Preemptive Antifungal Therapy for Febrile Neutropenic Hematological Malignancy Patients in China

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Background: The aim of this study was to evaluate the efficiency, adverse effects, and pharmacoeconomic impact of empirical and preemptive antifungal therapy for febrile neutropenic hematological malignancy patients in China.

Material/Methods: Patients with febrile neutropenia during hematological malignancy were randomly divided into an empirical group and a preemptive group. The preemptive antifungal treatment was initiated if patient status was confirmed by clinical manifestation, imaging diagnosis, 1-3-β-D glucan(G) testing, and galactomannan (GM) test. The treatment was ended 2 weeks later if the patient was recovered from neutropenia. Voriconazole was used as the first-line medicine. All patients received intravenous administration of voriconazole every 12 h, with an initiating dose of 400 mg, then the dose was reduced to 200 mg.

Results: The overall survival rate was 97.1% and 94.6% in the empirical group and preemptive group, respectively, with no significant difference observed (χ^2=1.051, P=0.305). However, the occurrence rate of invasive fungal disease (IFD) in the preemptive group was 9.2% *vs.* 2.2% in the empirical group. Moreover, the mortality rate due to IFD was 0.7% and 2.3% for the empirical group and preemptive group, respectively. The average duration and cost of preemptive antifungal therapy were 13.8±4.7 days and 8379.00±2253.00 RMB, respectively, which were lower than for empirical therapy. However, no significant differences were observed for incidence of adverse effects and hospital stay between the 2 groups.

Conclusions: Preemptive antifungal therapy for patients with febrile neutropenic hematological malignancy demonstrated a similar survival rate as with empirical therapy but is economically favorable in a Chinese population.

MeSH Keywords: Hematologic Agents • Hematologic Diseases • Hematologic Neoplasms

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Background

Patients with a hematological malignancy are generally considered as being susceptible to fungal infections, which leads to development of invasive fungal disease (IFD) caused by filamentous fungi [1,2]. Many predisposing or risk factors has been described for the development of IFD, such as intensity and duration of neutropenia, diagnosis of acute leukemia, and severe impairment of lymphocytic activity [3,4]. Currently, empirical antifungal therapy is the classical and standard of the care method for IFD in hematological patients. Generally, the use of antifungal drugs is initiated once clinical evidence of fungal infection is observed [3,5]. Empirical antifungal therapy is frequently recommended for patients with high or medium risk of IFD, such as those with fever for more than 3 days after broad-spectrum antimicrobial therapy [3,6,7]. However, empirical antifungal therapy has a low specificity and certain limitations, such as over-treatment of the patients, drug resistance induction, and higher medical expenses [3,8].

The concept of preemptive antifungal therapy was recently introduced for IFD therapy in hematological malignancy patients [9]. Briefly, preemptive antifungal therapy is a diagnosis-based therapy that uses antifungals based on the diagnosis of probable fungal infection by results from microbiological tests (e.g., GM testing) or chest computed tomography (CT) [9]. Preemptive antifungal therapy is intended to provide antifungal therapy to early-stage patients to achieve anticipated effects and reduce the overuse of antifungal agents [9,10]. A controlled trial systematically comparing empirical *vs.* preemptive antifungal therapy for high-risk, febrile, neutropenic patients concluded that although preemptive treatment increased the incidence of invasive fungal disease, it did not increase the overall mortality in patients and it reduced the expenses related to antifungal drugs used [11]. However, because this strategy depends on galactomannan testing (GM test) and chest CT, preemptive antifungal therapy has certain disadvantages, such as the delayed initiation of antifungal treatment [9], and the low sensitivity of galactomannan testing for some *Aspergillus fumigatus*-infected patients [12]. In addition, the image markers from chest CT (halo sign or reverse halo sign) are not specific and may be observed in many infectious and non-infectious diseases rather than fungal infection [13]. Therefore, some researchers still view empirical antifungal therapy as a more validated treatment of IFD in patients with hematological malignancy [3].

Recently, the CDC of China issued a revised guideline of the *Diagnosis Criteria and Treatment Regulation of Hematological Malignancy Patients with Invasive Fungal Disease* (the Forth Revised Edition). In this guideline, application of preemptive antifungal therapy is recommended. We designed this study to evaluate the benefits of preemptive antifungal therapy for Chinese patients.

Material and Methods

Ethics statement

Institutional Ethics Board approval was obtained from the Medical Ethics Committee of the Second Hospital of Hebei Medical University. All participating patients were formally informed of the purpose of this study and written informed consent was obtained from all participants.

