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Original Paper

Fluconazole Versus Amphotericin B as Empirical Antifungal Therapy of Unexplained Fever in Granulocytopenic Cancer Patients: a Pragmatic, Multicentre, Prospective and Randomised Clinical Trial

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Amphotericin B, despite its intrinsic servere toxicity, is the most commonly used empirical antifungal therapy in cancer patients with unexplained fever not responding to empirical antibacterial therapy. The aim of this study was to show whether fluconazole was as effective as, and less toxic than, amphotericin, with no effort made to compare the antifungal activity of the two drugs. A group of 112 persistently febrile (> 38°C) and granulocytopenic (< 1000 cells/mm³) cancer patients, not receiving any absorbable antifungal antibiotic for prophylaxis, with a mean age of 27 years (range 1–73 years), undergoing chemotherapy for a variety of malignancies and with a diagnosis of unexplained fever after at least 96 h of empirical antibacterial therapy, were randomised to receive either fluconazole (6 mg/kg/day up to 400 mg/day) or amphotericin B (0.8 mg/kg/day) as empirical antifungal treatment. Patients were required to have normal chest X-rays at randomisation, no previous history of aspergillosis and negative surveillance cultures for *Aspergillus*. The intention-to-treat analysis showed defervescence and survival without treatment modification in 42 of 56 patients (75%) in the fluconazole group and in 37 of 56 (66%) in the amphotericin B group ($P = 0.4$). Duration of therapy was 6 days (95% CI = 4–8 days) in both groups. Death occurred in 3 patients (5%) in the fluconazole and in 2 (4%) in the amphotericin B group. No fungal death was documented in either group. Adverse events developed in 18 of 56 patients (32%) in the fluconazole group and in 46 of 56 (82%) in the amphotericin B group ($P < 0.001$). In the amphotericin B group, 5 patients had treatment discontinued because of toxicity, versus none in the fluconazole group, a difference which approached statistical significance ($P = 0.06$). This study shows that fluconazole is by far less toxic than amphotericin B and suggests that it might be as effective as amphotericin B, in pragmatical terms and for this specific indication. However, numbers are too small to allow definitive conclusions about efficacy, and the use of fluconazole for this indication remains experimental. Future studies should try to identify patients more at risk of fungal infections, with the aim of individualising antifungal approaches.

Key words: cancer, neutropenia, antifungal therapy, fever
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INTRODUCTION

FEVER REPRESENTS the most common clinical presentation of infection in granulocytopenic cancer patients, and it is commonly considered as a medical emergency. It has been shown that if an empirical treatment is not promptly undertaken, mortality can approach 40% [1]. Based upon the presence or absence of a microbiological documentation and of any identified site of infection, each febrile episode is classified, *a posteriori*, as either microbiologically documented infection with or without bacteraemia, clinically documented infection or unexplained fever. Unexplained fevers, defined as

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febrile episodes compatible with an infectious aetiology, but in which a defined site of infection and/or a microbiological proof are lacking, usually account for about 40–50% of febrile episodes [2]. If patients do not defervesce within a reasonable period, empirical antifungal therapy is usually undertaken, assuming the presence of an occult fungal infection. Although tested in only two randomised trials in small groups of patients [3,4], this practice has become very popular among centres for the treatment of neoplastic diseases worldwide. Amphotericin B remains the drug of choice for this indication, despite its intrinsic severe toxicity [5]. The optimal time at which empirical antifungal therapy should be started remains undetermined, although most authors recommend to wait until the 5th or 7th day of persistent fever and granulocytopenia [5,6].

Fluconazole is a triazole derivative with favourable pharmacokinetics and a low incidence of adverse effects, that has been shown to be effective against many strains of *Candida* causing infection in cancer patients—with the exception of *C. kruzei* and *C. glabrata*—but not against *Aspergillus* [7,8]. In cancer patients, fluconazole is mainly used in prophylaxis, although the results of the clinical trials so far performed are not unequivocal. A large prospective randomised clinical trial showed that fluconazole was effective in reducing the incidence of candidiasis in bone marrow transplant recipients [9], but these results were not confirmed by two other studies [10,11]. In addition, the indiscriminate use of fluconazole in prophylaxis might have acted as a cofactor in the emergence of resistant yeasts, either as colonisers or as the cause of true infections [12,13].

This paper reports the results of a prospective, randomised, multicentre, open-label study comparing effectiveness and tolerability of fluconazole and amphotericin B in persistently febrile and granulocytopenic cancer patients not receiving any absorbable antifungal agent as prophylaxis, with a diagnosis of unexplained fever, not responding to empirical antibacterial therapy.

