MAJOR ARTICLE

Empirical versus Preemptive Antifungal Therapy for High-Risk, Febrile, Neutropenic Patients: A Randomized, Controlled Trial

Catherine Cordonnier,[1] Cécile Pautas,[1] Sébastien Maury,[1] Anne Vekhoff,[4] Hassan Farhat,[11] Felipe Suarez,[5] Nathalie Dhédin,[6] Francoise Isnard,[7] Lionel Ades,[12] Frédérique Kuhnowski,[8] Françoise Foulet,[2] Mathieu Kuentz,[1] Patrick Maison,[3] Stéphane Bretagne,[2] and Michaël Schwarzinger[9,10]

[1]Hematology and [2]Parasitology-Mycology Departments, and [3]Unité de Recherche Clinique, Henri Mondor Teaching Hospital, Assistance Publique–Hôpitaux de Paris (AP-HP) and Paris 12 University, Créteil, [4]Hematology Department, Hotel Dieu Teaching Hospital, [5]Hematology Department, Necker Teaching Hospital, [6]Hematology Department, Pitié-Salpêtrière Teaching Hospital, [7]Hematology Department, Saint-Antoine Teaching Hospital, and [8]Hematology Department, Cochin Teaching Hospital, AP-HP, and [9]INSERM, Unité Mixte de Recherche en Santé (UMR-S) 707, and [10]Université Pierre et Marie Curie, Université Paris 6, UMR-S 707, Paris, [11]Hematology Department, André Mignot Hospital, Le Chesnay, and [12]Hematology Department, Avicenne Teaching Hospital, Bobigny, France

(See the editorial commentary by de Pauw and Donnelly on pages 1052–4)

Background. Empirical antifungal therapy is the standard of care for neutropenic patients with hematological malignancies who remain febrile despite broad-spectrum antibacterial treatment. Recent diagnostic improvements may ensure the early diagnosis of potentially invasive fungal disease. Reserving antifungals for this stage may achieve similar survival rates and reduce treatment toxicity and costs.

Methods. In this multicenter, open-label, randomized noninferiority trial, we compared an empirical antifungal strategy with a preemptive one. Empirical treatment was defined as antifungal treatment of patients who have persistent or recurrent fever. Preemptive treatment was defined as treatment of patients who have clinical, imaging, or galactomannan-antigen-assay evidence suggesting fungal disease. First-line antifungal treatment was amphotericin B deoxycholate (1 mg/kg/day) or liposomal amphotericin (3 mg/kg/day), depending on daily renal function. The primary efficacy outcome was the proportion of patients alive at 14 days after recovery from neutropenia.

Results. The median duration of neutropenia (neutrophil count, <500 cells/mm^3) for the 293 patients enrolled was 18 days (range, 5–69 days). By intention-to-treat analysis, survival was 97.3% with empirical treatment and 95.1% with preemptive treatment. The lower 95% confidence limit for the difference in mortality was −5.9%, which was within the noninferiority margin of −8%. Probable or proven invasive fungal infections were more common among patients who received preemptive treatment than among patients who received empirical treatment (13 of 143 vs. 4 of 150; $P < .05$), and most infections occurred during induction therapy (12 of 73 patients in the preemptive treatment group vs. 3 of 78 patients in the empirical treatment group were infected during induction therapy; $P < .01$). Preemptive treatment did not decrease nephrotoxicity but decreased costs of antifungal therapy by 35%.

Conclusions. Preemptive treatment increased the incidence of invasive fungal disease, without increasing mortality, and decreased the costs of antifungal drugs. Empirical treatment may provide better survival rates for patients receiving induction chemotherapy.

Empirical antifungal therapy is the standard of care used to decrease the number of deaths due to invasive fungal infection (IFI) among neutropenic patients who have persistent or recurrent fever despite broad-spectrum antibacterial treatment [1, 2]. However, the appropriateness of using fever as the sole criterion for initiation of antifungal therapy has been widely debated [3–7]. Randomized trials of empirical therapy used resolution of fever as the primary end point [8, 9] or as a component of a composite end point [10–15]. However, fever is not specific to IFI, the early diagnosis of

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Reprints or correspondence: Dr. Catherine Cordonnier, Hematology Dept., CHU Henri Mondor, 94000 Créteil, France (carlcord@club-internet.fr).

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which has benefitted from new tools, such as CT and galactomannan antigenemia assay for *Aspergillus* infection [16–19].

