Empiric vs Preemptive Antifungal Strategy in High-Risk Neutropenic Patients on Fluconazole Prophylaxis: A Randomized Trial of the European Organization for Research and Treatment of Cancer

Johan Maertens,1 Tom Lodewyck,2 J. Peter Donnelly,3 Sylvain Chantepe,4 Christine Robin,5 Nicole Blijlevens,6 Pascal Turlure,6 Dominik Selleslag,2 Frédéric Baron,7 Mickael Aoun,8 Werner J. Heinz,9 Hartmut Bertz,10 Zdeněk Ráčil,11 Bernard Vandercam,12 Lobus Drsgona,13 Valerie Coiteux,14 Cristina Castilla Llorente,15 Cornelia Schaefer-Prokop,16 Marianne Paesmans,18 Lieveke Ameye,18 Liv Meert,16 Kin Jip Cheung,16 Deborah A. Hepler,17 Jürgen Loefler,18 Rosemary Barnes,18 Oscar Marchetti,20,21 Paul Verweij,3,26 Frederic Lamoth,20 Pierre-Yves Bochud,20 Michael Schwarzinger,22 and Catherine Cordonnier;1 for the Infectious Diseases Group and the Acute Leukemia Group of the European Organization for Research and Treatment of Cancer

1Department of Hematology, University Hospitals Leuven, Leuven, Belgium; 2Department of Hematology, Algemeen Ziekenhuis St Jan, Brugge, Belgium; 3Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands; 4Department of Hematology, Caen University Hospital, Caen, France; 5Department of Hematology, Centre Hospitalier Universitaire Henri Mondor, Créteil, France; 6Department of Hematology, Centre Hospitalier Universitaire Limoges, Limoges, France; 7Department of Hematology, University of Liège and University Hospital of Liège, Liège, Belgium; 8Department of Internal Medicine, Institut Jules Bordet, Brussels, Belgium; 9Department of Hematology/Oncology, Cantius Hospital, Bad Mergentheim, Germany; 10Department of Hematology/Oncology, Faculty of Medicine and Medical Centre, University of Freiburg, Freiburg, Germany; 11Department of Hematology, Masaryk University Brno and Institute of Hematology and Blood Transfusion, Prague, Czech Republic; 12Department of Internal Medicine/Infectious Diseases, Cliniques Universitaires St. Luc, Brussels, Belgium; 13Department of Oncohematology, Comenius University and National Cancer Institute, Bratislava, Slovakia; 14Service des maladies du sang, Centre Hospitalier Régional Universitaire Lille, Lille, France; 15Department of Hematology, Gustave Roussy Cancer Campus, Villejuif, France; 16European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium; 17Merck & Co, Inc, Kenilworth, New Jersey, USA; 18Department of Internal Medicine II, Universitätsklinikum, Würzburg, Germany; 19Department of Infection, Immunity and Biochemistry, Cardiff University, Cardiff, United Kingdom; 20Department of Medicine, Lausanne University Hospital, Lausanne, Switzerland; 21Department of Infectious Diseases, Ensemble Hospitalier de la Côte, Morges, Switzerland; and 22Translational Health Economics Network, Bordeaux University Hospital, Bordeaux, France

Background. Empiric antifungal therapy is considered the standard of care for high-risk neutropenic patients with persistent fever. The impact of a preemptive, diagnostic-driven approach based on galactomannan screening and chest computed tomography scan on demand on survival and on the risk of invasive fungal disease (IFD) during the first weeks of high-risk neutropenia is unknown.

Methods. Patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and allogeneic hematopoietic cell transplant recipients were randomly assigned to receive caspofungin empirically (arm A) or preemptively (arm B), while receiving fluconazole 400 mg daily prophylactically. The primary end point of this noninferiority study was overall survival (OS) 42 days after randomization.

Results. Of 556 patients recruited, 549 were eligible: 275 in arm A and 274 in arm B. Eighty percent of the patients had AML or MDS requiring high-dose chemotherapy, and 93% of them were in the first induction phase. At day 42, the OS was not inferior in arm B (96.7%; 95% confidence interval [CI], 93.8%–98.3%) when compared with arm A (93.1%; 95% CI, 89.3%–95.5%). The rates of IFDs at day 84 were not significantly different, 7.7% (95% CI, 4.5%–10.8%) in arm B vs 6.6% (95% CI, 3.6%–9.5%) in arm A. The rate of patients who received caspofungin was significantly lower in arm B (27%) than in arm A (63%; P < .001).