PATIENTS AND METHODS

Study design and patient selection

The main objective of the study was to show whether fluconazole was as effective as, and less toxic than, amphotericin B for the pragmatic indication of unexplained fever in granulocytopenic cancer patients. No effort was made to compare the antifungal activity of the two drugs. Febrile (>38°C, axillary temperature) and granulocytopenic (<1000 cells/mm^3) cancer patients (including autologous or allogeneic bone marrow transplantation for a neoplastic disease), not receiving any absorbable antifungal antibiotic as prophylaxis, not responding after at least 96 h (4 complete days) of empirical antibacterial therapy (or relapsing after an initial defervescence lasting no more than 48 h) and for whom no clinical or microbiological evidence of infection was obtained, were randomised to receive either amphotericin B (control regimen) or fluconazole (investigative regimen).

At the development of fever during granulocytopenia, investigators were free to start treatment with their preferred empirical antibacterial protocol and to modify this treatment by adding or replacing antibacterial drugs in non-responding patients. However, only one modification of the empirical antibacterial therapy was allowed before randomisation for the empirical antifungal therapy. In addition, in order to reduce the risk of attributing to the antifungal therapy an outcome that was actually due to the modification of the antibacterial therapy, at least 72 h of persistent fever were required between the modification of the antibacterial therapy and the subsequent randomisation for fluconazole or amphotericin B. Administration of oral non-absorbable antifungal prophylaxis was allowed before randomisation, but it had to be stopped at time of enrollment. Exclusion criteria included: (1) a diagnosis of bacterial, fungal, viral or protozoal infection that was microbiologically documented before randomisation; (2) a diagnosis of clinically documented infection (including pulmonary infiltrates and sinusitis), as internationally defined [14]; (3) a previous history of aspergillosis; (4) a positive surveillance culture for *Aspergillus* from the nasal cavities; (5) a history of hypersensitivity to azole compounds; (6) a previous history of severe reaction to amphotericin B; (7) refusal to participate; (8) a total bilirubin level > 5 mg/dl and/or serum creatinine > 2.5 mg/dl or creatinine clearance < 50 ml/min; and (9) a life-expectancy shorter than 48 h. Participation in the study was not recommended to centres reporting a high incidence of suspected or documented aspergillosis in the previous year. Only a single randomisation per patient was allowed and patients should not have received any absorbable antifungal agent in the 25 days preceding inclusion in this trial. Since the actual purpose of the trial was not to compare the antifungal activity of two antifungal drugs, but to test the pragmatic effectiveness of two treatment approaches in the clinical practice, all patients who received treatment were considered as evaluable. The study was conducted by an Italian Cooperative Group for the Study of Infections in Neutropenic Patients at 3rd level adult and paediatric referral hospitals for treatment of neoplastic diseases located in Genova, Firenze, Monza, Pavia, Perugia and Torino, and was coordinated by the investigators working at Genova University (C. Viscoli and E. Castagnola). The protocol was reviewed and approved by local ethical committees and patients, or their parents or guardians, gave informed consent before enrollment.

Clinical and laboratory assessment

Patients eligible and enrolled in the study underwent a complete physical examination, and a medical history was obtained. For detecting colonisation, defined as a single positive culture for a fungal pathogen from nasal cavities, oropharynx, urine or faeces, specimens for fungal culture were obtained at the development of fever. In addition, at least three blood cultures and cultures from any relevant clinical site were performed before randomisation. Daily blood cultures were also continued throughout treatment in persistently febrile patients. A chest X-ray was required before randomisation, in order to confirm the diagnosis of unexplained fever, as well as haematological (haemoglobin, white blood cell count with differential and platelet count), coagulation and biochemical (alanine amino-transferase, angiotensin sensitivity test, serum bilirubin, alkaline phosphatase, serum electrolytes and creatinine) tests. A complete urinalysis was also required. During the study period, patients were daily monitored for signs suggestive of fungal infection and for toxicity. Haematological tests and serum electrolytes were evaluated daily, and liver and renal function tests were performed at least every 3 days. All laboratory tests were repeated at study drug discontinuation.