Liposomal amphotericin B and caspofungin were approved as alternatives to amphotericin B for empirical antifungal therapy, with major safety gains but also a sharp increase in the cost of treatment [11, 15]. When febrile neutropenia persists despite antibacterial therapy, reserving antifungal treatment for patients who have early evidence of IFI obtained from daily clinical evaluations and noninvasive tests might reduce drug use, toxicity, and costs. In an open study, this preemptive, guided-treatment strategy reduced antifungal drug use by 78% [17]. However, a comparison of survival rates for the 2 treatment strategies is needed.

We conducted a randomized trial to compare survival with empirical treatment versus preemptive antifungal treatment in high-risk neutropenic patients who have persistent or recurrent fever despite antibacterial therapy. Survival at 2 weeks after recovery from neutropenia was the primary end point.

METHODS

Design overview. A prospective, randomized, open-label noninferiority trial was conducted from April 2003 through February 2006 in 13 French teaching hospitals. The trial was funded by the French Ministry of Health (Programme Hospitalier de Recherche Clinique 2002 AOR02028) and was sponsored by Assistance Publique–Hôpitaux de Paris (AP-HP). The study was registered at http://www.ClinicalTrials.gov (NCT001190463). Data were collected by the sponsor, were source documented, and were analyzed by one of the investigators (M.S.). The protocol and consent form were approved by the ethics committee of Henri Mondor Hospital. Written informed consent was obtained from all patients.

The primary objective was to compare survival with empirical therapy versus preemptive antifungal therapy in febrile neutropenic patients treated for hematological malignancies. The secondary objectives were to compare the incidence of IFI, adverse events, and antifungal drug consumption and costs. Noninferiority hypotheses were used in the analysis of survival and incidence of IFI. Superiority hypotheses were tested for antifungal drug toxicity, consumption, and costs.

Participants. Patients aged ⩾18 years were eligible if they had hematological malignancies and were scheduled for chemotherapy or autologous stem cell transplantation that was expected to cause neutropenia (neutrophil count, <500 cells/mm^3) for at least 10 days. Exclusion criteria were a planned allogeneic transplantation, a history of or symptoms consistent with IFI, previous severe toxicity from intravenous polyenes, a Karnofsky score <30%, and HIV seropositivity.

Randomization and interventions. Patients were enrolled at initiation of chemotherapy and no later than 48 h into the first febrile episode. Patients at each center were stratified by risk factors for IFI—namely, induction versus consolidation chemotherapy or stem cell transplantation [20]—and whether systemic antifungal prophylaxis was used (figure 1). Patients were assigned in a 1:1 ratio to the empirical or preemptive treatment arms with use of a computer-generated randomization scheme with blocks of 4.

Patients who became febrile while neutropenic had at least 2 blood cultures, a urine culture, and other microbiological tests performed as clinically indicated. They then received treatment with a broad-spectrum β-lactam, with or without an aminoglycoside, according to the local protocol. First-line glycopeptide therapy was reserved for patients with shock, grade 4 mucositis, colonization with methicillin-resistant *Staphylococcus aureus* or penicillin-resistant *Streptococcus pneumoniae,* or catheter infection, which met Infectious Diseases Society of America criteria [1]. Patients with persistent fever at 48 h after starting a β-lactam with no glycopeptide could receive add-on glycopeptides. No further changes were allowed to be made without microbiological guidance.

Antifungal prophylaxis was given according to each center's protocol. The randomly allocated antifungal strategy was started on day 4 of persistent fever and antibacterial treatment or, for patients with recurrent fever between day 4 and day 14, on the day of the recurrence. In the empirical treatment arm, persistent or recurrent fever led to initiation of antifungal therapy. In the preemptive treatment arm, antifungal treatment was guided by any of the following occurrences at any time after 4 days of fever and antibacterial treatment: clinically and imaging-documented pneumonia or acute sinusitis, mucositis of grade ⩾3, septic shock, skin lesion suggesting IFI, unexplained CNS symptoms, periorbital inflammation, splenic or hepatic abscess, severe diarrhea, *Aspergillus* colonization, or ELISA results positive for galactomannan antigenemia. Treatment of patients with fever for >14 days was at the discretion of the investigator. All patients were screened twice weekly for galactomannan antigenemia (Platelia Aspergillus; Bio-Rad) until recovery from neutropenia, and the results were available within 24 h; a positive result was defined as a galactomannan index ⩾1.5, as recommended by the manufacturer at study initiation. Investigators were encouraged to confirm positive results of ELISA with a second sample and to obtain a chest radiograph within 24 h and then a chest CT if the findings of chest radiograph were normal. All other items of clinical management complied with each center's protocol.