Conclusions. The preemptive antifungal strategy was safe for high-risk neutropenic patients given fluconazole as prophylaxis, halving the number of patients receiving antifungals without excess mortality or IFDs.

Clinical Trials Registration. NCT01288378; EudraCT 2010-020814-27.

Keywords. neutropenia; empiric; preemptive; antifungal; galactomannan.

Prolonged and profound neutropenia, defined as <500 neutrophils/mm³ (<0.5 x 10⁹/L neutrophils) for at least 10 days, is a major factor for developing life-threatening invasive fungal diseases (IFDs) in patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) receiving remission-induction or reinduction chemotherapy or undergoing myeloablative allogeneic hematopoietic cell transplantation (HCT). These patients benefit from antifungal agents when they present with neutropenic fever that has not been reduced after 3 to 7 days of broad-spectrum antibiotics. This empiric use of antifungals, which was explored in the 1980s when only culture and microscopy were available to diagnose IFD, became
the standard of care [1, 2], supported by international guidelines [3, 4]. However, empiric use of the recommended antifungals liposomal amphotericin B and caspofungin [5, 6] most likely leads to overtreatment with increased toxicity and costs.

The availability of nonculture-based tests, such as the Platelia galactomannan enzyme-immunoassay (EIA) [7–10], and of computed tomography (CT) scanning [11, 12] has formed the basis of a so-called preemptive or diagnostic-driven approach. Instead of unexplained fever, abnormalities seen on a chest CT scan or mycologic test results trigger the start of antifungals [13]. Although several open-label and observational studies have reported promising results in terms of clinical outcomes and cost-effectiveness [14–25], there is still no consensus on the optimal design of a preemptive strategy.

Previously, both strategies were compared in the randomized PREVERT study [23]. However, there were too few patients with prolonged neutropenia to rule out the noninferiority of survival with the preemptive strategy. Therefore, the Infectious Diseases Group and the Acute Leukemia Group of the European Organization for Research and Treatment of Cancer (EORTC) initiated this new trial with overall survival as the primary end point.

METHODS

Study Design and Participants

The EORTC 65091-06093 study was an open-label, phase 3, randomized, parallel, multicenter, strategy trial comparing the efficacy and safety of a fever-driven antifungal approach (empiric, arm A) to a diagnostic-driven approach (preemptive, arm B) in neutropenic patients at high risk of developing IFD.

We recruited patients aged ≥18 years who were scheduled for remission-induction chemotherapy for newly diagnosed AML or MDS or in first relapse after remission of at least 6 months, or to start a myeloablative conditioning regimen [26] for a first allogeneic HCT. The main exclusion criteria were clinically documented pneumonia, uncontrolled infection, or previous IFD. Detailed eligibility criteria are provided in the Supplementary File S1.

Trial Oversight

The trial was sponsored by the EORTC and funded by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, which also provided caspofungin but had no further role in the trial or in writing the manuscript. The trial statisticians performed the analyses and vouched for the integrity and validity of the analyses. The authors affirm that the trial was conducted as specified in the protocol and agreed with the final manuscript and approved it for publication.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the institutional review board and ethic committee at each center. All patients provided written informed consent before undergoing any trial-specific procedures. A data review committee (DRC) reviewed eligibility criteria, compliance with the protocol, criteria for IFD, and causes of death. A blinded radiologist reviewed all the CT scans with no or inconclusive reports.

End Points

The primary end point was overall survival (OS) 42 days after randomization. Key prespecified secondary end points assessed at day 42 and day 84 after randomization included OS, rates of proven or probable IFD (using the 2008 EORTC/National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) definitions [27]), compliance with the allocated treatment arm, survival free of proven or probable IFD, number of days of caspofungin administration, and safety. Adverse events (AEs) and serious AEs (SAEs) were assessed according to Common Terminology Criteria for Adverse Events criteria v4.0.