Randomisation procedure and drug administration

Patients were randomly allocated by drawing consecutive sealed envelopes to one of the following regimens: fluconazole

(experimental regimen) or amphotericin B (control regimen). The randomisation was performed according to a computer-generated randomisation schedule provided by the coordinating centre. Fluconazole was administered intravenously at a dosage of 6 mg/kg/day up to 400 mg once daily. The maximum rate of infusion was 10 ml/min. In patients with impaired renal function, dosage of fluconazole was modified according to manufacturer's suggestions. The oral route was excluded because these patients are usually unable to take oral medications because of severe mucositis. Amphotericin B was administered at a dosage of 0.8 mg/kg/day as an intravenous infusion in at least 100 ml of 5% dextrose in water over a period of 4–6 h. The administration of a dose-test of 1 mg in adults and 0.1–0.5 mg in children was recommended. Dose reduction was not recommended in case of renal insufficiency, unless serum creatinine was higher than 3 mg/dl. Addition and/or replacement of antifungal and/or antibacterial drugs for any reason after randomisation was considered as failure (see below for further definition). Investigators were required to continue the same treatment for at least 4 days after randomisation, unless otherwise indicated by objective clinical or laboratory reasons. These included the appearance of a clinically documented infection that was not evident at randomisation, the appearance of a life-threatening adverse effect and the documentation of a non-fungal infection from culture taken or reported after randomisation. Recommendations for the control of amphotericin B-related reactions were included in the trial protocol. It was recommended, whenever possible, to avoid using steroids for controlling amphotericin B-related reactions and not to give premedications indiscriminately, but rather to treat the first reaction and then to give only prophylaxis of reactions thereafter. Meperidine was reserved for reactions not responding to paracetamol or antihistaminic drugs.

Definition of endpoints

In the light of the pragmatic nature of the study, the analysis was performed based on an intention-to-treat criterion and all patients were considered as evaluable both for effectiveness and for toxicity. Success was defined as defervescence (< 38°C) and survival 30 days from randomisation, in absence of any modification of the antifungal or antibacterial treatment in terms of addition or replacement of antibiotics after randomisation. Failure was defined as any modification of therapy (addition or replacement of antibiotic) performed after randomisation. Modifications were allowed only for the following reasons: (1) absence of clinical response with persistence of fever (> 38°C) unrelated to amphotericin B infusion after at least 4 days of empirical antifungal therapy; (2) appearance of signs and symptoms of a clinically documented infection that was not evident at randomisation; (3) diagnosis of a microbiologically documented non-fungal infection obtained from culture performed or available after randomisation (this was considered as evidence that the wrong choice was made, i.e. that the patient should not have received empirical antifungal therapy because he/she actually had a bacterial infection); and (4) development of life-threatening adverse events. In addition, a patient's death from any cause within 30 days from randomisation was classified as failure, even if not attributable to infection. All adverse events were recorded, regardless of their causal relationship with the study drugs, according to an intention-to-treat approach. Acute adverse events included the onset of fever, chills and tremors either during study drug infusion or within 1 h from its end. Nephrotoxicity was defined as an increase of serum creatinine higher than 0.5 mg/dl from baseline values or a decrease of more than 50% in creatinine clearance. Hypokalaemia was defined as a decrease of more than 1 mgEq/L of serum potassium in patients not receiving any potassium supplementation (> 0.5 mEq/L in those already receiving potassium for parenteral nutrition). Hepatotoxicity was defined as an increase in transaminase levels 1.5 times the upper baseline values and normal range. Life-threatening adverse events requiring treatment discontinuation included bronchospasm, anaphylactic reactions, cardiac abnormalities and tremors not responding to symptomatic therapy, as well as an increase in serum creatinine of more than 2.5 mg/dl from baseline. The occurrence of adverse events was not solicitated with leading questions.

Statistical considerations

This study was designed to test the hypothesis that the outcome of granulocytopenic cancer patients with unexplained fever treated with fluconazole was not worse than that of those receiving amphotericin B and that fluconazole was by far less toxic than amphotericin B. Literature data [2,4] show that nearly 50% of febrile episodes occurring in granulocytopenic cancer patients are usually classified as unexplained fevers. About 30% of these episodes do not respond to initial empirical antibacterial therapy and require addition of empirical antifungal therapy. Assuming that the proportion of patients responding to empirical amphotericin B is 45–50%, a study based on 350 patients randomised in two equally sized groups would have ensured an 80% possibility of obtaining statistically significant results ($P < 0.05$), if the success percentage of fluconazole was lower by 15%. Intention-to-treat statistical analysis between the two groups was performed by chi-square test for heterogeneity or by Fisher's exact test for differences in categorical variables. Unpaired *t*-test was used for differences in continuous variables, while the log-rank test was applied to the evaluation of differences in time to failure. All tests were two-sided. In all cases, a P value less than 0.05 was considered as statistically significant.