Patients and groups

We enrolled 268 patients with hematological malignancy admitted to the Department of Hematology in the Second Hospital of Hebei Medical University from October 2013 to December 2014. All patients were subjected to cytomorphology, histological chemistry and biopsy of bone marrow, subtyping by flow cytometry, detection of fusion gene, and chromosome examination to confirm the occurrence of hematological malignancy. The IFD diagnosis criteria and standard of therapeutic effect were referenced to the *Diagnosis Criteria and Treatment Regulation of Hematological Malignancy Patients with Invasive Fungal Disease* (Forth Revised Edition). All patients were randomly assigned to either the empirical antifungal therapy group (n=138) or the preemptive antifungal therapy group (n=130).

Inclusion and exclusion criteria

All patients included in this study met the following criteria: older than 18 years, had hematological malignancy, had a plan of chemotherapy treatment, and had severe neutropenia (less than 0.5 ×10^9 neutrophils/L for a minimum duration of 10 days). Patients with any of the following situations were excluded: had received hematopoietic stem cell transplantation, had experience or symptoms of IFD, demonstrated low tolerance to triazoles, HIV-positive, and Karnofsky Performance Status score less than 30 according to the accepted scale system [14]. Moreover, patients were excluded if they had no neutropenia or fever, were treated with antifungal therapy within 4 days of developing a fever, started antifungal therapy without proof of IFD at 4–14 days, or had no antifungal treatment but had proof of IFD at 4–14 days.

Medical intervention

The medical intervention was conducted as previously described [11]. Briefly, 2 blood cultures, 1 urine culture, and related microbiological analysis were conducted for all patients. Patients received broad-spectrum β-lactam antibiotic with or without combination of aminoglycosides according to clinical manifestation. Glycopeptides antibiotics were administrated immediately if the following symptoms occurred: infectious shock, stage IV mucositis according to WHO diagnostic

criteria, colonization of infection caused by methicillin-resistant *Staphylococcus aureus* or *Streptococcus pneumoniae,* or catheter-related infections. Glycopeptide antibiotics were added if the fever persisted for 48 h after administration of broad-spectrum β-lactam antibiotic.

For the empirical treatment group, antifungal therapy was started within 4 days of start of persistent fever and antibacterial treatment. If there was recurrent fever between day 4 and day 14, antifungal therapy was initiated on the day of the recurrence. For the preemptive treatment group, antifungal therapy was initiated immediately if any of the flowing situations occurred: clinical or imaging examination suggested pneumonia, acute sinusitis, stage III mucositis, or most importantly, infectious shock, IFD-related skin damage, central nerve system symptoms due to unknown reason, periorbital inflammation, abscess of liver or spleen, severely diarrhea, colonization by aspergilloma, or (1,3)-β-D-glucan test (G test)-positive and galactomannan test (GM test)-positive. The antifungal therapy was continued until patients recovered from febrile neutropenia. If a patients had fever after 14 days, the chief physician decided if additional treatment should be administered.

The therapeutic effect was tested by G testing and GM testing twice a week until patients recovered from febrile neutropenia. Examination by chest CT was conducted weekly. The liver and renal function was examined weekly. Routine analysis for blood was tested once for every 2 days.

Voriconazole was used as the first-line treatment for patients in every 12 h via I.V. injection. The initiating injection dose of voriconazole was 400 mg, then the dose was decreased to 200 mg for subsequent injections. The chief physician decided if the treatment was ineffective or if an adverse effect occurred. The end-point for the antifungal treatment was patient recovery from febrile neutropenia or when a patient quit treatment due to any reason.

Outcomes and follow-up

The survival rate of patients who recovered from neutropenia by Day 14 was set as the primary end-point. Patients with severe neutropenic within a maximum of 60 days after receiving treatment or who demonstrated severe adverse events were excluded from data analysis. The ratio of diagnosed IFD patients and duration of persistent fever were used as the secondary end-points. The safety of the treatment was demonstrated as the rate of patients quitting treatment due to ineffectiveness or adverse events during the treatment. The indicators of cost-effectiveness were the ratio of patients who received antifungal therapy, duration and expenses of antifungal therapy, and patient hospitalization.

Statistical analysis

The data analysis was conducted by use of SPSS (release 17.0, SPSS, Inc., Chicago, IL, USA). For categorical variables, data were compared using χ^2 tests or Fisher's exact probability test. Measurement variables were tested by the 2 independent-samples Wilcoxon rank sum test. Subgroup analysis was used in the stratification of induction and consolidation chemotherapy.