Randomization and Data Collection

Eligible patients underwent central randomization in a 1:1 ratio using the EORTC online system, stratified according to trial site, allogeneic HCT, and the use of laminar-airflow or high-efficiency particulate-air filtered rooms. Randomization was done within 3 days after the start of chemotherapy or conditioning regimen.

Definitions of major protocol violations are listed in the Supplementary File S2.

Study Design

Arm A (Empiric Arm)

Patients allocated to arm A were given caspofungin either for unexplained fever after 4 days of broad-spectrum antibacterials or for a new febrile episode more than 2 days after resolution of the first episode while continuing broad-spectrum antibacterials (Figure 1). Patients allocated to this study arm were not screened for blood galactomannan before starting caspofungin.

Arm B (Preemptive Arm)

Patients in arm B were screened twice weekly on site for blood galactomannan with the enzyme immunoassay (Platelia, Bio-Rad Laboratories, Marnes-La-Coquette, France), according to the manufacturer’s instructions. A positive galactomannan assay (optical density index above 0.5), a new pulmonary infiltrate on chest X ray, or the recovery of Aspergillus in sputum prompted a chest CT scan. Patients were given caspofungin when there was a single positive galactomannan test result (even when asymptomatic), a new pulmonary infiltrate on chest X ray and IFD could not be readily excluded per the investigator’s judgment, a new pulmonary infiltrate on chest CT scan consistent with an IFD (a nodule, with
or without a halo; a cavity; an air crescent sign), or/and the re-
covery of Aspergillus species by culture from sputum [27].

Study Procedures
All patients received fluconazole 400 mg/day to prevent Candida infection and remained in the hospital for the dura-
tion of neutropenia. All patients who developed a first episode
of febrile neutropenia (temperature ≥ 38.3°C once or ≥ 38.0°C
twice consecutively with an absolute neutrophil count [ANC] <500 neutrophils/mm³ or expected to fall within 48 hours) un-
derwent a diagnostic workup with clinical examination, chest X
ray, or chest CT scan according to institutional practice; at least
2 separate sets of blood cultures; and appropriate specimens
from any other potential sites of infection (as clinically indicat-
ed) for microbiology before starting broad-spectrum antibacte-
rials according to local standards and consistent with the
Infectious Diseases Society of America guidelines [3].

Once the study arm–specific criteria for starting caspofungin
treatment were met, additional blood cultures were taken in
both arms, as well as appropriate cultures from other sites,
whenever clinically indicated. A chest X ray was ordered for pa-
ients in arm A, and a chest CT scan was ordered for patients in
arm B. Following the initiation of caspofungin, blood samples
for the detection of galactomannan were collected twice weekly
in both study arms. Additional examinations, including cul-
tures, imaging, bronchoscopy with bronchoalveolar lavage,
and/or needle aspirates or biopsies, were performed on clinical
indication.

Caspofungin
Caspofungin was given at a loading dose of 70 mg on day 1, there-
after 50 mg/day (70 mg if body weight exceeded 80 kg) until neu-
trophil recovery (ANC ≥ 500 neutrophils/mm³) or until the
diagnosis of a proven or probable IFD, whichever occurred first.
Fluconazole prophylaxis was stopped, and no other systemic anti-
fungal was allowed during administration of caspofungin. In case
of proven or probable IFD, caspofungin was stopped and further
antifungal therapy was given according to local guidelines.

Statistical Analyses
Patients were considered eligible if they satisfied all the entry cri-
teria and met none of the exclusion criteria. All eligible patients
constituted the modified intention-to-treat (mITT) population
and were included in the primary analysis. The per-protocol
(PP) population included only cases without any major protocol
violation as defined by the DRC.

Our aim in this study was to show that the overall survival 42
days after randomization of the preemptive strategy (arm B)
was not inferior to that of the empiric strategy (arm A). Every death was taken into consideration, regardless of the
cause, for assessing the primary end point.

We estimated an 87% survival rate at day 42 in arm A based
on the results of high-risk patients receiving fluconazole
prophylaxis [28]. The greatest relative risk for death acceptable for the noninferiority of arm B was set at 1.62. With a power of 80% for rejecting the null hypothesis, we calculated that 556 patients were needed for the study.