Because of the high number of patients required and the expected slow patients' accrual, a 'masked' interim analysis was planned after the data were available for 100 and 200 patients enrolled. At the interim analysis, study discontinuation could be recommended: (1) if there was an higher than expected proportion of failure in the group receiving the investigational treatment (i.e. fluconazole); and/or (2) if there was a relevant difference in the toxicity rate between the two treatments.

RESULTS

At the time of the first interim analysis, a statistically significant higher toxicity rate in one of the two groups of patients became apparent (46 of 56, 82%), with 5 cases of life-threatening toxicity requiring treatment discontinuation, clearly exceeding that observed in the other group (18 of 56, 32%) in which no case of treatment discontinuation was seen ($P < 0.001$). For this reason, investigators decided to discontinue the trial, being aware that this would have resulted in a patient accrual insufficient to show equivalence in effectiveness between the two drugs. At this point, 114 patients had been randomised, 57 in the fluconazole arm and 57 in the amphotericin B arm. Of these, 1 patient in each arm did not receive any study drug. Thus, the study comprised 112 patients, 56 in each treatment group.

Patients' characteristics

Main clinical and demographic patient's characteristics are reported in Table 1. The two groups were well matched for all main variables. In particular, there was no difference in the underlying disease distribution and in the respective proportion of patients who received bone marrow transplantation. Unfortunately, we cannot provide information about the duration of neutropenia before fever. Fungal colonisation was present in 14 of 56 (25%) cases in the fluconazole group and 11 of 56 (20%) in the amphotericin B group. *Candida albicans* was the colonising yeast in 9 patients randomised for fluconazole and in 6 randomised for amphotericin B, while other non-speciated *Candida* strains were detected in 5 patients in both groups. The number of patients receiving antifungal prophylaxis with non-absorbable antibiotics were 33 (59%) in the fluconazole and 32 (57%) in the amphotericin B group. First-line empirical antibacterial therapy comprised a single β-lactam antibiotic in 3 patients in the fluconazole arm and in 6 patients in the amphotericin B arm. A combination of two drugs was administered to 48 patients receiving fluconazole (a β-lactam and an aminoglycoside in 47 and a β-lactam and a polipeptide drug in 1) and in 42 receiving amphotericin B (a β-lactam and an aminoglycoside in 38, a double β-lactam combination in 3 and a β-lactam and a polipeptide drug in 1). A triple combination (β-lactam, aminoglycoside and polipeptide) was administered in 5 patients receiving fluconazole and in 7 patients receiving amphotericin B. The difference in the type of initial empirical antibacterial therapy between the two groups was not statistically significant ($P = 0.37$). Initial antibacterial therapy was empirically changed in 23 patients before randomisation for the empirical antifungal treatment. Of these, 14 were subsequently randomised in the fluconazole arm and 9 in the amphotericin B arm ($P = 0.35$). In most cases, the modification consisted of the addition of an anti Gram-positive drug (12 of 14 in the fluconazole arm and 8 of 9 in the amphotericin B arm). The mean granulocyte count at randomisation was 124 cells/mm^3 (95% CI = 56–193) in the fluconazole group and 137 (95% CI = 73–201) in the amphotericin B group. The mean temperature at randomisation was the same in both groups (38.8°C; range 38–40°C). The mean time from the onset of fever to randomisation for empirical antifungal therapy was 5.87 days in the amphotericin B arm (95% CI = 4.9–6.8 days) and 6.09 (95% CI = 5.4–6.7 days) in the fluconazole arm. In patients for whom the initial antibacterial regimen was not changed, the mean time to randomisation was 5 days (95% CI = 4–6 days). In those whose initial treatment was changed, the mean time from the modification to randomisation was 4 days (95% CI = 3–5 days).

Therapy outcome

In the 112 patients who received treatment, fluconazole and amphotericin B were administered for a mean of 13 (95% CI = 10–16) and 10 (95% CI = 9–12) days, respectively ($P = 0.07$). The intention-to treat analysis showed an overall response rate of 75% (42 of 56) (95% CI = 61–85) in the fluconazole group and of 66% (37 of 56) (95% CI = 52–78) in the amphotericin B group ($P = 0.4$). The difference in the response rate between the study groups was 9% (95% CI = −10 to 27%). In patients failing treatment, change of therapy

