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CLINICAL THERAPEUTICS

Primary Fungal Prophylaxis in Hematological Malignancy: a Network Meta-Analysis of Randomized Controlled Trials

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ABSTRACT Several new antifungal agents have become available for primary fungal prophylaxis of neutropenia fever in hematological malignancy patients. Our aim was to synthesize all evidence on efficacy and enable an integrated comparison of all current treatments. We performed a systematic literature review to identify all publicly available evidence from randomized controlled trials (RCT). We searched Embase, PubMed, the Cochrane Central Register of Controlled Clinical Trials, and the www.ClinicalTrials.gov website. In total, 54 RCTs were identified, including 13 treatment options. The evidence was synthesized using a network meta-analysis. Relative risk (RR) was adopted. Posaconazole was ranked highest in effectiveness for primary prophylaxis, being the most favorable in terms of (i) the RR for reduction of invasive fungal infection (0.19; 95% confidence interval [CI], 0.11 to 0.36) and (ii) the probability of being the best option (94% of the cumulative ranking). Posaconazole also demonstrated its efficacy in preventing invasive aspergillosis and proven fungal infections, with RR of 0.13 (CI, 0.03 to 0.65) and 0.14 (CI, 0.05 to 0.38), respectively. However, there was no significant difference among all of the antifungal agents in all-cause mortality and overall adverse events. Our network meta-analysis provided an integrated overview of the relative efficacy of all available treatment options for primary fungal prophylaxis for neutropenic fever in hematological malignancy patients under myelosuppressive chemotherapy or hematopoietic cell transplantation. On the basis of this analysis, posaconazole seems to be the most effective prophylaxis option until additional data from head-to-head randomized controlled trials become available.

KEYWORDS antifungal agents, antifungal therapy, hematology, meta-analysis

Invasive fungal infections (IFIs) are a significant cause of morbidity and mortality following dose-intensive chemotherapy or hematopoietic cell transplantation in patients with neutropenic fever. The risk of IFIs is particularly increased in hematological malignancy patients (1, 2). Furthermore, invasive mold infections often occur exclusively in high-risk patients with profound neutropenia (<100 cells/mm^3) that lasts longer than 10 to 15 days (3–5). Now that the threats posed by bacterial and viral infections have been somewhat reduced, IFIs have become one of the main infective causes of mortality in this population (6).

Currently, *Aspergillus* and *Candida* species account for 95% of all cases of IFIs, but the epidemiological characteristics of IFIs evolve due to the selection pressure of antimicrobials and other factors (7, 8). With the increasing use of intensive immunosuppressive cancer therapeutic modalities (9, 10), IFIs have become an important reason for delays and reduced response to therapies for hematological cancer (11–13).

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Over recent decades, a series of studies have assessed the effect of antifungal agents on the prevention of IFIs. Although numerous antifungal agents are available, IFIs remain a serious problem because of obstacles to timely diagnosis and protracted initiation of therapy, the high morbidity and mortality rates associated with limited activity of antifungal agents, drug side effects, and increasing use of high-dose corticosteroids (14). Therefore, primary prevention of fungal infections, which had been repeatedly demonstrated to reduce IFIs and all-cause mortality, remains essential (15, 16). The ideal prophylactic antifungal therapy should be safe and well tolerated for long-term use, being effective against a wide spectrum of organisms and available as intravenous and oral formulations with good bioavailability (17). Recent randomized controlled trials (RCTs) (18–21) and meta-analyses (22–24) showed a marked reduction of IFIs in patients who used triazoles and echinocandins. The currently available multiple polyenes, echinocandins, and triazoles fulfill some of the requirements for an ideal prophylactic antifungal agent; however, some areas for improvement remain.

Network meta-analysis may be a more robust methodology which allows full comparisons of all relevant interventions in a single analytical model, including those which lack head-to-head comparisons (25, 26). The clinical requirement for comparison of all relevant treatments is almost impossible for current clinical trial design because of the cost and regulatory approval-driven strategies. Commonly, new interventions are compared with placebo or current standard intervention (27, 28). The synthesis analysis takes advantage of both direct (as used in the standard meta-analysis) and indirect comparisons between a number of treatments, which may strengthen the relative efficacy estimate and allow the designation of the best treatment simultaneously.

There is no single agent that will prevent all fungal infections; therefore, careful monitoring and treatment of emergent breakthrough IFIs throughout the high-risk period are essential. The aim of this study was to examine all of the evidence from qualified randomized controlled trials that have guided antifungal choices and to compare the clinical efficacy and safety of the antifungal agents for primary IFI prophylaxis in hematological malignancy patients undergoing myelosuppressive chemotherapy or hematopoietic cell transplantation.

RESULTS

The algorithm of this systematic literature review is shown in Fig. 1. A total of 331 citations were retrieved from the databases. After removing duplicates, 286 citations were screened based on the title and abstract and 203 studies were excluded from further analysis. In the second phase, 83 full texts were screened, 29 of which were excluded. A total of 54 citations were included for qualitative analysis. These citations comprised 53 full publications and 1 doctoral dissertation (19). There were 18 double-blind trials and 23 multicenter studies. All studies had an acceptable quality assessment of trials and none exhibited high risk of bias in randomization, and allocation concealment domains were found. Thirty-three trials were open-label design; 27 trials had a quality assessment score of $\geq$5. Overall, 12,832 cases were enrolled. The details of the search process are demonstrated in the appendix posted at https://goo.gl/6AAXgq, pages 2 to 6.

In total, 54 trials were identified, including 13 arms: (i) oral polyene, (ii) intravenous conventional amphotericin B (iAMB), (iii) aerosolized amphotericin B (aAMB), (iv) liposomal amphotericin B (LAMB), (v) amphotericin B lipid complex (ABLC), (vi) ketoconazole (KTCZ), (vii) fluconazole (FLCZ), (viii) itraconazole (ITCZ), (ix) voriconazole (VOCZ), (x) posaconazole, (xi) micafungin (MCFG), (xii) caspofungin (CASP), and (xiii) placebo.

Table 1 lists the summary of the characteristics of the included trials. The median age ranged from 6.08 to 62.17 years; half of the patients received intensive chemotherapy, and 27% received hematopoietic cell transplantation. The trials were distributed across North America, South America, Europe, Asia, and Africa. Most of the studies enrolled patients with an absolute neutrophil count of less than 1,000/μl. However, the time point for primary fungal prophylaxis administration was inconsistent among the trials.