First-line intravenous antifungal therapy was the same in both arms. Amphotericin B deoxycholate (1 mg/kg/day) was used for patients whose creatinine clearance was >60 mL/min or was 40–59 mL/min without concomitant nephrotoxic drugs. Liposomal amphotericin (3 mg/kg/day) was given to patients whose creatinine clearance was 26–39 mL/min or was 40–59 mL/min with concomitant nephrotoxic drugs. Creatinine clear-

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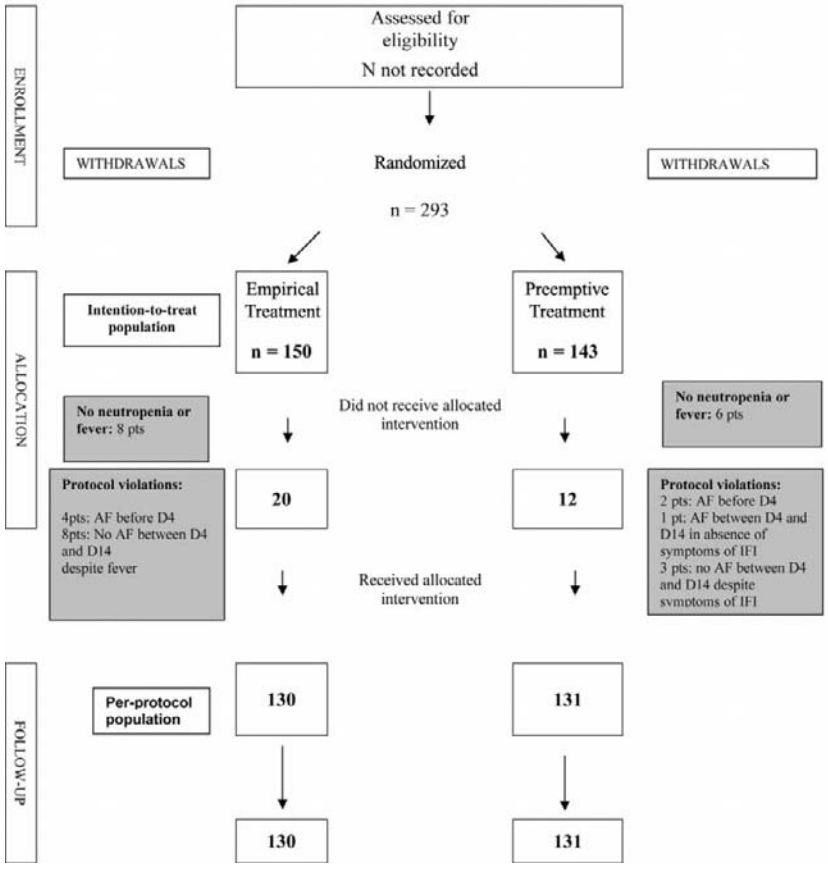

Figure 1. Consort flow chart. AF, antifungal prophylaxis; D4, day 4; D14, day 14; IFI, invasive fungal infection; pts, patients.

ance <25 mL/min was considered to be a severe adverse event (SAE), the management of which was at the investigator's discretion. In the absence of SAEs, antifungal therapy was continued until recovery from neutropenia.

Outcomes and follow-up. The primary efficacy outcome was the proportion of patients alive at 14 days after recovery from neutropenia or, for patients with persistent neutropenia at 60 days after inclusion in the study or an SAE, at the time that these patients were censored. The secondary efficacy outcome measures were fever duration and the proportion of patients with proven or probable IFI. Survival was also assessed at 4 months after inclusion.

Safety outcomes included the change in creatinine clearance (<60 mL/min) and the proportion of patients with SAE (creatinine clearance <25 mL/min or septic shock). Economic outcomes during the hospital stay included the proportion of patients receiving any systemic antifungal agent; the duration and cost of antifungal therapy, including treatment of IFI (with use of the average wholesale purchase price, in 2005 €, of conditioning at AP-HP); and length of hospital stay.

An independent, blinded adjudication committee reviewed the reasons for starting antifungal therapy, diagnoses of IFI, and causes of death. Proven and probable IFIs were defined according to the European Organization for Research and Treatment of Cancer-Mycoses Study Group [19]. Possible infections were not considered. Baseline IFI cases were those documented by procedures performed before or within 24 h after the first dose of antifungal agent. Breakthrough IFI cases were those documented by procedures performed at ⩾24 h after the first dose of antifungal agent.