Table 1. Patients' characteristics

	Fluconazole ($n = 56$)	Amphotericin B ($n = 56$)	P value
Sex			0.53
Male	38 (68)	42 (75)	
Female	18 (32)	14 (25)	
Mean age (years)	27	24	0.47
Range	1–73	1–71	
Underlying disease			0.99
Acute lymphoblastic leukaemia (ALL)	10 (18)	10 (18)	
Acute non-lymphoblastic leukaemia (ANLL)	17 (30)	18 (32)	
Chronic myeloid leukaemia in blast crisis	8 (14)	7 (13)	
Lymphoma	8 (14)	9 (16)	
Solid tumour	7 (13)	8 (14)	
Other neoplastic disease	6 (11)	4 (7)	
Bone marrow transplantation			0.73
No	25 (45)	28 (50)	
Autologous	6 (11)	7 (13)	
Allogeneic	25 (45)	21 (38)	
Patients with antifungal prophylaxis	33 (59)	32 (57)	1.00
Nystatin	2	5	
Oral amphotericin B	8	6	
Mepartricine	23	20	
Other	0	1	
Patients with fungal colonisation			0.78
No	42 (75)	45 (80)	
Yes	14 (25)	11 (20)	
Mean granulocyte count at randomisation (cells/mm^3)	124 (95% CI = 56–193)	137 (95% CI = 73–201)	0.2
Mean temperature at randomisation (°C)	38.8	38.8	

Numbers in parentheses are percentages, unless otherwise indicated.

was performed after a mean of 6 days in both the fluconazole (95% CI = 4–8 days) and the amphotericin B (95% CI = 4–8 days) groups (P = 0.87). Table 2 reports the causes of treatment failure. No statistically significant difference was shown in the cause of failure between the two groups (P = 0.19). A clinically documented infection unlikely to have a fungal cause or a microbiologically documented bacterial infection developing after randomisation were observed in 3 patients receiving fluconazole (*S. epidermidis* bacteraemia, severe ulcerative stomatitis and interstitial pneumonia) and in 4 receiving amphotericin B (*Pseudomonas* bacteraemia in two episodes, *Escherichia coli* bacteraemia and *Staphylococcus epidermidis* bacteraemia).

Although no difference in the overall response rate was seen, patients receiving fluconazole defervesced faster than those receiving amphotericin B. The mean time to defervescence in responding patients was 3 days (95% CI = 3–4) in the fluconazole group and 5 days (95% CI = 4–5) in the amphotericin B group. This difference was statistically significant (P = 0.001) and might be a consequence of amphotericin B-related fever. Probably as an effect of the longer duration of fever in patients receiving amphotericin B, the granulocyte count at success was higher in this group of patients than in those receiving fluconazole (1210 cells/mm^3; 95% CI = 541–1879 versus 412 cells/mm^2; 95% CI = 265–558). This difference was statistically significant (P = 0.028).

Finally, in the fluconazole group, 3 of 56 (5%) patients died within 30 days from randomisation. Causes of death included progression of the underlying disease with persistent fever in 1 case, and haemorrhage in the 2 other cases. One was persistently febrile at the time of death. In the amphotericin B group, 2 of 56 (4%) patients died, one from *Pseudomonas* bacteraemia and the other from pneumonia of unknown aetiology. In no case was mortality attributable to a fungal infection, although no patients underwent autopsy.

Toxicity

As shown in Table 3, 18 of 56 patients (32%; 95% CI = 21–46%) in the fluconazole group and 46 of 56 (82%; 95% CI = 69–91%) in the amphotericin B group experienced at least one adverse event, other than death, during study drug treatment. This difference (48%; 95% CI 32–68%) was statistically significant ($P < 0.001$). More than one adverse event in the same patient were reported in 28 of 56 patients (50%) in the amphotericin B group, but in only 2 patients (3%) in the fluconazole group ($P < 0.001$). Types of adverse events in patients receiving fluconazole included transaminase increase (10 cases, 18%), nephrotoxicity (7 cases, 13%), skin rash (2 cases, 4%) and hypokalaemia (1 case, 2%). In the fluconazole group, no patient had treatment discontinued because of life-threatening adverse events compared with 5 such cases in the amphotericin B group, a difference which approached statistical significance (P = 0.06). These included an allergic reaction in 1 case, severe nephropathy in 3 cases (in 1 case associated with fever and rigors, and in another one associated with fever, chills, rigors and liver toxicity) and persistence of high fever and severe chills not responding to symptomatic therapy in 1 case. Following amphotericin B discontinuation, 3 of these patients did not receive any other antifungal therapy and 2 changed to fluconazole. Of the 3 patients who had amphotericin B discontinuation because of severe nephropathy, 1 underwent haemodialysis and then recovered and 2 had their renal function normalised after discontinuation. Adverse events included drug-related fever (27 cases), fever and chills (11 cases), fever, chills and tremors (4 cases), hypokalaemia (20 cases) and nephrotoxicity (10 cases). Hepatic enzyme abnormalities were seen in 6 cases, 2 patients had skin rashes and 1 developed phlebitis. No patient died as a consequence of an adverse event. All drug-related abnormalities disappeared after treatment discontinuation.