The survival rates at day 42 were estimated in each treatment arm using Kaplan–Meier estimates, and we calculated the survival rate at day 42 of each arm and considered arm B as noninferior to arm A if the ratio of the upper bound 95% confidence interval (CI) for arm B/the lower bound 95% CI of arm A was less than 1.62.

The safety analysis included all randomized patients with the worst degree of toxicity measured between randomization and day 84 being reported. Only the rates of patients developing at least 1 grade 3/4 AE or at least 1 SAE in each randomization arm are reported with 95% CIs.

A planned interim analysis was done by the EORTC Independent Data Monitoring Committee (IDMC) in February 2014 when 263 patients had a follow-up ≥ 42 days. The aim was to determine whether the survival rate in the empiric arm A was in the expected range. The survival rate in the control arm was higher than anticipated (94%; 95% CI, 89%–98%). However, the IDMC recommended that the sample size not be increased as the noninferiority margin that was chosen was stricter than that chosen for the PREVERT trial [23]. In addition, increasing the sample size would have jeopardized recruitment, delayed the trial results, and increased costs.

RESULTS

From 9 March 2012 to 30 September 2015, 556 patients were randomized at 15 sites in 6 European countries (Supplementary File S3): 279 in arm A and 277 in arm B (Figure 2). Seven patients were found ineligible by the DRC, resulting in an mITT population of 549 patients (Table 1). There was a major protocol deviation (Supplementary File S4) in 56 cases, 42 of 268 (15.7%) in arm A and 14 of 273 (5.1%) in arm B ($P < .001$). Another 8 patients were not evaluable, resulting in a PP population of 485 patients.

Characteristics of the mITT population (N = 549) are summarized in Table 1. The median duration (Q1–Q3) of neutropenia was 22 days (IQR, 18–28) in arm A and 21 days (IQR 17–26) in arm B ($P = .15$). Characteristics of the PP population (n = 485) are shown in Supplementary Table 1.

Overall Survival and Causes of Deaths

The OS in the mITT population at day 42 was not inferior in arm B compared with arm A considering the noninferiority margin of 1.62: arm B (96.7%; 95% CI, 93.8%–98.3%) and arm A (93.1%; 95% CI, 89.3%–95.5%; Figure 3). The OS at day 84 was similar (92.6%; 95% CI, 88.8%–95.2% in arm B vs 90.5%; 95% CI, 86.3%–93.4% in arm A). There was no significant difference in the OS at day 42 in the group of allogeneic HCT recipients (arm B, 94.8%; 95% CI, 84.7%–98.3% vs arm A, 92.4%; 95% CI, 81.0%–97.1%) when compared with those in the AML/MDS patients (arm B, 97.2%; 95% CI, 84.7%–98.3% vs arm A, 93.2%; 95% CI, 89.0%–95.9%).