Results

General information and characteristics of patients

There were 138 patients (86 males and 52 females) in the empirical group and 130 patients (75 males and 55 females) in the preemptive group. The median duration of neutropenia for all patients from both groups was 13 days, with no significant difference observed between groups. The median age for patients in the empirical group was 38 years (ranging from 18 to 77 years) and the median age for the preemptive group was 38 years (ranging from 18 to 81 years). Table 1 shows the cases of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), mixed-lineage acute leukemia (MAL), and multiple myeloma (MM) among all patients. The phase of chemotherapy (induction, relapse and consolidation), application of antifungal prophylaxis for patients, intensity and duration of neutropenia, and duration of fever are documented in Table 1.

Overall survival rate and causes of death

The overall survival rate for patients in the preemptive group was 94.6% compared with 97.1% in the empirical group (*P*=0.305), suggesting the survival rate was similar (Table 2).

There were 11 deaths recorded, including 4 IFD patients (1 in the empirical group and 3 in the preemptive group), 4 patients with bacterial septicemia, 2 with unclear septicemia, and 1 with cardiogenic shock. The IFD-associated death rates were 0.7% and 2.3% for the empirical and preemptive group (*P*=0.573), receptively, but this difference was not significant (Table 2).

Proven and probable IFD

IFD was observed in 12 (9.2%) patients in the preemptive group, which was significantly higher than the 3 (2.2%) cases in the empirical group (Table 2). Moreover, out of these 12 IFD cases in the preemptive group, 8 were pulmonary aspergillosis (including 6 cases of baseline IFD and 2 cases of breakthrough IFD) and the rest were candidiasis (including 2 cases of baseline IFD and 2 cases of breakthrough IFD). Among these 4 cases of candidiasis, there were 2 cases of *Candida albicans*, 1 case of *Candida tropicalis,* and 1 case of *Candida glabrata.*

Table 1. Patient characteristics in the per-protocol analysis.

Characteristics	Empirical (n=138)		Preemptive (n=130)	
Median age	38		38	
Age range	18–77		18–81	
Female sex (percentage)	52	(37.7%)	55	(42.3%)
Acute myeloid leukemia (AML)	95	(68.8%)	90	(69.2%)
Acute lymphoblastic leukemia (ALL)	35	(25.3%)	33	(25.4%)
Mixed-lineage acute leukemia (MAL)	6	(4.4%)	5	(3.8%)
Multiple myeloma(MM)	2	(1.5%)	2	(1.6%)
Phase of chemotherapy				
Induction therapy	38	(27.5%)	33	(25.4%)
Relapse therapy	35	(25.4%)	34	(26.1%)
Consolidation therapy	65	(47.1%)	63	(48.5%)
Antifungal prophylaxis				
Any	114	(82.6%)	108	(83.1%)
Fluconazole	15	(10.9%)	16	(12.6%)
Itraconazole	9	(6.5%)	6	(4.6%)
Neutropenia for >10 daysc	99	(71.7%)	94	(72.3%)
Duration of neutrophil count <500 neutrophils/mm³, days				
Median (IQR)	13	(9–19)	13	(9–20)
Range	4–56		4–50	
Neutropenia before chemotherapy	20	(14.5%)	19	(14.6%)
Duration of neutropenia before chemotherapy,				
Median days (IQR)	4	(3–7)	5	(4–7)
Duration of Fever(≥38.0°C)				
Days (IQR)	3	(2–6)	4	(2–5)
Range	1–16		1–16	

For IFD cases in the empirical group, only 2 cases of baseline IFD and 1 case of breakthrough IFD were observed (Table 2).

Application of antifungal therapy

According our data, application of antifungal therapy (26 cases, 20%, P<0.001) in the preemptive group was significantly lower than in the empirical group (43 cases, 31.2%) (Table 3), which is consisted with previous observation [11]. Among 26 cases in the preemptive group, 2 had persistent or recurrent fever; and the other 24 cases were clinical manifestations-positive or non-invasive diagnosis-positive, including 13 cases of pneumonia, 2 cases of severe mucositis, 3 cases of G test-positive,

3 cases of GM test-positive, 2 cases of sinusitis, and 1 case of diarrhea. In the empirical group, 25 cases had persistent or recurrent fever between day 4 and day 14 after antibacterial treatment initiation (Table 3). The other cases were 13 cases of pneumonia, 2 cases of severely mucositis, 2 cases of G test-positive, and 1 case of GM test-positive (Table 3).