DISCUSSION

In the 1960s and early 1970s, several autoptic studies drew attention to the increasing role of fungal infections as cause of death in leukaemic patients [15–17], and to the fact that early treatment with amphotericin B was apparently able to improve the prognosis of these infections [18], at least in the presence of rapid recovery of an adequate granulocyte count. Soon after, Burke and associates showed a decreased mortality rate from invasive mycosis in patients receiving empirical amphotericin B compared with historical controls [19]. These observations led two groups of investigators on both sides of the Atlantic to test the effectiveness of ths procedure in a randomised trial.

Pizzo and associates at the National Cancer Institute in Bethesda randomised patients who were still febrile and granulocytopenic after 7 days of empirical antibiotic therapy, in the absence of any documentation of infection, to discontinue all antibiotic treatments (16 patients), to continue the same empirical antibacterial antibiotic combination as for initial treatment (16 patients) and to add empirical amphotericin B (18 patients). Lack of addition of amphotericin B resulted in an increased incidence of fungal infections. In the group of patients who did not receive amphotericin B, there was 1

Table 2. Treatment outcome

	Fluconazole (n = 56)	Amphotericin B (n = 56)	P value
Success (%)	42 (75)	37 (66)	0.4
Failure (%)	14 (25)	19 (34)	
Causes of treatment modification and failure			0.19
Persistent fever (treatment modification allowed only after 4 full days of therapy)	8	8	
Documented infection after randomisation*	3	4	
Life-threatening adverse events	0	5	
Death within 30 days from randomisation	3	2	

*Clinically and/or microbiologically.

Table 3. Adverse events

	Fluconazole (n = 56)	Amphotericin B (n = 56)	P value
Patients experiencing adverse events (%)	18 (32)	46 (82)	<0.001
Total number of adverse events recorded	20	82	
Patients requiring treatment discontinuation because of life-threatening adverse events	0	5	0.06
Type of adverse events			
Allergic reaction	0	1	
Drug-related fever	0	27	
Drug-related fever and chills	0	11	
Drug-related fever, chills and tremors	0	4	
Transaminase increase	10	6	
Hypokalaemia	1	20	
Nephrotoxicity	7	10	
Phlebitis	0	1	
Rash	2	2	

bacterial infection and 5 fungal infections, 2 of which were fatal. One more patient, who died, had a disseminated fungal infection detected at autopsy. In the group of 18 patients randomised for receiving amphotericin B and to continue antibacterial therapy, only two documented infections developed (a disseminated *Cytomegalovirus* infection and a *Petriellidium boydii* pneumonia and arteritis) and both patients died. Antibiotic therapy discontinuation, as in the first group, resulted in the development of serious complication of both bacterial and fungal origin [20].

The International Antimicrobial Therapy Cooperative Group of the European Organisation for Research and Treatment of Cancer (EORTC) randomised 132 persistently febrile and granulocytopenic cancer patients, not responding to empirical antibacterial therapy and affected by unexplained fever or by a clinically documented infection, to receive empirical amphotericin B or for continuing their antibacterial coverage without modification. There was no statistically significant difference between the two groups in terms of defervescence and survival, although no death due to fungal infection occurred among the patients receiving empirical amphotericin B compared to four in the other group (P = 0.05), and the number of documented fungal infections was higher in patients not receiving amphotericin B (6 versus 1; P = 0.1). Interestingly, the addition of amphotericin B, which was not beneficial in the overall patient population, seemed to be effective in some patient subgroups (adult patients, patients not receiving antifungal prophylaxis and patients who were severely granulocytopenic), suggesting that the early antifungal therapy strategy should probably be reserved to selected groups of patients [4].

In both trials the statistical power of the observed results was relatively small, especially in subgroup analysis. This pitfall was actually acknowledged in the EORTC study, in which, for this reason, no definitive conclusion was drawn.

Nevertheless, the use of empirical amphotericin B in persistently febrile and granulocytopenic cancer patients without documented infections has become the rule in many oncological and bone marrow transplantation centres.