Sample size and statistical analysis. Expected survival with empirical therapy, estimated by pooling the results of published randomized trials of empirical treatment with polyenes [8–14, 21], was 1677 of 1846 (90.8%; 95% CI, 89.5%–92.2%). 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, which suggest the use of a −10% noninferiority margin for evaluation of new antibacterials whose expected success rate is 90% [22] and a −10% noninferiority margin in large, randomized trials of empirical antifungal therapy [11, 14, 15]. Given the 90% expected survival rate, 228 patients were needed in each treatment arm to establish the noninferiority of preemptive treatment with 80% power and a 1-sided 95% CI.

An independent Data and Safety Monitoring Board, composed of a hematologist, an infectiologist, and a statistician,

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Table 1. Patient characteristics in the intention-to-treat population ($n = 293$).

Characteristic	Empirical treatment arm ($n = 150$)	Preemptive treatment arm ($n = 143$)
Age, years		
Mean ± SD	52.0 ± 13.5	52.1 ± 14.1
Range	20–78	19–77
Female sex	64 (42.7)	58 (40.6)
Primary diagnosis		
Acute myeloid leukemia[a]	99 (66.0)	98 (68.5)
Acute lymphoblastic leukemia	8 (5.3)	3 (2.1)
Lymphoma[b]	39 (26.0)	36 (25.2)
Myeloma	4 (2.7)	6 (4.2)
Phase of therapy		
Induction therapy	70 (46.7)	67 (46.9)
Relapse treatment	8 (5.3)	6 (4.2)
Consolidation therapy	27 (18.0)	24 (16.8)
Autologous transplantation	45 (30.0)	46 (32.2)
Autologous transplantation including total body irradiation	8/45 (17.8)	6/46 (13.0)
Antifungal prophylaxis		
Any	63 (42.0)	69 (48.3)
Amphotericin orally	47 (31.3)	51 (35.7)
Fluconazole	17 (11.3)	19 (13.3)
Itraconazole	10 (6.7)	6 (4.2)
Neutropenia for ⩾10 days[c]	127/146 (87.0)	124/141 (87.9)
Duration of neutrophil count <500 neutrophils/mm^3, days		
Median (IQR)	18 (11–28)	17 (12–26)
Range	6–69	5–57
Duration of neutrophil count <100 neutrophils/mm^3, days		
Median (IQR)	13 (8–22)	13 (8–22)
Range	2–69	2–57
Neutropenia at baseline[c]	39/146 (26.7)	27/141 (19.1)
Duration of neutropenia before inclusion in the study, median days (IQR)	3 (1–6)	4 (2–8)
Neutropenia before chemotherapy[c]	22/146 (15.1)	18/141 (12.8)
Duration of neutropenia before chemotherapy, median days (IQR)	3 (1–5)	2 (2–5)
Neutropenia for >60 days	1	0

NOTE. Data are no. or proportion (%) of patients, unless otherwise indicated. IQR, interquartile range.

[a] Includes 3 patients with acute myeloid transformation of chronic myeloid leukemia treated with protocols for acute myeloid leukemia.

[b] Includes 3 patients with chronic lymphoid leukemia.

[c] Excludes 6 patients without neutropenia (4 in the empirical treatment group and 2 in the preemptive treatment group).

was appointed before study initiation. The board reviewed SAEs after inclusion of one-half of the planned sample size and performed an intermediate analysis of overall survival at $\alpha = 0.01$; in the event of study continuation, the sample size would be reestimated. At the intermediate analysis, overall survival was significantly better than expected (97.6%), and noninferiority was not shown (the lower 99% confidence limit of mortality difference [−10.1%] was outside the −8% noninferiority margin). The board had to choose between either decreasing the sample size to 146 patients in each arm without changing the noninferiority margin or reducing the noninferiority margin to −6% without changing the sample size [23]. The board decided to keep the −8% noninferiority margin and to decrease the sample size, because this choice decreased the number of patients exposed to life-threatening events.

The intention-to-treat analysis included all randomized patients. In the per-protocol analysis, we excluded patients without neutropenia or fever and those with protocol violations. Efficacy outcomes were analyzed using the Cochran-Mantel-Haenszel χ^2 test. Differences in survival times were assessed using a log-rank test. Exploratory analyses were conducted in the stratification subgroups. The incidence of IFI was computed using the cumulative incidence method with the risk of death as a competing risk, and differences between the cumulative

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Table 2. Efficacy end points in the intention-to-treat population (n = 293).