The average time of antifungal therapy for the empirical and preemptive groups were 20.0±4.7 days and 13.8±4.7, respectively, which is statistically significant (Table 3). The cost for each group was calculated and compared using the Chinese currency, Renminbi (RMB). The average expense of antifungal therapy for empirical and preemptive groups was RMB 12

Table 2. Efficacy and end points in the per-protocol analysis(n=268).

End point	Empirical (n=138)		Preemptive (n=130)		Difference (95%CI)	P value
Survival rate	134	(97.1%)	123	(94.6%)	−2.5 (−5.9 to 1.4)	0.305
Death cases	4	(2.9%)	7	(5.4%)	−	−
IFD cases	3	(2.2%)	12	(9.2%)	−7.0 (−12.3 to −1.7)	0.012
Baseline IFD						
Aspergillus	2	()	6	()	−	−
Candida	0	()	2	()	−	−
Breakthrough IFD						
Aspergillus	1	()	2	()	−	−
Candida	0	()	2	()	−	−
IFD related mortality	1	(0.7%)	3	(2.3%)	1.6 (−1.9 to 1.3)	0.573

Table 3. Antifungal therapy in the per-protocol analysis (n=268).

End point	Empirical (Intent to treat: n=138)		Preemptive (Intent to treat: n=130)		P value
Antifungal treated cases	43	(31.2%)	26	(20.0%)	<0.001
Reason for antifungal treatment					
Isolated fever between day 4 and day 14 after antibacterial treatment initiation	25	(58.1%)	2	(7.7%)	<0.001
Pneumonia	13	(30.2%)	13	(50.0%)	−
Severe mucositis	2	(4.7%)	2	(7.7%)	−
G test positive	2	(4.7%)	3	(11.5%)	−
GM test positive	1	(2.3%)	3	(11.5%)	−
Sinusitis or periorbital inflammation	0	(0%)	2	(7.7%)	−
Diarrhea	0	(0%)	1	(3.9%)	−
Duration of fever before antifungal treatment					
Median days (IQR)	4	(2–5)	5	(4–7)	0.001
Duration of fever after antifungal treatment					
Median days (IQR)	3	(2–5)	3	(2–5)	0.802
Duration of antifungal treatment					
Mean days ±SD	20.0±4.7		13.8±4.7		<0.001
Cost of antifungal(RMB)					
Mean ±SD	12104±3719		8379±2253		<0.001
Range	5776–25600		4560–14896		−
Length of hospitalization					
Mean days ±SD	34.0±11.3		32.7±9.3		0.283
Range	17–72		16–71		−
Treatment failure	6	(14.0%)	5	(19.2%)	0.810
Side effect	2	(4.7%)	1	(3.8%)	0.874

104±3719 and RMB 8379±2253, respectively. Length of hospital stay was similar between the 2 groups of patients (Table 3). Moreover, 6 patients in the empirical group and 5 patients in the preemptive group demonstrated inefficacious voriconazole treatment. Two patients in the empirical group and 1 patient in the preemptive group quit treatment due to adverse reactions to voriconazole.

Discussion

Empirical antifungal therapy is a commonly used strategy to treat hematological disease for reducing mortality of IFD patients. However, the effectiveness of this strategy is still controversial due to lack of reliable data [17,18]. Generally, empirical antifungal therapy is initiated if persistent fever or recurrent fever is observed in patients and is terminated at disappearance of fever [8,19–22]. However, it is questionable to set the appearance and disappearance of fever as the initiation and termination point of antifungal therapy, since fever is not a specific symptom of IFD [18,23–25]. Moreover, application of empirical antifungal therapy may result certain disadvantages, such as over-treatment or higher expense. However, since more diagnostic technologies, such as G test, GM test, Chest CT, and polymerase chain reaction (PCR), are now used for early detection of IFD, it is possible to determine more precise initiating points for antifungal treatment [9,26,27]. Therefore, diagnosis-based preemptive antifungal therapy has become an alternative strategy which allows patients receiving antifungal treatment as early as possible to achieve a better outcome and decrease overuse of antifungal drugs.

However, preemptive therapy is not recommended as standard care due to the insensitivity and un-specificity of diagnostic tools, and the initiating point of treatment is not yet well defined. Moreover, the delayed initiation of treatment may increase mortality. Segal et al. suggested that the initiation of antifungal therapy in febrile neutropenic patients could be determined by chest CT and experimental examinations [25]. In our study, antifungal therapy was recommended only to those patients who had clinical manifestations, even with normal results of G testing, GM testing, and chest CT.