In recent years, several articles about infections in cancer patients have emphasised an obvious but often unrecognised concept, i.e. that all cancer patients are not the same and that both antibacterial and antifungal measures should be tailored according to individual infectious risks [21–26]. With this in mind, and assuming that not all persistently febrile and granulocytopenic cancer patients with unexplained fever necessarily need amphotericin B, we conducted a multicentre, open, randomised clinical trial comparing efficacy and safety of fluconazole with that of amphotericin B in this clinical setting. Our aim was not that of comparing the antifungal activity of the two drugs, but rather that of testing if there was any pragmatic difference for the patient in receiving either amphotericin B or fluconazole. The results suggest that this pragmatic difference does exist in terms of tolerance and might not exist in terms of effectiveness. Patients seemed to do similarly well with both drugs, but had much more untoward effects affecting their quality of life with amphotericin B than with fluconazole. In addition only 1 patient developed bacteraemia after randomisation in the fluconazole group whereas 4 such cases occurred in the amphotericin B group. Patients treated with amphotericin B had a 66% response rate, but experienced an 82% adverse event rate in 5 cases leading to treatment discontinuation, compared to a 75% response rate in patients receiving fluconazole, with a 32% incidence of adverse events, in no case prompting treatment discontinuation. In accordance with our pragmatic aims, our adverse event definition was very strict and included abnormalities from any cause, including those clearly unrelated to the study drugs. For this reason, the adverse event rate in the fluconazole group was higher than that usually observed in patients treated with this drug [27]. In contrast, the adverse event rate in patients receiving empirical amphotericin B was in accordance with current experience. Indeed, Gallis and associates reported an incidence of nephrotoxicity as high as 80% within 2 weeks of therapy in patients receiving amphotericin B [5]. We found an incidence of nephrotoxicity (creatinine increase) of 18% and of hypokalaemia of 36%, which makes a total of 30 of 56 patients (54%) with some evidence of renal damage. Gallis and colleagues noticed that fever and chills occurred in more than half the patients receiving amphotericin B, while we found that 15 of 56 patients (27%) experienced fever and chills.

The results of this study in terms of pragmatic effectiveness must be treated with caution because the sample size was inadequate to unequivocally demonstrate that the two regimens were equally effective. As long as equal efficacy is not

demonstrated, fluconazole use in empirical antifungal therapy should be considered experimental, especially in patients at high risk of fungal infection resulting from prolonged neutropenia. Interestingly, the incidence of bacterial infections documented after randomisation for empirical antifungal therapy was relatively high (5 of 112, 5%), suggesting that occult bacterial infections resistant to antibacterial regimens are not exceptional.

In conclusion, the population of granulocytopenic cancer patients not responding to empirical antibacterial therapy and remaining persistently febrile without any documentation of infection is probably multifaceted. Some might not require antifungal therapy, while others do. Among the latter, some may need amphotericin B, but others could do similarly well with other less toxic antifungal drugs (e.g. fluconazole). Further studies are needed in order to provide a means of identifying these patients in advance. This study draws attention to the high toxicity rate experienced by patients treated empirically with intravenous amphotericin B, something which is well known but probably not adequately recognised. In addition, this pilot study suggests that the approach to empirical antifungal therapy should be reconsidered, and that fluconazole might be as effective as amphotericin B, at least in some patient subgroups. This strategy might be seen as an alternative to the long-term use of fluconazole in prophylaxis, especially in the light of the possible development of resistance to triazoles related to prolonged use, as described in AIDS patients [28].

