first-line treatment. Micafungin is an alternative prophylactic agent[38], as studies have shown it to be better than fluconazole for preventing possible or documented fungal infections[18-20,22], but use of micafungin as a prophylactic agent is limited by the necessity of i.v. infusion and higher cost.

In this meta-analysis, we observed that the use of echinocandins is associated with a lower risk of liver injury. Since echinocandins and fluconazole are mostly used for the treatment of candidiasis and not aspergillosis, this may partially contribute to the low prevalence of hepatic dysfunction associated with these drugs. Amphotericin B and the echinocandins are available only in intravenous formulations. The availability of both oral and intravenous formulations of fluconazole and voriconazole has made these agents easier to use in HSCT recipients, as the patient can be switched between dosage forms as needed.

Conclusions

The systematic reviews and the underlying randomized controlled trials demonstrate that antifungal prophylaxis with the new agents, micafungin and voriconazole, does reduce the occurrence of invasive fungal infections. This meta-analysis is confined to new antifungal agents appears to be well tolerated with manageable side effects and beneficial in the prophylaxis of IFI. Despite premedication and the development of tolerance, voriconazole and is associated with less infusional toxicity than liposomal amphotericin B[39]. Both azoles and echinocandins cause less nephrotoxicity than amphotericin B. No difference in the rates of nephrotoxicity have been seen when micafungin and fluconazole were compared. The conclusions drawn from these comparative analyses remain less definitive than those from randomized prospective studies. Further work needs to be done with large scale of random controlled trials on the effect of definite regimen and definite diseases on the outcome.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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