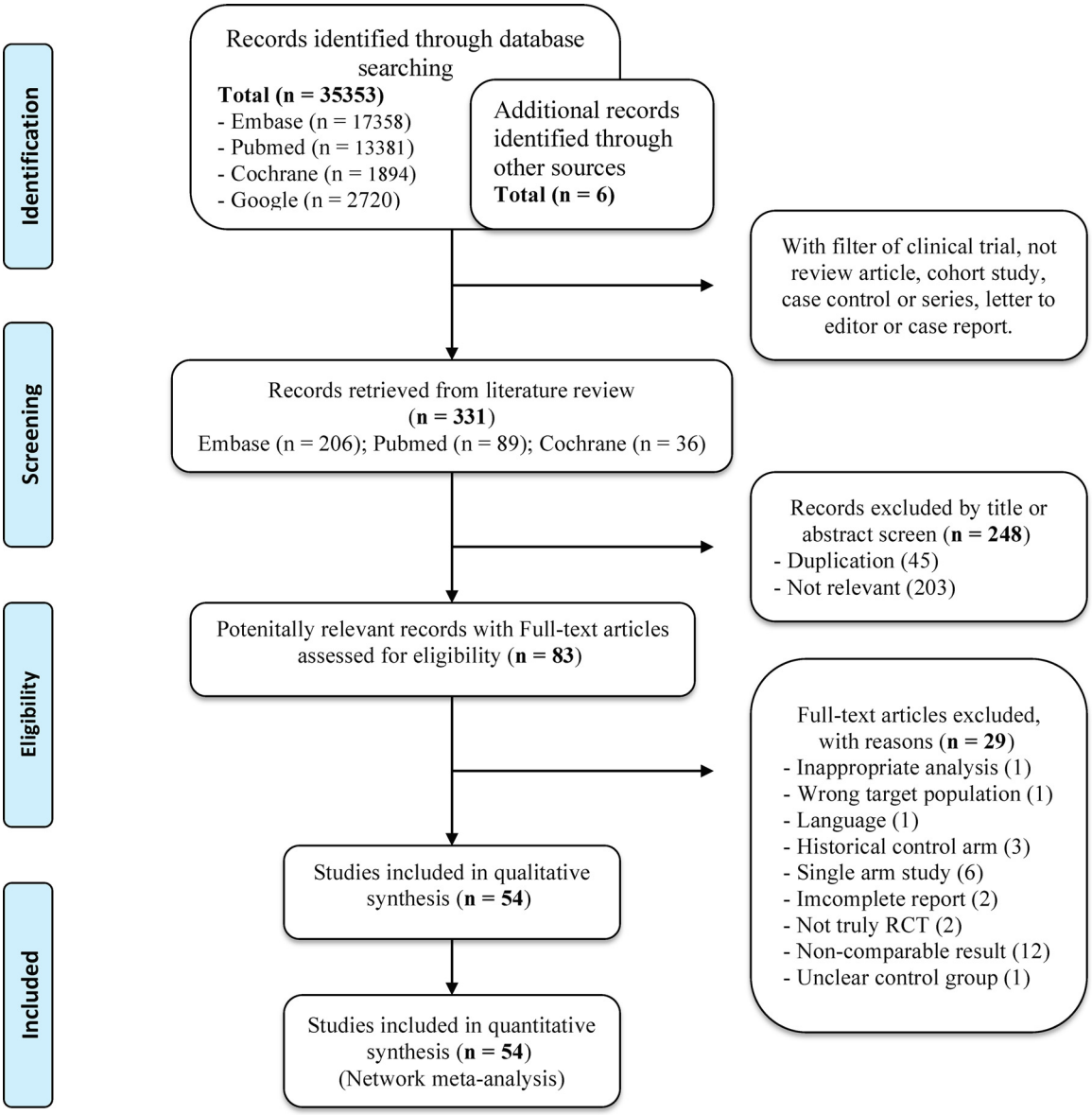


FIG 1 PRISMA flowchart of network meta-analysis.

Network meta-analysis. Figure 2 describes the integral network for primary fungal prophylaxis of hematological malignancy patients. To include all of the trials within one framework, we assumed that there were no differences in efficacy regardless of the dosage scheme and durations.

Invasive fungal infection in the overall population. Figure 3 presents the network meta-analysis results of the overall IFI incidence in a total of 54 studies (13 arms, 12,832 cases) that used placebo as the comparator. All treatments were sorted based on their ranking, along with their relative risk (RR) and 95% confidence intervals (CI), compared with that of the placebo. The probability scores for being the most effective treatment were also listed. Among the antifungal agents, posaconazole, liposomal amphotericin B, micafungin, itraconazole, voriconazole, aerosol amphotericin B, and fluconazole all revealed significantly lower invasive fungal infection incidence, with RR ranging from 0.19 to 0.51 compared with that of the placebo. Posaconazole was ranked highest in the prevention of invasive fungal infection (RR, 0.19; 95% CI, 0.11 to 0.36; probability [P] score, 94%).

TABLE 1 Basic characteristics of included randomized trials[a]