Efficacy end point	Empirical treatment arm (n = 150)	Preemptive treatment arm (n = 143)	Difference (95% CI)	P[a]
Primary				
Alive at study completion	146 (97.3)	136 (95.1)	−2.2 (−5.9 to 1.4)	.31
Secondary				
IFI	4 (2.7)	13 (9.1)	−6.4 (−10.9 to −1.9)	<.02
Baseline IFI due to				
Aspergillus species	2	6	…	
Candida species	0	3	…	
Breakthrough IFI due to				
Aspergillus species	2	2	…	
Candida species	0	2	…	
IFI-related mortality	0 (0)	3 (2.1)	−2.1 (−4.1 to 0.0)	.11
Duration of temperature ≥38°C,[b] days				
Median (IQR)	13 (5–21)	12 (5–20)	…	NS
Range	1–42	1–59	…	

NOTE. Data are no. (%) of patients, unless otherwise indicated. IFI, invasive fungal infection; IQR, interquartile range; NS, not significant.

[a] By Cochran-Mantel-Haenszel test for qualitative variables; by Wilcoxon sum-rank test for skewed quantitative variables.

[b] Excludes 14 patients without fever (8 in the empirical treatment group and 6 in the preemptive treatment group).

incidence estimates were assessed using Gray's test [24]. The cumulative incidence of antifungal treatment was calculated with the risk of death or IFI as a competing risk. All analyses except the noninferiority analysis were based on 2-sided P values, and P values <.05 were considered to indicate statistical significance. All analyses were performed using SAS, version 8.12 (SAS Institute).

RESULTS

Patient population. The study enrolled 293 patients, who constitute the intention-to-treat population: 150 in the empirical treatment arm and 143 in the preemptive treatment arm. The median duration of neutropenia (neutrophil count, <500 cells/mm^3) was 18 days. A single patient, who was in the em-

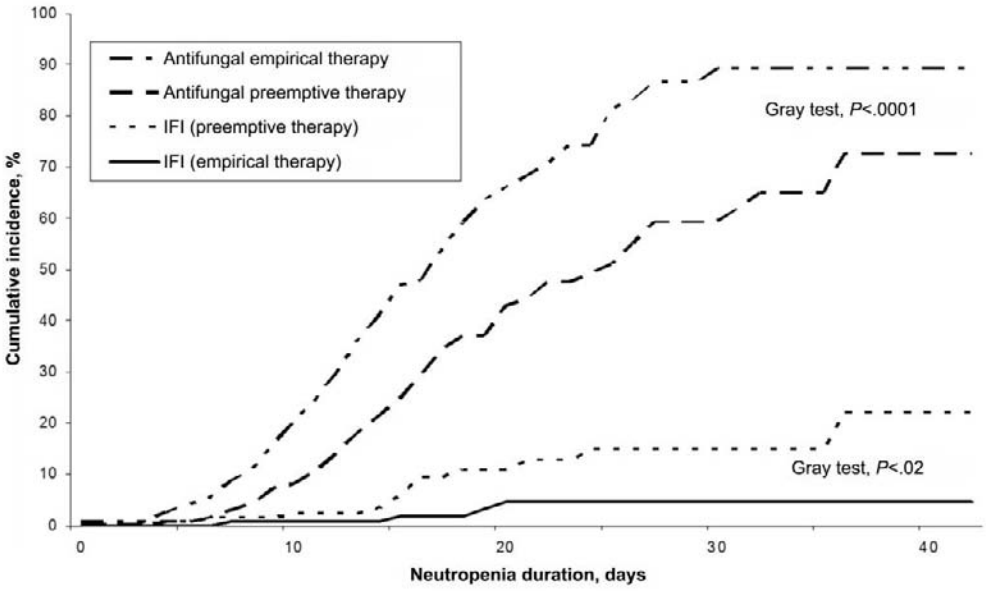

Figure 2. Cumulative incidence of antifungal therapy and invasive fungal infection (IFI) during neutropenia (n = 287)

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Table 3. Antifungal therapy in the intention-to-treat population ($n = 293$).