In arm B, 20 patients died within 84 days after randomization from IFD plus another cause (n = 5), another cause without IFD (n = 12), or from another cause with an unknown fungal status (n = 3). In arm A, 26 patients died within 84 days after randomization from IFD alone (n = 1), from IFD plus another cause (n = 2), from another cause without IFD (n = 13), and from another cause with an unknown fungal status at time of death (n = 10).
### Table 1. Patient Characteristics of the Modified Intention-to-treat Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm A: Empirical Antifungal Therapy (n = 275)</th>
<th>Arm B: Preemptive Antifungal Therapy (n = 274)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AML/MDS (n = 222)</td>
<td>Allogeneic HCT (n = 53)</td>
</tr>
<tr>
<td>Age at randomization, years</td>
<td>55.1 ± 13.7</td>
<td>39.4 ± 12.9</td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>59 (18 to 78)</td>
<td>41 (18 to 70)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male: 121 (54.5%)</td>
<td>Female: 101 (45.5%)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>De novo AML: 162 (73.0%)</td>
<td>Secondary AML: 44 (19.8%)</td>
</tr>
<tr>
<td></td>
<td>Acute lymphoblastic leukemia: 11 (4.1%)</td>
<td>Myelodysplastic syndrome with myelodysplasia: 11 (4.1%)</td>
</tr>
<tr>
<td></td>
<td>Other underlying diseases: 1 (0.4%)</td>
<td>Other underlying diseases: 1 (0.4%)</td>
</tr>
<tr>
<td>Chemotherapy administered for AML or MDS</td>
<td>Ara-C (200 mg/m²; 7 days) + anthracycline (3 days; idarabine or daunorubicin) (n = 162)</td>
<td>Intermediate-1 (17.3%)</td>
</tr>
<tr>
<td></td>
<td>Intermediate-2 (17.3%)</td>
<td>Intermediate-2 (17.3%)</td>
</tr>
<tr>
<td></td>
<td>Ara-C + anthracycline + etoposide (n = 17)</td>
<td>Other (n = 17)</td>
</tr>
<tr>
<td>Conditioning regimen chemotherapy in allogeneic HCT</td>
<td>Cyclophosphamide + total body irradiation 12 gray (n = 30)</td>
<td>Busulfan + cyclophosphamide (n = 13)</td>
</tr>
<tr>
<td></td>
<td>Conditioning regimen chemotherapy in allogeneic HCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration of neutropenia (absolute neutrophil count &lt;0.5 x 10⁹/L), days</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>24.1 ± 10.8</td>
<td>18.5 ± 5.6</td>
</tr>
<tr>
<td>Median (Q1–Q3)</td>
<td>22 (18 to 28)</td>
<td>18 (15 to 22)</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; Ara-C, cytarabine; HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndrome; SD, standard deviation.

* Other underlying diseases. Arm A: biphenotypic acute leukemia (n = 1), high-risk myelodysplastic syndrome (n = 1); plasmocytoma (n = 1), primary myelofibrosis (n = 2), myelodysplasia with eosinophilia (n = 1), sickle-cell disease (n = 1). Arm B: myelodysplastic syndrome with myelofibrosis (n = 1), myelofibrosis complicating polycythemia vera (n = 1).

* Other induction chemotherapies for AML or MDS. Arm A: regimens including Ara-C plus idarubicin, daunorubicin, or idarubicin and/or clofarabine or fludarabine (n = 14); regimens including Ara-C, mitoxantrone, and etoposide (n = 1); idarubicin alone (n = 2). Arm B: regimens including Ara-C plus idarubicin, daunorubicin, or idarubicin and/or clofarabine or fludarabine (n = 13); regimens including Ara-C, mitoxantrone, and etoposide (n = 6); idarubicin alone (n = 2); regimen including Ara-C and gemtuzumab ozogamicin (n = 2).

* Other conditioning regimens in allogeneic HCT. Arm A: regimens including cyclophosphamide, idarubicin, and total body irradiation (n = 5); regimens including fludarabine and thiopeta (n = 2); regimens including fludarabine and busulfan or cyclophosphamide (n = 3). Arm B: regimens including cyclophosphamide, idarubicin, and total body irradiation (n = 4); regimens including fludarabine and thiopeta (n = 1); regimens including cyclophosphamide and total body irradiation of 9 gray (n = 2); regimens including busulfan and cyclophosphamide (n = 1); other myeloablative regimens (n = 4).
The OS for the PP population in arm B was not inferior to that in arm A (Supplementary Figure 1).

**Invasive Fungal Diseases**

The rates of proven and probable IFD within 84 days after randomization were 7.7% in arm B and 6.6% in arm A ($P = .61$; Table 2) in the mITT population. There was no statistically significant difference in the IFD rates between the subgroups of AML/MDS patients and the HCT recipient group. Among the 39 proven or probable IFDs observed, 33 (84.6%) occurred before day 42. Eight of the 11 proven cases and 25 of the 28 probable cases were diagnosed within 42 days after randomization; the remainder were diagnosed between day 42 and day 84. Most proven IFDs were due to *Candida*, and all probable IFDs were aspergillosis.

**Fungal-Free Survival**

In the mITT population, there was no difference in survival free of proven or probable IFD at day 42: arm B, 90.6% (95% CI, 86.3%–93.6%) and arm A, 88.3% (95% CI, 83.8%–91.7%) or at day 84: arm B, 88.6% (95% CI, 83.7%–92.1%) and arm A, 85.5% (95% CI, 80.0%–89.5). Similar features were observed in the PP population (data not shown).