Reference	Trial design	Country, total no. of cases	Mean age (yr)	Main therapy[f]	Leukemia (%)	Inclusion criterial[c]	Treatment arm[e]		Involved results[d]	Quality (Cochrane risk of bias)
							A	B		
Donnelly et al. (55)	RCT	UK, 36	37.38	C/T	91.60	NA	KTCZ, 400 mg, p.o., QD	AMB, 100 mg, p.o., QID	1, 2, 3	4
Palmblad et al. (56)	RCT	Sweden, 107	50.47	C/T	100	>15 years, ANC < 500, >5 days	KTCZ, 200 mg, p.o., QD	Placebo	1, 2, 3	7
Akiyama et al. (57)	OP, RCT	Japan, 130	43.32	C/T	98.40	>15 yr, ANC < 500, >10 days	FLCZ, 200 mg, p.o., QD	AMB, 800 mg, p.o., TID	1, 2	3
Philpott-Howard et al. (58)	OP, MC, RCT	International, 536	45.90	C/T, 87.5%	75.50	ANC < 500, >5 days	FLCZ, 50 mg, p.o., BID	AMB, 100 mg, p.o., QID	1, 2, 4	3
Vreugdenhil et al. (59)	DB, RCT	Netherlands, 92	49.50	C/T	88.00	>15 yr, ANC < 1,000, >3 days	ITCZ, 200 mg, p.o., BID	Placebo	1, 2, 3, 4	6
Winston et al. (60)	DB, MC, RCT	International, 256	43.48	C/T	100	ANC < 1,000, >7 days	FLCZ, 400 mg, p.o., QD	Placebo	1, 2, 3, 4	6
Chandrasekar et al. (61)	DB, RCT	USA, 46	38.00	NA	76.10	>13 yr, ANC < 1,000, >5 days	FLCZ, 400 mg, p.o., QD	Placebo	1, 2	5
Ellis et al. (62)	RCT	Saudi Arabia, 90	0.00	NA	NA	<18 yr, ANC < 1,000, >2 days	FLCZ, 200 mg, p.o., QD	Polyene, Clotrimazole, 10 mg, p.o., BID	1, 2	3
Ninane et al. (63)	OP, MC, RCT	International, 502	6.80	C/T	52.80	<18 yr, ANC < 1,000, >2 days	FLCZ,3 mg/kg, p.o., QD	AMB, 25 mg/kg, p.o., QID	1, 2, 4	3
Riley et al. (64)	DB, RCT	USA, 35	38.00	SCT	60	ANC < 500	AMB, 0.1 mg/kg, i.v., QD	Placebo	1, 2, 3	7
Bodey et al. (65)	OP, RCT	USA, 77	46.47	NA	100	>16 yr, ANC < 500, >5 days	FLCZ, 400 mg, p.o./i.v., QD	iAMB, 0.5 mg/kg, i.v., QID	1, 2, 4	3
Behre et al. (66)	OP, RCT	Germany, 115	43.00	C/T	67.80	>18 years ANC < 500, >10 days	aAMB, 10 mg, IH, BID	Placebo	1, 2, 3	4
Egger et al. (67)	OP, RCT	Switzerland, 89	38.42	C/T, 67%	64.00	>14 yr, ANC < 1,000, >5 days	FLCZ, 400 mg, p.o./i.v., QD	Nystatin, p.o., QID	1, 2	6
Schaffner et al. (68)	OP, RCT	Switzerland, 151	39.50	NA	37.70	ANC < 500, >5 days	FLCZ, 400 mg, p.o., QD	Placebo	1, 2, 3	7
Annaloro et al. (69)	OP, RCT	Italy, 53	33.62	SCT	NA	NA	FLCZ, 300 mg, p.o., QD	ITCZ, 400 mg, p.o., QD	1, 2, 3	3
Kern et al. (70)	OP, MC, RCT	International, 68	48.71	C/T	100	>18 ANC < 500, >7 days	FLCZ, 400 mg, p.o., QD	AMB, 40 mg, p.o., Q4H	1, 2, 3, 4	5
Kelsey et al. (71)	DB, MC, RCT	International, 161	39.92	SCT, 83.8%	72.60	>16 yr, ANC < 1,000, >5 days	AMB, 2 mg/kg, p.o., TID	Placebo	1, 2, 3, 4	7
Menichetti et al. (72)	DB, MC, RCT	Italy, 405	44.00	C/T, 63.9%	75.50	>18 ANC < 1,000, 7 days	ITCZ, 2.5 mg/kg, p.o., BID	Placebo	1, 2, 3	5
Rotstein et al. (74)	DB, MC, RCT	Canadian, 274	46.44	C/T, 56%	56.20	>18 ANC < 500, >7 days	FLCZ, 400 mg, p.o., QD	Placebo	1, 2, 3, 4	7
Schwartz et al. (75)	OP, MC, RCT	Germany, 382	46.81	NA	83.20	>18 ANC < 500, >7 days	aAMB, 10 mg, IH, BID	Placebo	1, 2, 3	5
Young et al. (76)	DB, MC, RCT	International, 164	43.23	NA	94.50	>16 yr, ANC < 1,000, >5 days	FLCZ, 200 mg, p.o., QD	Nystatin, 6MIU, p.o., QD	1, 2, 4	7
Huijgens et al. (70)	DB, RCT	Netherlands, 202	15.15	NA	38.60	>18 yr, ANC < 500, >14 days	FLCZ, 50 mg, p.o., BID	ITCZ, 100 mg, p.o., BID	1, 2, 3	5
Morgenstern et al. (73)	MC, RCT	International, 445	44.55	C/T, 78.9%	84.50	ANC < 100, >7 days	FLCZ, 100 mg, p.o., QD	ITCZ, 2.5 mg/kg, p.o., BID	1, 2	3
Harousseau et al. (77)	DB, RCT	International, 557	48.74	C/T, 81.3%	70.70	>18 yr, ANC < 500, >14 days	ITCZ, 2.5 mg/kg, p.o., BID	AMB, 500 mg, p.o., QID	1, 2, 3, 4	7
Laverdière et al. (78)	DB, RCT	Canada, 266	46.32	C/T, 56%	58.60	>18 yr, ANC < 500, >7 days	FLCZ, 400 mg, p.o., BID	Placebo	1, 2	5
Nucci et al. (79)	DB, MC, RCT	Brazil, 210	27.77	C/T, 85.3%	80	ANC < 1,000, >7 days	ITCZ, 100 mg, p.o., BID	Placebo	1, 2, 3	7
Wolff et al. (80)	OP, MC, RCT	USA, 355	42.55	SCT	NA	>18 yr, ANC < 500, >10 days	FLCZ, 400 mg, p.o./i.v., QD	iAMB, 0.2 mg/kg, i.v., QD	1, 3, 4	3
Boogaerts et al. (81)	OP, MC, RCT	Finland, 277	46.92	C/T	67	>16 yr, ANC < 500 >10 days	ITCZ, 100 mg, p.o., BID	AMB, 500 mg, Nystatin, 2 MIU, p.o., QID	1, 2, 3, 4	3
Koh et al. (82)	OP, RCT	Singapore, 186	29.69	SCT	66.60	ANC < 1,000, >7 days	FLCZ, 200 mg, p.o., QD	iAMB, 0.2 mg/kg, i.v., QD	1, 2, 3	3
Kaptan et al. (83)	RCT	NA, 55	35.58	C/T	100	>18 yr, ANC < 500, >7 days	ITCZ, 200 mg, p.o., BID	Placebo	1, 2, 3	3
Lass-Flörl et al. (84)	RCT	Austria, 106	43.94	C/T	78.30	>18 yr	ITCZ, 5 mg/kg, p.o., QD	AMB, 1,000 mg, p.o., TID	1, 2, 3	3
Winston et al. (4)	OP, MC, RCT	International, 138	39.54	SCT	69.50	>13 yr	FLCZ, 400 mg, p.o./i.v., QD	ITCZ, 200 mg, p.o., BID	1, 2, 3, 4	4
Marr et al. (85)	OP, RCT	USA, 299	0.00	SCT	NA	>13 yr, ANC < 500, >10 days	FLCZ, 400 mg, p.o./i.v., QD	ITCZ, 2.5 mg/kg, p.o./i.v., TID	1, 2, 3	3
Van Burik et al. (86)	DB, MC, RCT	USA, 830	42.52	SCT	29.20	≥6 months, ANC < 500, >4 days	FLCZ, 8 mg/kg, i.v., QD	MCFG, 1 mg/kg, i.v., QD	1, 2, 3, 4	7
Hiemenz et al. (87)	DB, RCT	USA, 74	43.24	SCT	NA	≥18 yr, ANC < 500	FLCZ, 400 mg, i.v., QD	MCFG, 5 mg/kg, i.v., BID	1, 2, 3, 4	3
Penack et al. (91)	OP, RCT	Germany, 219	53.76	NA	79.50	>18 yr, ANC < 500	LAMB, 50 mg, i.v., QD	Placebo	1, 2, 3	5
Glasmacher et al. (88)	OP, RCT	Finland, 494	0.00	NA	88.60	ANC < 500, >10 days	FLCZ, 400 mg, p.o./i.v., QD	ITCZ, 5 mg/kg, p.o., BID	1, 2, 3, 4	5
Oren et al. (90)	RCT	Israel, 195	49.49	SCT	43.50	>15 yr, ANC < 500, >7 days	FLCZ, 400 mg, p.o./i.v., QD	ITCZ, 200 mg, p.o./i.v., BID	1, 2, 3	3
Mattiuzzi et al. (89)	OP, RCT	USA, 197	62.17	C/T, 93.4%	75.10	>15 yr, ANC < 500, >7 days	ITCZ, 200 mg, i.v., QD	CASP, 50 mg, i.v., QD	1	5
Vehreschild et al. (93)	DB, MC, RCT	Germany, 25	53.60	NA	NA	>18 yr, ANC < 500, >5 days	VOCZ, 200 mg, p.o., BID	Placebo	1, 2, 4	7
Ullmann et al. (34)	DB, MC, RCT	International, 579	41.30	SCT	71.8	>13 yr, ANC < 500, >7 days	FLCZ, 200 mg, p.o., TID	p.o.CZ, 200 mg, p.o., TID	1, 2, 4	5
Cornely et al.[b] (27)	OP, MC, RCT	International, 592	49.44	C/T	86.20	>13 yr, ANC < 500, >7 days	p.o.CZ, 200 mg, p.o., TID	FLCZ, 400 mg, p.o., QD	1, 4	3
Ito et al. (92)	MC, RCT	Japan, 209	55.46	C/T	88.40	>18 yr, ANC < 1,000	FLCZ, 200 mg, p.o., QD	ITCZ, 200 mg, p.o., QD	1, 2, 4	3
Rijnders et al. (95)	DB, RCT	Netherlands, 271	49.49	C/T, 68.2%	48.70	ANC < 500, >10 days	aAMB, 12.5 mg, INH, QD	Placebo	1, 3	7
Hiramatsu et al. (94)	OP, RCT	Japan, 100	46.90	SCT	19	≥18 yr, ANC ≤ 500/μl	FLCZ, 400 mg, i.v., QD	MCFG, 150 mg, i.v., QD	1, 2, 3, 4	6
Sawada et al. (96)	RCT	Japan, 107	6.01	C/T, 76.6%	27	<18 yr, ANC < 500	FLCZ, 10 mg/kg, i.v., QD	MCFG, 2 mg/kg, i.v., QD	1, 2, 4	4
Mattiuzzi et al. (89)	OP, RCT	USA, 123	59.42	C/T	55.30	>18 yr, ANC < 500, >5 days	VOCZ, 400 mg, i.v., QD	ITCZ, 200 mg, i.v., BID	1, 3, 4	5
Wingard et al. (28)	DB, MC, RCT	USA, 600	43.00	NA	76.50	>2 yr, ANC < 500, >5 days	FLCZ, 200 mg, p.o., BID	VOCZ, 200 mg, p.o., BID	1, 2, 3	6