End point	Empirical treatment group	Preemptive treatment group	P[a]
Antifungal treatment	92/150 (61.3)	56/143 (39.2)	<.001
Reason for starting antifungal treatment[b]			
Isolated fever between day 4 and day 14 after antibacterial treatment initiation	55 (59.8)	1 (1.8)	<.001[c]
Pneumonia	6 (6.5)	26 (46.4)	
Severe mucositis	8 (8.7)	10 (17.9)	
Isolated fever beyond day 14	11 (12.0)	7 (12.5)	
Septic shock	5 (5.4)	3 (5.4)	
Positive result of galactomannan antigen test	2 (2.2)	3 (5.4)	
Skin lesion	2 (2.2)	2 (3.6)	
Sinusitis or periorbital inflammation	0 (0.0)	3 (5.4)	
Neurological symptoms	2 (2.2)	0 (0.0)	
Diarrhea	1 (1.1)	1 (1.8)	
Duration of fever before antifungal treatment,[b] median days (IQR)	7 (5–11)	13 (6–17)	<.01
Duration of fever after antifungal treatment,[b] median days (IQR)	9 (4–15)	7 (5–13)	NS
Duration of antifungal treatment, mean days ± SD			
Any antifungal agent	7.0 ± 8.5	4.5 ± 7.3	<.01
High-cost antifungal agents (liposomal AmB, caspofungin, or voriconazole)	3.7 ± 7.6	2.6 ± 5.8	NS
Low-cost antifungal agents (AmB deoxycholate)	3.5 ± 5.2	2.0 ± 4.6	<.01
Cost of antifungal drugs, 2005 €			
Mean ± SD	2252 ± 4050	1475 ± 3329	<.001
Range	0–20,726	0–18,500	
Estimated cost of antifungal drugs if liposomal AmB had been used instead of AmB deoxycholate, 2005 €			<.001
Mean ± SD	4261 ± 4760	2509 ± 4099	
Range	0–21,727	0–18,500	
Length of hospital stay, days			
Mean ± SD	30.3 ± 10.5	30.3 ± 10.2	
Range	11–100	14–80	NS

NOTE. Data are no. or proportion (%) of patients, unless otherwise indicated. AmB, amphotericin B; IQR, interquartile range; NS, not significant.

[a] By χ^2 test or Fisher's exact test for qualitative variables; by Wilcoxon rank-sum test for skewed quantitative variables.

[b] Estimates were computed for patients who received antifungal treatment: 92 patients in the empirical treatment group and 56 patients in the preemptive treatment group.

[c] By χ^2 test comparing isolated fever before day 14 with other situation.

pirical treatment arm, was still neutropenic on day 60 because rescue chemotherapy was given after failure of first-line chemotherapy (table 1 and figure 1).

The per-protocol analysis included 261 patients, after we excluded 14 patients without neutropenia or fever and 18 patients with protocol violations. The results of the per-protocol analysis duplicated those of the intention-to-treat analysis and are not shown.

Primary efficacy end point, overall survival, and causes of death. Overall survival was not lower with preemptive treatment (95.1%) than with empirical treatment (97.3%), and the 95% CI for the difference was −5.9% to 1.4%. Thus, the lower boundary of the 95% CI was within the noninferiority margin (−8%). Of the 293 patients, 11 died; the causes of death were IFI (3 patients, all in the preemptive treatment group), bacterial sepsis (4 patients), nondocumented sepsis (2 patients), cardiogenic shock (1 patient), and coma of unknown origin (1 patient). Kaplan-Meier analysis indicated that the proportion of survivors at 4 months after inclusion in the study was not different between the preemptive treatment group and the empirical treatment group (log-rank $\chi^2 = 0.27$; $P = .60$).

Proven and probable IFIs. The incidence of IFI was significantly higher in the preemptive treatment arm than in the empirical treatment arm (9.1% vs. 2.7%; 95% CI for the difference, −10.9% to −1.9%). Of the 293 patients, 17 (5.8%) experienced IFI. The 12 cases of aspergillosis (2 proven and 10 probable) involved the lungs, and 1 also involved the CNS. The 5 cases of candidiasis were documented by blood cultures (3 due to *Candida albicans*, 1 due to *Candida tropicalis*, and 1 due to an undetermined *Candida* species) (table 2 and figure 2).

Among 32 patients with pneumonia before antifungal therapy, 3 of 6 in the empirical treatment group and 7 of 26 in the preemptive treatment group were subsequently found to have proven or probable aspergillosis; 22 (69%) of the 32 had abnormal chest radiograph findings, with no significant difference between the 2 groups ($P = 1.00$), and 5 of the re-

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Table 4. Subgroup analysis of patients receiving consolidation therapy or stem cell transplantation compared with patients receiving induction therapy, in the intention-to-treat population ($n = 293$).