**Antifungal Therapies**

The rate at which mITT patients received caspofungin treatment according to the randomized strategy was 27% in arm B vs 63% in arm A ($P < .001$), but with no difference in the caspofungin treatment duration (Table 3). The rates of administration of other antifungals were similar between arms. The number of patients who started preemptive caspofungin on the basis of each triggering criterion (or combination of criteria) is summarized in Supplementary Table 5.

**Safety**

The rates for patients experiencing at least 1 grade 3, 4, or 5 AE or at least 1 SAE were not different between arms (Supplementary File S6).

**DISCUSSION**

This study shows that a preemptive antifungal strategy that includes twice weekly galactomannan screening and CT scan on demand does not prejudice the overall survival of adults with prolonged neutropenia who are at high risk for IFD while receiving fluconazole prophylaxis. In addition, the strategy is not associated with an increased risk of proven or probable IFD. Indeed, the strategy reduces the use of antifungals by half, which should prove cost-saving.
This study adds important information to previous trials, especially the French PREVERT study that was not sufficiently powered to establish the noninferiority of the preemptive strategy in the subgroup of patients receiving AML induction chemotherapy [23].

Several differences should be noted between the 2 trials. The present study was exclusively focused on long-term neutropenia; allogeneic HCT recipients were included; all patients received fluconazole prophylaxis; the IFDs were defined according to the EORTC/MSG 2008 consensus definitions [27], not the earlier version [29]; and caspofungin was used exclusively for both empiric and preemptive therapy. In the PREVERT study, the rate of IFDs in the AML-induction group (with a median duration of neutropenia of 26 days) that was preemptively managed was 16.4% and significantly higher than the rate of the empiric group (3.8%). Although this difference could partly be explained by more diagnostic procedures used in the preemptive arm, it could also be due to use of the original 2002 EORTC/MSG definitions rather than the revised 2008 definitions. It could also be attributed to an increased risk for IFD due to the administration of antifungals to fewer patients for a shorter time in the preemptive strategy.

Others also reported an excess risk for IFD with a preemptive strategy [16, 21]. Even though an AML patient may initially survive the IFD, having an IFD impacts the long-term outcome.

<table>
<thead>
<tr>
<th>Table 2. Proven and Probable Invasive Fungal Diseases Within 84 Days After Randomization in the Modified Intention-to-Treat Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive Fungal Disease</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Acute myeloid leukemia/myelodysplastic syndrome</td>
</tr>
<tr>
<td>Proven</td>
</tr>
<tr>
<td>Probable</td>
</tr>
<tr>
<td>Proven or probable</td>
</tr>
<tr>
<td>Allogeneic hematopoietic cell transplantation</td>
</tr>
<tr>
<td>Proven</td>
</tr>
<tr>
<td>Probable</td>
</tr>
<tr>
<td>Proven or probable</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Proven</td>
</tr>
<tr>
<td>Probable</td>
</tr>
<tr>
<td>Proven or probable</td>
</tr>
<tr>
<td>Causes of proven IFD</td>
</tr>
<tr>
<td>Candidemia</td>
</tr>
<tr>
<td>Candida albicans</td>
</tr>
<tr>
<td>Candida nonalbicans</td>
</tr>
<tr>
<td>Geotrichum capitatum</td>
</tr>
<tr>
<td>Rhizomucor sp.</td>
</tr>
<tr>
<td>Causes of probable IFD</td>
</tr>
<tr>
<td>Aspergillosis</td>
</tr>
<tr>
<td>Documented by positive culture of BAL</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
</tr>
<tr>
<td>Aspergillus niger</td>
</tr>
<tr>
<td>Aspergillus species</td>
</tr>
<tr>
<td>Documented by cytology in BAL</td>
</tr>
<tr>
<td>Documented by galactomannan in blood</td>
</tr>
<tr>
<td>Documented by galactomannan in BAL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Antifungal Therapies Administered Within 84 Days After Randomization in the Modified Intention-to-Treat Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungal Therapy</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Caspofungin administered according to the study protocol</td>
</tr>
<tr>
<td>No. of treated patients (%)</td>
</tr>
<tr>
<td>Median duration of treatment (IQR, Q1−Q3), wks</td>
</tr>
<tr>
<td>Caspofungin or other echinocandins administered outside of the study protocol</td>
</tr>
<tr>
<td>No. of treated patients (%)</td>
</tr>
<tr>
<td>Mold active azole</td>
</tr>
<tr>
<td>No. of treated patients (%)</td>
</tr>
<tr>
<td>Median duration of treatment (IQR, Q1−Q3), wks</td>
</tr>
<tr>
<td>Intravenous amphotericin B</td>
</tr>
<tr>
<td>No. of treated patients (%)</td>
</tr>
<tr>
<td>Median duration of treatment (IQR, Q1−Q3), wks</td>
</tr>
</tbody>
</table>