(Continued on next page)

TABLE 1 (Continued)

Reference	Trial design	Country, total no. of cases	Mean age (yr)	Main therapy	Leukemia (%)	Inclusion criterial[c]	Treatment arm[e]		Involved results[d]	Quality (Cochrane risk of bias)
							A	B		
Marks et al. (97)	OP, MC, RCT	International, 465	0.00	C/T	66.20	>12 yr, ANC < 500, >7 days	VOCZ, 200 mg, p.o., BID	ITCZ, 200 mg, p.o., BID	1, 2, 3, 4	5
Chaftari et al. (98)	OP, RCT	USA, 40	55.48	SCT	NA	>18 yr, ANC < 500, >7 days	p.o.CZ, 200 mg, p.o., TID	ABLC, 7.5 mg/kg, i.v., QD	1, 2, 4	3
Huang et al. (99)	OP, MC, RCT	China, 283	32.72	SCT	49	≥18 yr, ANC ≤ 500	ITCZ, 5 mg/kg, p.o., QD	MCFG, 50 mg, i.v., QD	1, 2, 4	5
Shen et al. (35)	OP, MC, RCT	China, 234	40.00	NA	88.00	>18 yr, ANC < 500, >7 days	p.o.CZ, 200 mg, p.o., TID	FLCZ, 400 mg, p.o., QD	1, 3, 4	5
Park et al. (100)	OP, RCT	South Korea, 250	46.66	SCT	40.80	>20 yr, ANC < 1,000, >5 days	FLCZ, 400 mg, p.o., QD	MFCG, 50 mg, i.v., QD	1, 2, 3, 4	3
Mahmoud et al. (19)	OP, RCT	Egypt, 70	7.35	C/T	NA	<18 yr, ANC < 500, >7 days	VOCZ, 4 mg/kg, i.v., BID	MCFG, 50 mg, i.v., QD	1, 2, 3	3

[a]C/T, chemotherapy; SCT, stem cell transplant; MC, multi-center; DB, double blind; OP, open label; NA, not applicable.
[b]Cornely et al. (27) had three treatment arms: (i) p.o.CZ, 200 mg, p.o., TID; (ii) FLCZ, 400 mg, p.o., QD; (iii) ITCZ, 200 mg, p.o., BID.
[c]Inclusion criteria included age, ANC definition, and neutropenia duration.
[d]Involved results included the following groups: (1) invasive fungal infection, overall; (2) fungal infection, proven; (3) mortality, all cause; (4) adverse event, all causes.
[e]p.o., *per os*; i.v., *in vitro*; QD, once a day; BID, twice a day; TID, three times a day.
[f]Percentages indicate the percentages of patients receiving the indicated main therapy.

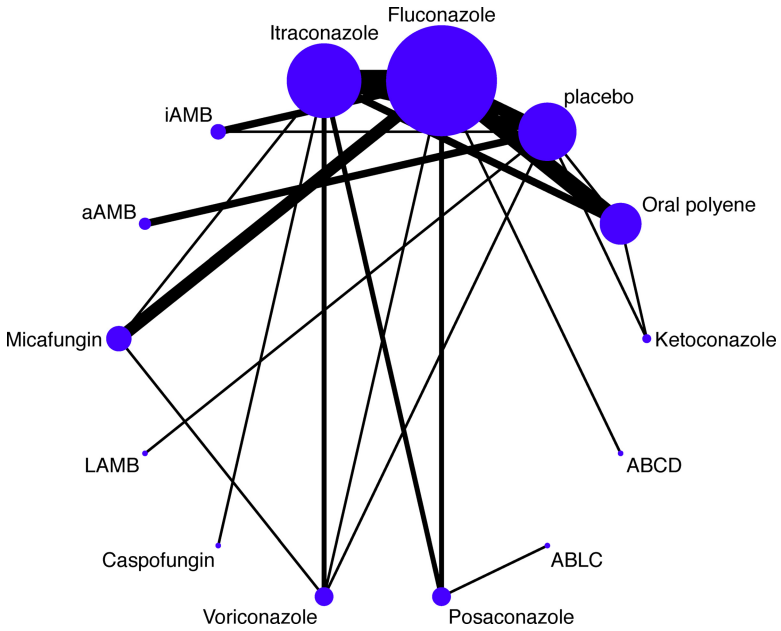


FIG 2 Schematic of the network of evidence used in network meta-analysis. Directly comparable treatments are linked with a line. iAMB, intravenous conventional amphotericin B; aAMB, aerosol amphotericin B; LAMB, liposomal amphotericin B; ABLC, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion.