End point	Consolidation therapy or transplantation			Induction therapy		
	Empirical treatment group ($n = 72$)	Preemptive treatment group ($n = 70$)	P[a] or difference (95% CI) in efficacy outcomes	Empirical treatment group ($n = 78$)	Preemptive treatment group ($n = 73$)	P[a] or difference (95% CI) in efficacy outcomes
Duration of neutrophil count <500 neutrophils/mm^3,[b] days						
Median (IQR)	11 (9–16)	12 (10–16)	NS	26 (21–31)	26 (18–32)	NS
Range	6–41	6–39		9–69	5–57	
Alive at study completion	72 (100)	68 (97.1)	−2.9 (−6.1 to 0.4)	74 (94.9)	68 (93.2)	−1.7 (−8.0 to 4.6)
Invasive fungal infection						
All	1 (1.4)	1 (1.4)	0 (−3.3 to 3.3)	3 (3.8)	12 (16.4)	−12.6 (−20.6 to −4.6)
Due to *Aspergillus* species	1 (1.4)	1 (1.4)	NS	3 (3.8)	7 (9.6)	NS
Due to *Candida* species	0 (0)	0 (0)	NS	0 (0)	5 (6.8)	<.05
Antifungal prophylaxis	40 (55.6)	40 (57.1)	NS	23 (29.5)	29 (39.7)	NS
Antifungal treatment	28 (38.9)	13 (18.6)	<.01	64 (82.1)	43 (58.9)	<.01
Duration of fever before antifungal treatment, median days (IQR)	6 (4–8)	6 (3–13)	NS	8 (6–14)	14 (8–18)	<.05
Change in creatinine clearance (at end of study minus at baseline), mean ± SD	−3.4 ± 15.5	−3.6 ± 15.3	NS	−13.7 ± 23.8[c]	−7.8 ± 35.0	<.05
Total costs of antifungal drugs, 2005 €						
Mean ± SD	1175 ± 2615	377 ± 1319	<.02	3246 ± 4832	2528 ± 4230	<.05
Range	0–11,122	0–7500		0–20,726	0–18,500	
Length of hospital stay, mean ± SD, days	25.4 ± 6.3	25.4 ± 7.4	NS	34.8 ± 11.5	35.0 ± 10.3	NS

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; NS, not significant.

[a] By χ^2 test or Fisher's exact test for qualitative variables; by Wilcoxon rank-sum test for skewed quantitative variables.

[b] Excludes 6 patients without neutropenia (4 in the empirical treatment group—including 1 in the autologous stem cell transplant subgroup, 1 in consolidation therapy subgroup, and 2 in the induction therapy subgroup—and 2 in the preemptive treatment group, both of whom were in the induction therapy subgroup).

[c] $P < .001$ by the paired t test comparing changes in creatinine clearance from baseline to study completion.

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maining 10 patients had abnormal CT findings, with no significant difference between the 2 groups ($P = .36$).

Safety. Creatinine clearance decreased significantly during the study period in both arms. Although the mean decrease ± SD was larger in the empirical treatment group than in the preemptive treatment group (−8.7 ± 20.8 vs. −5.8 ± 27.2), the difference was not significant. SAEs occurred in similar proportions among patients in the 2 groups. Overall, 101 (34.5%) of the 293 patients had creatinine clearance <60 mL/min, and 10 (3.4%) had septic shock.

Use of antifungal agents. Antifungal use was significantly lower in the preemptive treatment group. Among treated patients, antifungal therapy was given for isolated persistent or recurrent fever to 55 (59.8%) of 92 patients in the empirical treatment arm and 1 (1.8%) of 56 patients in the preemptive treatment arm ($P < .001$). In the remaining 37 patients (40.2%) who received empirical treatment, persistent or recurrent fever coincided with a clinical sign. Results positive for galactomannan antigenemia with persistent fever was present in 2 patients in the empirical treatment group and 3 in the preemptive treatment group. If 0.5 had been used instead of 1.5 as the galactomannan cutoff [25], 2 additional patients in the preemptive treatment arm would have been treated 4–14 days into the first febrile episode; neither patient died or had IFI (table 3 and figure 2).

The total number of days of antifungal treatment and the mean costs of antifungal drugs were significantly lower for the preemptive treatment group. If liposomal amphotericin B had been used for all treated patients, the cost difference would have been 40%.

Subgroup analysis. An exploratory analysis was conducted in the subgroups defined by the stratification criteria (induction vs. consolidation therapy; median duration of 26 and 12 days, respectively) (table 4). For the induction therapy subgroup, survival was 94.9% in the empirical treatment group and 93.2% in the preemptive treatment group. The 95% CI for the difference was −8.0% to 4.6%, which included the noninferiority margin (−8%), so inferiority could not be ruled out. In the consolidation therapy subgroup, survival was not lower in the preemptive treatment group (97.1%) than in the empirical treatment group (100%), and the lower boundary of the 95% CI for the difference (−6.1%) was within the noninferiority margin (−8%). Of the 17 IFI cases, 15 occurred in the induction therapy subgroup, and 2 in the consolidation therapy subgroup (16.4% vs. 3.9%; $P < .01$).