Abbreviations: BAL, bronchoalveolar lavage; CI, confidence interval; IFD, invasive fungal disease.

This study adds important information to previous trials, especially the French PREVERT study that was not sufficiently powered to establish the noninferiority of the preemptive strategy in the subgroup of patients receiving AML induction chemotherapy [23].

Several differences should be noted between the 2 trials. The present study was exclusively focused on long-term neutropenia; allogeneic HCT recipients were included; all patients received fluconazole prophylaxis; the IFDs were defined according to the EORTC/MSG 2008 consensus definitions [27], not the earlier version [29]; and caspofungin was used exclusively for both empiric and preemptive therapy. In the PREVERT study, the rate of IFDs in the AML-induction group (with a median duration of neutropenia of 26 days) that was preemptively managed was 16.4% and significantly higher than the rate of the empiric group (3.8%). Although this difference could partly be explained by more diagnostic procedures used in the preemptive arm, it could also be due to use of the original 2002 EORTC/MSG definitions rather than the revised 2008 definitions. It could also be attributed to an increased risk for IFD due to the administration of antifungals to fewer patients for a shorter time in the preemptive strategy.

Others also reported an excess risk for IFD with a preemptive strategy [16, 21]. Even though an AML patient may initially survive the IFD, having an IFD impacts the long-term outcome.
due to the risk of IFD recurrence, leading to modifying or post-
poning subsequent courses [30]. Hence, relying only on surviv-
al of less than 3 months could miss the consequences of IFD on
the final outcome. In the present study, we did not observe any
excess IFDs with the experimental strategy, so this fear can be
allayed. With an IFD rate of 7% in the AML group, our results
are consistent with the 8% rate in the Prospective Invasive Mould
Disease Audit (PIMDA) study [31]. Similarly, our IFD rate of
4.5% assessed within 12 weeks after starting the conditioning
regimen in HCT recipients is consistent with recent data show-
ing that currently two-thirds of the aspergillosis cases observed
after allogeneic HCT occur after day 100 post-transplant [32].

The preemptive strategy is applicable as long as the center
uses routine screening of galactomannan, has ready access to
CT scans, and the costs are balanced by the reduced use of an-
tifungals. Today, many centers use some hybrid strategy, mixing
empiric administration of antifungals and a biomarker or imag-
ing screening, which adds the cost of overuse of antifung-
als to the costs of biologic screening and CT scan.

Our study has several strengths. First, we chose survival as a
hard and objective primary end point, considering that survival
is a prerequisite for a favorable outcome. This end point high-
lights the need for the best strategies to be used during high-risk
neutropenia. Second, our groups were well balanced in terms of
AML risk and neutropenia duration, precluding any impact of
these parameters on survival. Third, we assessed only proven
and probable IFDs and did not consider possible IFDs where
fungal causality is less certain. Last, the size of the AML cohort
allowed us to be confident of the overall results and to general-
ize them to such patients as a whole.

No study is free of limitations. First, the comparison of 2
strategies with different diagnostic workup and triggering fac-
tors for antifungal administration made a blinded design im-
possible to apply. Second, we chose not to use antimal prophy-
axis as it lowers the sensitivity of galactomannan for
screening. So, while our preemptive strategy would not be
suitable for those centers that do use antimal prophylaxis
[33], either strategy would be useful to those centers that do
not use it or in patients who cannot continue on mold-active
azole prophylaxis due to AEs or clinically important drug-
drug interactions.