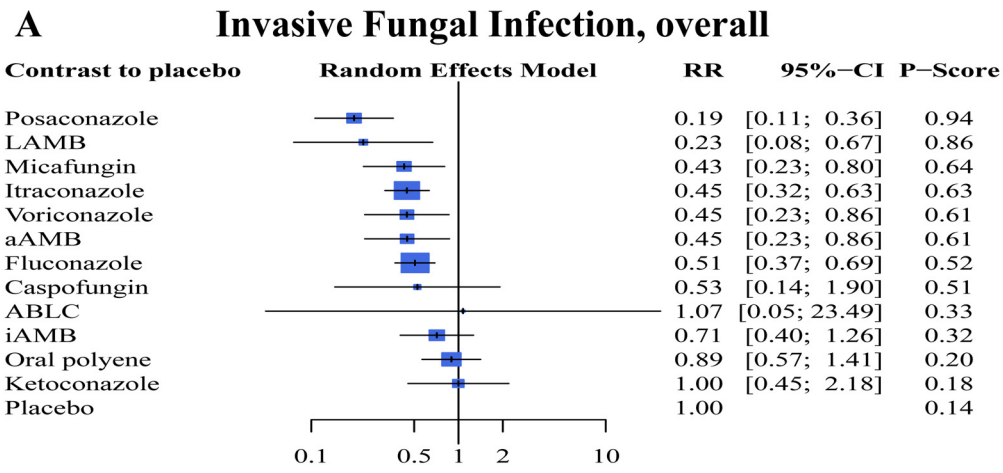
Furthermore, we conducted subgroup analyses to explore the potential spectrum of prophylaxis for invasive aspergillosis and invasive candidiasis. Posaconazole was also considered the superior choice to prevent invasive aspergillosis (RR, 0.13; 95% CI, 0.03 to 0.65), with significance of results (see the URL mentioned above, page 11). Compared with placebo, micafungin, fluconazole, posaconazole, voriconazole, and itraconazole had no difference in decreasing the incidence of invasive candidiasis (see the URL mentioned above, page 11).

Proven invasive fungal infection. The clinical judgement of a probable fungal infection would be uncertain and inconsistent among different physicians. Proven fungal infection has a more specific definition, which includes invasive mold infection that is demonstrated as fungal elements in tissues, evidence of associated tissue damage on biopsy specimens, and a proven invasive yeast infection based on isolation of yeast in the culture of a sample obtained by a sterile procedure from a normally sterile site, usually blood.

Based on the network meta-analysis results of the overall proven fungal infections (48 trials, 11,050 cases), posaconazole, micafungin, itraconazole, and fluconazole showed promising reduction of proven fungal infections, with RRs ranging from 0.14 to 0.54 (Fig. 4A). Among them, posaconazole was ranked highest in prevention of proven fungal infections (RR, 0.14; 95% CI, 0.05 to 0.38). In terms of the potential prophylaxis efficacy for different fungal spectra, posaconazole was the most effective for reduction of proven aspergillosis (RR, 0.13; 95% CI, 0.03 to 0.65) (Fig. 4B). Itraconazole, caspofungin, fluconazole, and intravenous conventional amphotericin B showed significantly decreased incidences of proven candidiasis; among them, itraconazole was ranked highest (RR, 0.21; 95% CI, 0.11 to 0.39) (Fig. 4C).

Figure 5 demonstrates the scatterplot of cumulative probabilities of being the most effective prophylactic antifungal agent for both invasive fungal infections and proven fungal infections. The scatterplot indicates that posaconazole is the most effective.

All-cause mortality and adverse events in the overall population. A total of 38 studies (8 arms, 8,447 cases) recorded the all-cause mortality outcome. The appendix at https://goo.gl/6AAXgq, page 12, demonstrates that there was no significant difference in the all-cause mortality rate between the 10 antifungal agents and placebo. Based on



B **Invasive Fungal Infection, overall**

aAMB	-	-	-	-	-	-	-	-	-	**0.447 (0.231 to 0.864)**	-	-
0.416 (0.018 to 9.783)	**ABLC**	-	-	-	-	-	-	-	-	-	5.500 (0.267 to 113.367)	-
0.850 (0.200 to 3.616)	2.042 (0.074 to 56.376)	**CASP**	-	-	1.178 (0.340 to 4.076)	-	-	-	-	-	-	-
0.883 (0.426 to 1.831)	2.120 (0.098 to 45.860)	1.039 (0.292 to 3.696)	**FLCZ**	0.685 (0.387 to 1.212)	1.314 (0.938 to 1.841)	-	-	1.203 (0.642 to 2.254)	**0.608 (0.386 to 0.959)***	**0.428 (0.291 to 0.631)**	**2.243 (1.191 to 4.226)**	1.068 (0.516 to 2.212)
0.628 (0.262 to 1.504)	1.508 (0.067 to 34.046)	0.739 (0.188 to 2.900)	0.711 (0.424 to 1.193)	**iAMB**	-	-	-	-	-	0.605 (0.187 to 1.953)	-	-
1.001 (0.476 to 2.108)	2.404 (0.111 to 52.167)	1.178 (0.340 to 4.076)	1.134 (0.871 to 1.476)	1.594 (0.899 to 2.826)	**ITCZ**	-	-	0.308 (0.058 to 1.648)	**0.435 (0.241 to 0.787)**	0.647 (0.386 to 1.084)	**3.468 (1.578 to 7.620)**	2.076 (0.531 to 8.117)
0.449 (0.161 to 1.251)	1.077 (0.045 to 25.993)	0.528 (0.117 to 2.377)	0.508 (0.220 to 1.174)	0.714 (0.272 to 1.877)	0.448 (0.191 to 1.049)	**KTCZ**	-	-	0.370 (0.015 to 8.947)	1.069 (0.476 to 2.401)	-	-
1.983 (0.557 to 7.058)	4.761 (0.181 to 125.486)	2.332 (0.433 to 12.562)	2.245 (0.727 to 6.934)	3.156 (0.927 to 10.751)	1.980 (0.635 to 6.177)	**4.420 (1.159 to 16.857)**	**LAMB**	-	-	**0.225 (0.076 to 0.666)**	-	-
1.047 (0.420 to 2.614)	2.515 (0.111 to 57.135)	1.232 (0.310 to 4.896)	1.186 (0.679 to 2.073)	1.667 (0.780 to 3.565)	1.046 (0.573 to 1.910)	2.334 (0.856 to 6.366)	0.528 (0.151 to 1.854)	**MCFG**	-	-	-	0.333 (0.066 to 1.695)
0.500 (0.224 to 1.115)	1.200 (0.054 to 26.459)	0.588 (0.160 to 2.162)	**0.566 (0.392 to 0.818)**	0.796 (0.423 to 1.496)	**0.499 (0.337 to 0.739)**	1.114 (0.456 to 2.723)	**0.252 (0.078 to 0.817)**	**0.477 (0.246 to 0.927)**	**oPOLY**	0.392 (0.039 to 3.942)	-	-
0.447 (0.231 to 0.864)	1.072 (0.049 to 23.489)	0.525 (0.145 to 1.905)	**0.506 (0.371 to 0.689)**	0.711 (0.402 to 1.258)	**0.446 (0.316 to 0.629)**	0.995 (0.454 to 2.182)	**0.225 (0.076 to 0.666)**	**0.426 (0.226 to 0.803)**	0.893 (0.566 to 1.409)	**PLACEBO**	-	6.187 (0.350 to 109.387)
2.290 (0.932 to 5.629)	5.500 (0.267 to 113.367)	2.694 (0.690 to 10.518)	**2.594 (1.509 to 4.459)**	**3.646 (1.728 to 7.694)**	**2.288 (1.307 to 4.005)**	**5.106 (1.899 to 13.727)**	1.155 (0.333 to 4.009)	**2.187 (1.009 to 4.742)**	**4.582 (2.414 to 8.697)**	**5.130 (2.787 to 9.442)**	**POCZ**	-
1.003 (0.396 to 2.541)	2.408 (0.105 to 55.018)	1.180 (0.294 to 4.735)	1.136 (0.628 to 2.053)	1.597 (0.729 to 3.496)	1.002 (0.536 to 1.871)	2.236 (0.808 to 6.183)	0.506 (0.143 to 1.795)	0.958 (0.448 to 2.048)	**2.006 (1.007 to 3.995)**	**2.246 (1.167 to 4.322)**	**0.438 (0.198 to 0.970)**	**VOCZ**