According to previously reports, analysis conducted by pooling the results of published randomized trials of empirical treatment with polyenes demonstrated the expected survival rate of empirical therapy was 1677 of 1846 (90.8%; 95% CI, 89.5–92.2%) [11,15]. The same reports also suggested that a noninferiority margin of −8% was chosen on the basis of guidelines issued by the Center for Drug Evaluation and Research and the Committee for Proprietary Medicinal Products [11], and the use of a −10% non-inferiority margin for evaluation of new

antibacterials whose expected success rate is 90% [16]. In the preemptive group of our study, only 26 (18.6%) of the intent-to-treat cases received antifungal therapy, and the overall survival rate was 94.6%, which is similar to previous reports of the survival rate in empirical therapy [11,15]. Therefore, application of preemptive therapy did not increase the mortality of the intent-to-treat group in a Chinese population, and is consistent with previous reports from Western countries [11].

The survival rates of the preemptive and empirical groups were similar in our study, and we also noticed that the incidence of IFD cases was significantly higher (12 cases, 9.2%) in the preemptive group than in the empirical group (3 cases, 2.3%). A previous report evaluated the feasibility of preemptive therapy based on clinical symptoms, galactomannan antigenemia (cut-off for antigen level, 0.5 ng/mL), lung CT, and bronchoalveolar lavage [9]. The data indicated that fewer patients meet criteria for preemptive treatment than empirical treatment, which is consistent with our observations. However, due to it open design, this report could not determine whether preemptive treatment was non-inferior to empirical treatment [9]. In another trial, the incident rate of IFD cases was also higher in the preemptive group than in the empirical group (9.1% vs. 2.7%)4[11]. Taken together, these findings may suggest that the low IFD incidence rate may reflect the lower positive predictive value of diagnostic investigations when the incidence of IFD is low [11]. Therefore, the fact that more patients in the empirical group received antifungal treatment may have decreased the incidence rate of IFD but conferred little benefit to overall survival rate. We also noticed that the IFD-related deaths in the preemptive mainly occurred in elderly patients or patients whose performance score (PS) was higher than 2 (data not shown). This observation suggests that empirical therapy may be preferable for elderly or high PS patients to avoid IFD-related death, while preemptive treatment is recommended for younger or low PS patients. However, further investigation is needed to validate this speculation.

The average durations of antifungal therapy for empirical and preemptive groups were 20.0±4.7 days and 13.8±4.7 days, respectively. Moreover, the average expense for preemptive antifungal treatment was 8379.00±2253.00 CNY in this study. Although this result was not concluded by a completely randomized analysis, the duration and expense for antifungal therapy was significantly lower in the preemptive group. In China, due to the large population and relatively scarce hospitals, treatments with lower costs and shorter regimens are preferred. As a broad-spectrum antifungal agent, the therapeutic effect of voriconazole is comparable with amphotericin B liposome. We found voriconazole was well tolerated, and only 2 patients in the empirical group and 1 in the preemptive groups quit treatment.

Conclusions

Our data demonstrate that the preemptive antifungal therapy did not increase the IFD mortality compared to empirical therapy in patients with febrile neutropenic hematological malignancy, but preemptive antifungal therapy is an economically preferable medical practice in China. However, the increased incidence of IFD in the preemptive antifungal therapy group also suggest that the age and PS score of patients were factors for selecting the strategy. Moreover, to apply the preemptive strategy more accurately, clinical manifestations, physical signs, and more diagnostic methods (e.g., different imaging technics, biological markers, or PCR) have to be carefully assessed to achieve more effective preventive antifungal therapy.

References:

1. Walsh TJ, Anaissie EJ, Denning DW et al: Treatment of aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis, 2008; 46: 327–60

2. Maertens J, Marchetti O, Herbrecht R et al: European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3 – 2009 update. Bone Marrow Transplant, 2011; 46: 709–18

3. Vallejo C, Barberan J: Empirical antifungal treatment: A valid alternative for invasive fungal infection. Rev Esp Quimioter, 2011; 24: 117–22

4. Pagano L, Caira M, Candoni A et al: The epidemiology of fungal infections in patients with hematologic malignancies: The SEIFEM – 2004 study. Haematologica, 2006; 91: 1068–75

5. Fortun J, Carratala J, Gavalda J et al: [Guidelines for the treatment of invasive fungal disease by Aspergillus spp. and other fungi issued by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). 2011 Update]. Enferm Infecc Microbiol Clin, 2011; 29: 435–54