DISCUSSION

Survival among our neutropenic patients with persistent or recurrent fever was 97% with empirical treatment and 95% with preemptive treatment guided by clinical parameters, imaging studies, and serum galactomannan antigenemia. For the overall population, our results are consistent with noninferiority of preemptive treatment, compared with empirical treatment, with regard to mortality 2 weeks after recovery from neutropenia. However, neutropenia duration was the main factor associated with IFI. In patients receiving consolidation chemotherapy or who underwent autologous stem cell transplantation, the median duration of neutropenia was 12 days, and preemptive treatment decreased the use and cost of antifungal drug therapy without affecting survival. In patients receiving induction chemotherapy, whose median duration of neutropenia was 26 days, the incidence of IFI was significantly higher with preemptive treatment, of which the noninferiority in ensuring survival, compared with empirical treatment, could not be ruled out. Although empirical treatment is almost universally used in hematology wards [3] in accordance with international guidelines [1, 2], there is no reliable study supporting the efficacy of this strategy. Our study suggests that empirical antifungal treatment may result in higher survival rates than would preemptive treatment among patients receiving induction chemotherapy.

Preemptive antifungal treatment of IFI is not standardized. Segal et al. [7] suggested combining chest CT and laboratory markers to decide whether antifungal treatment was appropriate for neutropenic, febrile patients receiving antimold prophylaxis. In contrast, in our study, patients with suggestive clinical symptoms received antifungals even if their galactomannan test results and chest CT findings were normal. In our preemptive treatment group, fewer patients received antifungals, and the treatment was started later than it was in the empirical treatment group (median, 13 vs. 6 days). However, the median duration of fever was not different between the groups (12 days for both groups), suggesting that fever is indeed not specific to IFI. An open study established the feasibility of preemptive treatment based on clinical symptoms, galactomannan antigenemia (cutoff for antigen level, 0.5 ng/mL), lung CT, and bronchoalveolar lavage [17]. Whereas 35% of 117 neutropenic febrile episodes met criteria for empirical treatment, only 7.7% were treated on the basis of the preemptive treatment criteria, and only 1 of 22 cases of IFI was missed. However, given the open design, this study could not determine whether preemptive treatment was noninferior to empirical treatment [17]. In our trial, the percentage of IFI cases was significantly higher in the preemptive treatment arm than in the empirical treatment arm (9.1% vs. 2.7%), possibly reflecting the lower positive predictive value of diagnostic investigations when the incidence of IFI is low (5.8% in our study vs. 20% in the aforementioned study [17]).

In our study, 15 of the 17 cases of IFI occurred during induction chemotherapy, more commonly in the preemptive treatment arm than in the empirical treatment arm. In addition, all 5 candidemia cases involved patients in the preemptive treat-

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ment group who were not receiving azole prophylaxis. Although patients were stratified according to the use of antifungal prophylaxis, its indication and type were decided by the center. Of interest, posaconazole has been shown to be a more effective prophylaxis than fluconazole or itraconazole and significantly decreased the use of empirical therapy, from 34% to 22% of patients [26].

Our results are limited by the open-label design of the study, although the side effects of intravenous amphotericin B make a blinded study irrelevant. Our results are also limited to the preemptive antifungal strategy used in our study (compared with, for example, repeated CTs at regular intervals). When the experimental treatment is intended to prevent death, justification of even the smallest noninferiority margin is debatable [27]. On the other hand, the 2 open-label trials that led to empirical therapy becoming standard practice [8, 21] did not include placebo arms and were insufficiently powered to show significant effects on mortality. Moreover, the lack of early diagnosis methods at the time the studies were conducted and changes in clinical management constitute major obstacles to making comparisons with current practices.

Our randomized study showed that preemptive antifungal treatment—guided by clinical symptoms, imaging findings, and/or galactomannan antigen levels suggestive of IFI—given to neutropenic patients with persistent or recurrent fever despite antibacterial therapy was not inferior to empirical treatment in terms of survival. Of 17 IFI cases, 15 occurred in patients receiving induction chemotherapy. A subgroup analysis failed to establish noninferiority of preemptive treatment versus empirical treatment for patients receiving induction chemotherapy. For the subgroup receiving consolidation chemotherapy or undergoing stem cell transplantation, among which the incidence of IFI was very low, the results suggested noninferiority of preemptive treatment. Therefore, further studies are needed to investigate preemptive antifungal treatment and should use a broader spectrum of diagnostic methods, including imaging modalities and biological markers such as β-D-glucan [28, 29] or PCR [30], as well as effective antifungal prophylaxis.

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