1. Armstrong D, Young LS, Meyer RD, Blevins AH. Infectious complications of neoplastic disease. *Med Clin North Am* 1971, **55**, 729–745.
2. Klastersky J, Zinner SH, Calandra T, *et al.* Empiric antimicrobial therapy for febrile, granulocytopenic cancer patients: lessons from 4 EORTC trials. *Eur J Cancer Clin Oncol* 1988, **24** (Suppl. 1), s35–s45a.
3. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med* 1982, **72**, 101–111.
4. EORTC International Antimicrobial Therapy Cooperative Group. Empiric antifungal therapy in febrile granulocytopenic patients. *Am J Med* 1989, 86, 668–672.
5. Gallis HA, Drew RH, Pickard A. Amphotericin B: 30 years of clinical experience. *Rev Infect Dis* 1990, **12**, 308–329.
6. Walsh TJ. Management of immunocompromised patients with evidence of invasive mycosis. *Hematol Oncol Clin North Am* 1993, **5**, 1003–1026.
7. Milatovic D, Vos A. Efficacy of fluconazole in the treatment of systemic fungal infections. *Eur J Clin Microbiol Infect Dis* 1992, **11**, 395–402.
8. Meunier F. Fluconazole treatment of fungal infections in the immunocompromised host. *Semin Oncol* 1990, **17** (Suppl. 6), 19–23.
9. Goodman JL, Winston DJ, Greenfield RA, *et al.* A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med* 1992, **326**, 845–851.
10. Winston DJ, Chandrasekar PH, Lazarus HM, *et al.* Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. *Ann Intern Med* 1993, **118**, 495–503.
11. Menichetti F, Del Favero A, Martino P, *et al.* and the Gimema Infection Program. Preventing fungal infection in granulocytopenic patients with acute leukemia: fluconazole compared with oral Amphotericin B. *Ann Intern Med* 1994, **120**, 913–918.
12. Wingard JR, Merz WG, Rinaldi MG, *et al.* Increase in *Candida krusei* infection among patients with bone marrow transplantation and granulocytopenia treated prophylactically with fluconazole. *N Engl J Med* 1991, **325**, 1274–1277.
13. Wingard JR, Merz WG, Rinaldi MG, Miller CB, Karp JE, Saral R. Association of *Torulopsis glabrata* infection with fluconazole prophylaxis in granulocytopenic bone marrow transplant patients. *Antimicrob Agents Chemother* 1993, **37**, 1847–1849.
14. Consensus Panel of the Immunocompromised Host Society. The design, analysis and reporting of clinical trials on the empirical antibiotic management of the granulocytopenic patient. *J Infect Dis* 1990, **161**, 397–401.
15. Bodey J. Fungal infections complicating acute leukemia. *J Chronic Dis* 1966, **19**, 667–687.
16. Mirsky HS, Cuttner J. Fungal infection in acute leukemia. *Cancer* 1972, **30**, 348–352.
17. Myerwitz RL, Pazin GJ, Allen CM. Disseminated candidiasis. Changes in incidence, underlying disease and pathology. *Am J Clin Pathol* 1977, **68**, 29–38.
18. Aisner J, Schimpff S, Wiernik H. Treatment of invasive aspergillosis: relation of early diagnosis and treatment to response. *Ann Intern Med* 1977, **86**, 539–543.
19. Burke PJ, Braine HG, Rathbun HK, *et al.* The clinical significance and management of fever in acute myelocytic leukemia. *John Hopkins Med J* 1976, **139**, 1–12.
20. Pizzo PA, Robichaud KJ, Gill FA, *et al.* Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med* 1982, 72, 101–110.
21. Talcott JA, Findberg R, Mayer RJ, Goldman L. The medical course of cancer patients with fever and neutropenia. *Arch Intern Med* 1988, **148**, 2561–2567.
22. Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* 1992, **10**, 316–322.
23. Viscoli C, Bruzzi P, Castagnola E, *et al.* and the International Antimicrobial Therapy Cooperative Group of the EORTC. Factors associated bacteraemia in febrile, granulocytopenic cancer patients. *Eur J Cancer* 1994, **30A**, 430–437.
24. Guiot HFL, Fibbe WE, van't Wout. Risk factors for fungal infection in patients with malignant hematologic disorders: implications for empirical therapy and prophylaxis. *Clin Infect Dis* 1994, **18**, 525–532.
25. O'Donnell MR, Schmidt GM, Tegtmeier GM, *et al.* Prediction of systemic fungal infection in allogeneic marrow recipients: impact of amphotericin B prophylaxis in high-risk patients. *J Clin Oncol* 1994, **12**, 827–834.
26. Walsh TJ, Hiemenz J, Pizzo PA. Editorial response: evolving risk factors for invasive fungal infections—All neutropenic patients are not the same. *Clin Infect Dis* 1994, **18**, 793–798.
27. Viscoli C, Castagnola E, Fioredda F, Ciravegna B, Barigione G, Terragna A. Fluconazole in the treatment of candidiasis in immunocompromised children. *Antimicrob Agents Chemother* 1991, **35**, 365–367.
28. Ruhnke M, Eigler A, Tennagen I, Geiseler B, Engelmann E, Trautmann M. Emergence of fluconazole-resistant strains of *Candida albicans* in patients with recurrent oropharyngeal candidosis and human immunodeficiency virus infection. *J Clin Microbiol* 1994, **32**, 2092–2098.

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