Treatment comparison for incidence of invasive fungal infection consistency analysis based on network. Drugs are reported in alphabetical order. The top half of the table shows the results of direct comparisons (Relative Risks and 95% Confidence Intervals), whereas the bottom half shows the results of network meta-analysis (RRs and 95% CIs). RRs lower than 1 favour the first drug in alphabetical order. " # "Statistical heterogeneity was found (p-for-heterogeneity <0.1 or I²>50%). Significant results are in bold and underscored.

FIG 3 NMA results (presented as risk ratio) for invasive fungal infection overall. (A) Forest plot of invasive fungal infections. (B) Multiple treatment comparisons for incidence of invasive fungal infection using consistency analysis based on network. P score was determined by SUCRA (surface under the cumulative ranking curve). CI, confidence interval; iAMB, intravenous conventional amphotericin B; aAMB, aerosol amphotericin B; LAMB, liposomal amphotericin B; ABLC, amphotericin B lipid complex; KTCZ, ketoconazole; FLCZ, fluconazole; ITCZ, itraconazole; VOCZ, voriconazole; POCZ, posaconazole; MCFG, micafungin; CASP, caspofungin.

cumulative ranking, liposomal amphotericin B tended to be the better choice for reduction of mortality (RR, 0.44; 95% CI, 0.14 to 1.39), but the difference was not significant (see the URL mentioned above, page 12).

A total of 28 studies (7,872 cases) documented the all-cause adverse events outcome (see the URL mentioned above, page 13). According to the results of the network meta-analysis, there was no significant difference in the incidence of overall adverse events between the antifungal agents and placebo. Based on the ranking probability scores, micafungin tended to have the lowest rate of overall all-cause adverse events (RR, 0.83; 95% CI, 0.53 to 1.31), but the difference was not significant (see the URL mentioned above, page 13). Based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (29), we did subgroup analyses of the mild (grades 1 and 2) and severe (grade >2) adverse events groups. Micafungin, posaconazole, and fluconazole had significantly lower incidences of mild adverse events than oral polyenes (RRs ranged from 0.62 to 0.65) (see the URL mentioned above, page 13). For the severe adverse events, there were no significant differences among the antifungal agents (see the URL mentioned above, page 13). Based on the cumulative ranking, micafungin tended to be the safest prophylactic antifungal agent with the lowest incidence of adverse events, no matter what the severity (see the URL mentioned above, page 13). From the limited data, we analyzed the RR of common hepatic impairment and gastrointestinal upset in antifungal agent prevention. In terms of hepatic impairment,

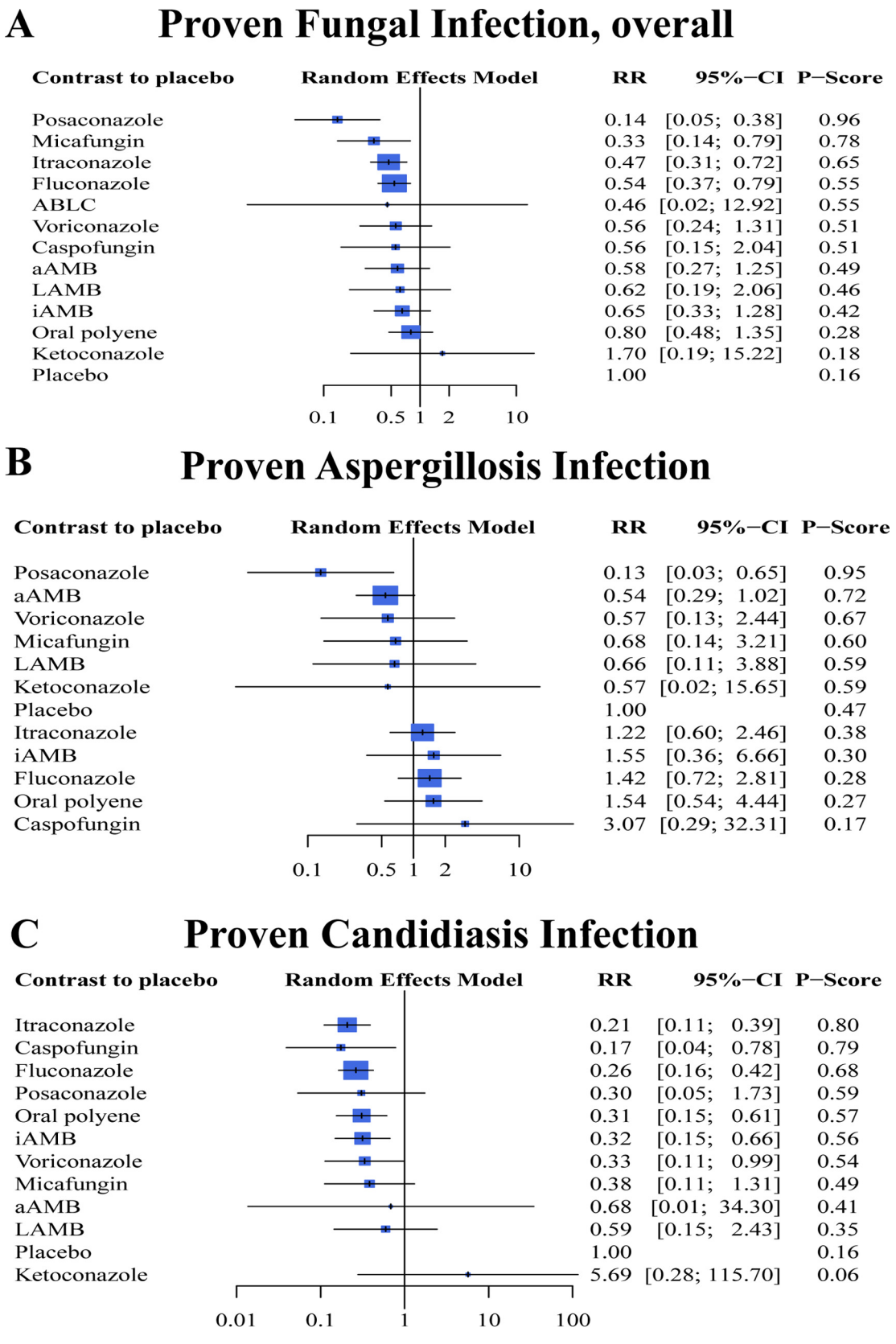


FIG 4 NMA results (presented as risk ratio) for proven fungal infection. (A) Forest plot of proven fungal infection. (B) Forest plot of proven aspergillosis infection. (C) Forest plot of proven candidiasis infection. P score was determined by SUCRA (surface under the cumulative ranking curve). CI, confidence interval; iAMB, intravenous conventional amphotericin B; aAMB, aerosol amphotericin B; LAMB, liposomal amphotericin B; ABLC, amphotericin B lipid complex.