6. Mikolajewska A, Schwartz S, Ruhnke M: Antifungal treatment strategies in patients with haematological diseases or cancer: From prophylaxis to empirical, pre-emptive and targeted therapy. Mycoses, 2012; 55: 2–16

7. Freifeld AG, Bow EJ, Sepkowitz KA et al., and Infectious Diseases Society of Amreica: Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis, 2011; 52: 427–31

8. Turner SJ, Chen SC, Slavin MA, Kong DC: Pharmacoeconomics of empirical antifungal use in febrile neutropenic hematological malignancy and hematopoietic stem cell transplant patients. Expert Rev Pharmacoecon Outcomes Res, 2013; 13: 227–35

9. Maertens J, Theunissen K, Verhoef G et al: Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: A prospective feasibility study. Clin Infect Dis, 2005; 41: 1242–50

10. Stefani PM, Gottardi M, Zanetti F et al: Preemptive antifungal therapy among neutropenic patients. Clin Infect Dis, 2006; 42: 1507–8; author reply 1508–9

11. Cordonnier C, Pautas C, Maury S et al: Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: A randomized, controlled trial. Clin Infect Dis, 2009; 48: 1042–51

12. Hachem RY, Kontoyiannis DP, Chemaly RF et al: Utility of galactomannan enzyme immunoassay and (1,3) beta-D-glucan in diagnosis of invasive fungal infections: Low sensitivity for *Aspergillus fumigatus* infection in hematologic malignancy patients. J Clin Microbiol, 2009; 47: 129–33

13. Georgiadou SP, Sipsas NV, Marom EM, Kontoyiannis DP: The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts. Clin Infect Dis, 2011; 52: 1144–55

14. Friendlander AH, Ettinger RL: Karnofsky performance status scale. Spec Care Dentist, 2009; 29: 147–48

15. Empiric antifungal therapy in febrile granulocytopenic patients. EORTC International Antimicrobial Therapy Cooperative Group. Am J Med, 1989; 86: 668–72

16. Rohmel J: Statistical considerations of FDA and CPMP rules for the investigation of new anti-bacterial products. Stat Med, 2001; 20: 2561–71

17. Castagnola E, Mikulska M, Barabino P et al: Current research in empirical therapy for febrile neutropenia in cancer patients: what should be necessary and what is going on. Expert Opin Emerg Drugs, 2013; 18: 263–78

18. Bennett JE, Powers J, Walsh T et al: Forum report: Issues in clinical trials of empirical antifungal therapy in treating febrile neutropenic patients. Clin Infect Dis, 2003; 36: S117–22

19. Vallejo Llamas JC, Ruiz-Camps I: [Invasive fungal infection in haematology patients]. Enferm Infecc Microbiol Clin, 2012; 30: 572–79

20. Mizuno H, Sawa M, Yanada M et al: Micafungin for empirical antifungal therapy in patients with febrile neutropenia: Multicenter phase 2 study. Int J Hematol, 2013; 98: 231–36

21. Kim SJ, Cheong JW, Min YH et al: Success rate and risk factors for failure of empirical antifungal therapy with itraconazole in patients with hematological malignancies: A multicenter, prospective, open-label, observational study in Korea. J Korean Med Sci, 2014; 29: 61–68

22. Walsh TJ, Teppler H, Donowitz GR et al: Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med, 2004; 351: 1391–402

23. de Pauw B: Preventative use of antifungal drugs in patients treated for cancer. J Antimicrob Chemother, 2004; 53: 130–32

24. de Pauw BE: Between over- and undertreatment of invasive fungal disease. Clin Infect Dis, 2005; 41: 1251–53

25. Segal BH, Almyroudis NG, Battiwalla M et al: Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. Clin Infect Dis, 2007; 44: 402–9

26. Wheat LJ, Walsh TJ: Diagnosis of invasive aspergillosis by galactomannan antigenemia detection using an enzyme immunoassay. Eur J Clin Microbiol Infect Dis, 2008; 27: 245–51

27. Marr KA, Balajee SA, McLaughlin L et al: Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: Variables that affect performance. J Infect Dis, 2004; 190: 641–49

28. Athanasakis K, Petrakis I, Kyriopoulos J: Posaconazole *vs.* fluconazole/itraconazole in the prophylaxis of invasive fungal infections in immunocompromised patients: A cost-effectiveness analysis in Greece. J Med Econ, 2013; 16: 678–84