Empiric antifungal therapy has been the gold standard for
managing IFD in neutropenic patients and will remain so for
centers with limited diagnostic resources that rely on a clinically
driven approach. The results of our study now provide a vi-
able alternative.

**Supplementary Data**

**Supplementary materials** are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors; so questions or comments should be addressed to the corresponding author.

**Notes**

**Acknowledgments.** The authors thank the patients and their families and the healthcare providers who participated in the trial.

**Financial support.** This work was supported by Merck Sharp & Dohme Corp, USA, through an educational grant.

**Potential conflicts of interest.** J. M. reports consulting fees and payment of honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from MSD, Gilead Sciences, and Pfizer, including participation on a data and safety monitoring board or advisory board (DSMB) for MSD, Gilead, and Pfizer. T. L. reports payment for participation on virtual European Society for Blood and Marrow Transplantation meeting, J. P. D. reports consulting fees from F2G and Gilead Sciences, including payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from F2G, Gilead Sciences, and Pfizer, and unpaid leadership or fiduciary role in other board, society, committee, or advocacy group for the European PCR Initiative Foundation. C. R. reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Gilead and Sandoz and support for attending meetings and/or travel for Gilead, MSD, Pfizer, and Sandoz. N. B. reports participation as the chair on a DSMB for the SHORT trial and roles as the president of the Dutch Society of Hematology (unpaid), Treasurer Board member for HOVON (unpaid), chair of the Horizonscan WP Hematology Dutch Healthcare Institute (vacancy fee), and member of the board of supervisors for Matchis (compensation according to Dutch law). D. S. reports grants or contracts from Pfizer, Novartis, BMS, AbbVie, MSD, and Takeda, including consulting fees from Pfizer, Novartis, AbbVie, BMS, Takeda, MSD, Janssen-Cilag, and Astellas; payment or honoraria for lectures, presenta-
tions, speakers bureaus, manuscript writing, or educational events from Pfizer, Novartis, AbbVie, BMS, Takeda, MSD, and Janssen-Cilag; support for attending meetings and/or travel from Pfizer, Novartis, BMS, AbbVie, Takeda, MSD, and Janssen-Cilag; and a leadership or fiduciary role for other board, society, committee, or advocacy groups, paid or un-
paid for Belgian College for Reimbursement of Orphan Drugs. F. B. reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie and Sanofi; support for attending an international meeting from Novartis and Pfizer; and partici-
pation on a DSMB or advisory board for some academic studies (no fee) and Maatpharma (paid to institution). W. J. H. reports payment or hono-
raria for presentations from AbbVie, Amgen, AstraZeneca, Celgene/BMS, Gilead Sciences, and Janssen; support for attending meetings from IPSEN Pharma, Amgen, and Abbvie; and support for attending adboards for Amgen, AstraZeneca, Celgene/BMS, Gilead Sciences Janssen, MSD, and Sanofi-Aventis. B. V. reports payment or honoraria for lectures, presenta-
tions, speakers bureaus, manuscript writing, or educational events from Pfizer, Sanofi, and Al Miral; support for attending meetings and/or travel for ViV; and participation on a DSMB or advisory board for Pfizer. L. D. reports consulting fees from MSD, Pfizer, and Teva; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from MSD, Pfizer, Teva, and Sandoz; support for attending meetings and/or travel from Sandoz; and participation on an ad-
visory board for Pfizer. C. C. L. reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Gilead and Kite and support for attending meetings and/or travel for Gilead and Kite. C. S. P. reports book royalties from Elsevier and Thieme and honoraria for lectures from Canon Medical Systems. R. B. reports consulting fees from Gilead; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Gilead; and support for attending meetings and/or travel for Gilead. P. E. V. reports research grants from ZonMW, Welcome Trust, Eurostars, EORTC, and RIVM; con-
sulting fees from F2G, Gilead Sciences, and Pfizer; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Gilead Sciences and Pfizer. F. L. reports research grants from Merck, Sharpe & Dohme, Gilead, Pfizer, and Novartis and consulting fees (advisory board) from Gilead and Pfizer. P. Y. B. reports payment or honor-
aria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Gilead Sciences Switzerland AG and Pfizer PFE.
References