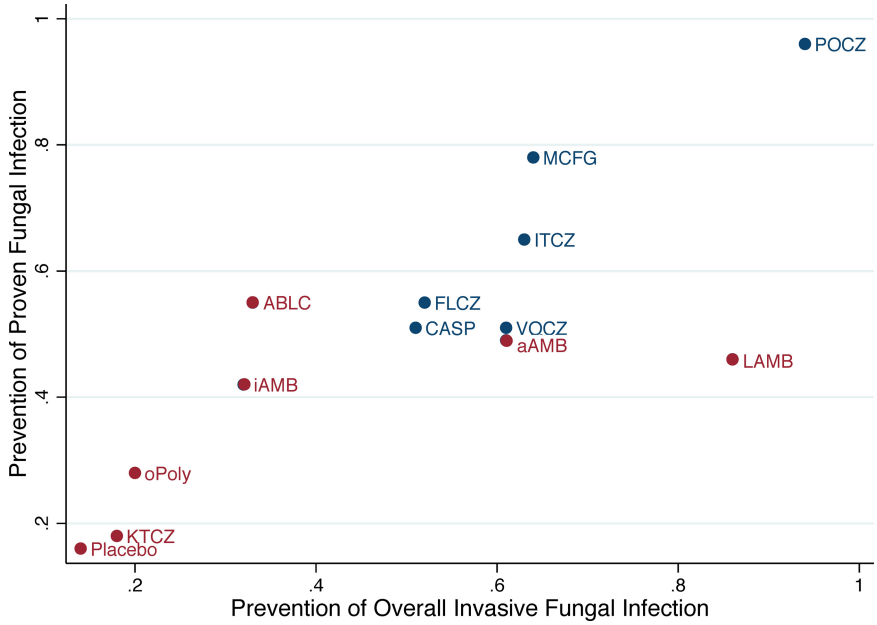


FIG 5 Scatter plot presenting the cumulative probability of prophylactic antifungal agent for overall invasive fungal infection and proven fungal infections. *x* axis, the probability of prevention for overall invasive fungal infections; *y* axis, the probability of prevention for proven fungal infections. Blue color means the probability scores of IFIs and PFIs are both above 50%, and red color means neither are.

voriconazole had a significantly increased risk (RR, 2.39; CI, 1.43 to 3.98); fluconazole, micafungin, itraconazole, and posaconazole did not show differences from the placebo (see the URL mentioned above, page 17). Furthermore, fluconazole, micafungin, itraconazole, posaconazole, and voriconazole had no statistically significant difference in the incidence of gastrointestinal upset compared to that of the placebo (see the URL mentioned above, page 17).

Sensitivity test. Due to including extensive antifungal agent studies, we assessed whether the prophylactic effect for the primary outcome was robust in subgroup analyses and sensitivity test using study year, study quality, study precision (i.e., small study effect), and homophilic pattern in antifungal agent trials (30). The appendix summarizes the definitions of covariates, and the results did not change substantially (see the URL mentioned above, page 16). The preference for fluconazole comparisons and avoidance of head-to-head new drug comparisons in antifungal trials was pointed out by Rizos et al. (30). In our present research, 25 trials used comparisons with fluconazole, accounting for nearly 46% of the included studies. After excluding the studies of fluconazole comparisons, the sensitivity test showed no substantial difference for the original network meta-analysis. Although the values of relative risk were changed, posaconazole was ranked as the most effective, and micafungin, voriconazole, and caspofungin had similar cumulative ranking results (see the URL mentioned above, page 16). We used comparison-adjusted funnel plots to investigate whether results in imprecise trials differ from those in more precise trials. Net-funnel plot (see the URL mentioned above, page 14) and egger graph (see the URL mentioned above, page 14) demonstrated no significant publication bias. Furthermore, the design-by-treatment interaction model and side-splitting model reported no significant inconsistency.

DISCUSSION

There is an emerging need for synthesis of evidence on primary fungal prophylaxis in hematological malignancy patients with neutropenic fever, especially because a myriad of novel treatments has become available in the past decade. Several systematic reviews focused on separate antifungal agent comparisons. Only one network meta-analysis has synthesized the evidence on IFI prophylaxis in hematological cancer on the

basis of pooled odds ratios from randomized controlled trials (31). However, the evidence shown by Leonart et al. (31) was focused on double-blind trials; among 25 trials, there were 19 trials that compared a single antifungal with placebo instead of head-to-head studies. Currently, conclusions on the comparisons across prior network meta-analyses cannot be clearly made.

Our purpose was to pool all qualifying evidence and enable an integrated comparison of all current antifungal agents for IFI prevention in hematological malignancy patients with febrile neutropenia. In this study, RR was adopted as the effect measure for IFI incidence, more recent treatments were included, and all pieces of evidence were combined into a single network. Indeed, we were able to combine within one network the evidence from 54 enrolled RCTs on a total of 12,832 cases, including 13 treatment arms, using random-effect network meta-analysis. Our analyses provided crucial information on health care decision-making for primary fungal prophylaxis in such patients. Of the 13 treatment options, posaconazole was the top priority in our network meta-analysis, both in terms of ranking and probability of being the most effective treatment. Based on pooled evidence, posaconazole was ranked highest in reduction of the overall IFIs, including invasive aspergillosis. These results strongly supported the current Infectious Disease Society of America guidelines for primary prophylaxis in patients with acute leukemia and post-stem cell transplant (32). For proven fungal infections, the overall incidence was significantly reduced with posaconazole, micafungin, itraconazole, and fluconazole. Moreover, posaconazole was the better choice for prevention of proven aspergillosis. For proven candidiasis prophylaxis, itraconazole, fluconazole, caspofungin, and intravenous conventional amphotericin B presented with significantly good efficacy. For patients who live in regions with a high prevalence of candidiasis, the above-mentioned drugs would be the optimal choice.

We proved that posaconazole prophylaxis was associated with significant reductions in overall invasive, proven fungal infection and invasive aspergillosis but did not have a significant impact on all-cause mortality. These discordant results had been disclosed in clinical trials (33–35), meta-analyses (15, 16, 36, 37), and real-word data (38–40). The absence of a significant difference in all-cause mortality might be explained by the following hypotheses. The first possible explanation for the insignificant effect on all-cause mortality is that empirical treatment with voriconazole is associated with substantially improved prognosis of invasive aspergillosis (41, 42). The second possible reason for the discrepancy between significant reduction in the incidence of invasive fungal infection and the lack of impact on all-cause mortality is associated with the use of galactomannan tests. Marr et al. (43) reported that mold-active azole agents could interfere with the sensitivity of this test, and Kim et al. (44) showed micafungin would limit galactomannan detection, thus the true reduction of invasive fungal diseases observed with mold-active agents may be overestimated. The third possibility is that mold-active prophylaxis increases non-IFI-related deaths. It is also possible that drug interactions further contributed to increased patient deaths.

Our analysis on overall adverse events did not show any significant differences, except for the use of conventional iAMB, which was significantly ranked at the bottom of the list. Subgroup analyses revealed that micafungin had a significantly lower rate of mild adverse events, which may be a valuable clinical concern for rotating antifungal agents. These results were somewhat in line with clinical experience and earlier observations (45).

All available prophylaxis options in hematological cancer were systematically obtained from the published domain and were pooled in a conventional and mathematically transparent way. Therefore, this systematic literature review and network meta-analysis are reproducible and could compare all treatment options that are currently available for primary prophylaxis in such patients.

To examine the potential biases in antifungal agent studies, we assessed whether the prophylactic effect for the primary outcome was robust in subgroup analyses and sensitivity tests. The important variables of quality scores, sample sizes, publication years, and preference of fluconazole pattern were detected. No substantial biases existed in the sensitivity test. Consequently, with included emerging studies comparing

new drugs to each other, our present network meta-analysis is considered more robust. However, we did not consider differences in dosing schemes and modes of administration; among the studies, the most apparent were changes in the mode of fluconazole and itraconazole administration from oral to intravenous due to intolerance. However, in clinical practice, shifting from oral to intravenous administration and differences in bioavailability are probably common. Therefore, differences in dosing schemes and modes of administration remain a subject of further research. Readers should be aware that our results, similar to the results of each trial, apply to the average patient. Although this study might assist doctors and patients in evidence-based decision-making, selecting the most appropriate treatment option also depends on the individual patient characteristics and preferences.

With our best effort, we provided evidence that in hematological malignancy patients who develop neutropenic fever after myelosuppressive chemotherapy or hematopoietic cell transplantation, posaconazole is a somewhat superior option for primary fungal prophylaxis. For patients living in areas with a high incidence of candidiasis infection, micafungin, itraconazole, and fluconazole would be more effective options. When there is a need to rotate antifungal agents due to adverse events, micafungin would be a safer choice. Despite the limitations of this study, our results provided insight on the rank order of efficacy and safety of these treatment options. This can facilitate evidence-based decision-making in the clinical setting, where most treatment agents have not been compared in head-to-head RCT settings or have not been previously compared using evidence synthesis. Nevertheless, we emphasize that it remains essential to conduct phase III trials to obtain more direct head-to-head evidence. Until such evidence becomes available, our results are highly important for informed decision-making in everyday clinical practice.

MATERIALS AND METHODS

We conducted a network meta-analysis in a frequentist framework and used the *Cochrane Handbook for Systematic Reviews of Interventions* approach to evaluate the quality of evidence (46). This study has been registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO) with registration number CRD42017058429.

Search methods and criteria for considering studies for inclusion. We performed an extensive electronic search (see the appendix at https://goo.gl/6AAXgq, pages 2 to 6) of the Cochrane Central Register of Controlled Trials, PubMed, and Embase for RCTs. We further sought details of the trials or protocols from https://clinicaltrials.gov to establish the eligibility of potential trials. No language restrictions were applied. Our latest search was completed on 19 February 2017. Two reviewers (C.H.L. and C.L.) screened the titles and abstracts of the retrieved articles to search for the eligible RCTs.

Types of studies. All available RCTs that compared the prophylactic efficacy and safety of antifungal agents in hematological cancer were enrolled. Placebo-designed studies were included to serve as a reference comparator for estimating the relative effectiveness of antifungal agents. In the present study, we assumed no relative differences in effectiveness between placebo and no prophylaxis. RCTs with quasi-experiment and crossover designs were excluded. Study design of comparison of different dosage, the comparator of historical control, intervention with non-FDA-approved antifungal agents, and unclear control groups (like standard policy) were also excluded.

Types of participants. We enrolled patients, of any age, with a diagnosis of hematological malignancy and who were under myelosuppressive chemotherapy or hematopoietic cell transplantation and developed neutropenic fever, which was defined as an absolute neutrophil count of $<$1,500/μl for at least 3 days. Autogenic or allogeneic stem cell transplants were not limited. Those who received concomitant antibacterial agents were included. Patients who received antifungal agents for prophylaxis or empirical treatment prior to enrollment in the trial were excluded.

Types of interventions and comparison. The trials included were those that evaluated the prophylactic efficacy and safety of polyenes, azoles, and echinocandins. The traditional amphotericin B formulations are now prescribed less frequently due to drug toxicity, and these were designated the reference comparator because of several studies of head-to-head comparisons with other antifungal agents in past years. Furthermore, we also chose to enroll trials involving oral polyene and ketoconazole because, despite not being recommended in clinical practice any longer for invasive fungal infection prophylaxis, we did not want to lose any evidence from the literature. The dosage and duration of the prophylactic or antifungal agent were not limited.

Types of outcomes. RCTs that assessed the efficacy of primary fungal prophylaxis using the following outcomes were included: (i) IFI incidence rates (the classification criteria for possible, probable, and proven fungal infections were based on the 2008 criteria by the EORTC and MSG [47]), (ii) all-cause or drug-related mortality, and (iii) all-cause or drug-related adverse events (defined based on the Common Terminology Criteria of Adverse Events, v4.03) (29). We chose the longest follow-up time (end of follow-up or death) as the measurement time point for all outcomes.

Risk of bias assessment. The study quality was assessed by two reviewers (C.H.L. and C.L.) using the methodology and categories described in the Cochrane Collaboration handbook (46). In case of disagreement, a group discussion was done to reach a consensus. In the assessment of other issues, we focused on the baseline imbalance and source of financial support (48).

Data extraction. Two reviewers (C.H.L. and C.L.) independently assessed the eligibility of all identified citations and extracted data from original trial reports using a specifically designed form that captured information on the study characteristics, patient characteristics, and sample sizes and details of interventions with comparisons and outcomes. To lower the chances of entry error, double data entry and cross-checking were performed.

Data synthesis and statistical analysis. A network meta-analysis was conducted to simultaneously compare 13 antifungal treatment options for each outcome. The network meta-analysis in the present study was performed by using the netmeta package (0.9-7) in R, version 3.4.1 (49). The incidence of IFIs was defined as the primary outcome. RR with 95% CI was calculated using the random-effect model by following UK NICE guidelines (50). A *P* value of less than 0.05 was considered statistically significant.

A network plot that represented the overall information of the trials included in the analysis was generated (51). The contribution of each direct comparison to each network estimate was calculated according to the variance of the direct treatment effect and the network structure (52). Network meta-analysis is a method for global assessment of the current evidence; therefore, we needed to carefully compare indirect evidence with the direct estimates. Inconsistency referred to the differences between the various direct and indirect effects that were estimated for the same comparison. Inconsistency was evaluated by design-by-treatment interaction model and side-splitting model.

A forest plot of the estimated summary effects, along with the CI for all comparisons, was generated to summarize the relative mean effects, the predictions on each comparison in one plot (53). We estimated the probability of a treatment being ranked at a specific place according to the outcome (P score) using surface under the cumulative ranking curve (SUCRA), which is a simple transformation of the mean rank to provide a hierarchy of the treatments and to account for the location and variance of all relative treatment effects. A higher SUCRA value reflected a higher possible ranking of the treatment (54). The P score represented the SUCRA value in the forest plot.

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