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Itraconazole versus amphotericin B plus nystatin in the prophylaxis of fungal infections in neutropenic cancer patients

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The efficacy and safety of itraconazole oral solution and a combination of amphotericin B capsules plus nystatin oral suspension were compared in the prophylaxis of fungal infections in neutropenic patients. In an open, randomized, multicentre trial, 144 patients received itraconazole oral solution 100 mg bd, and 133 patients received amphotericin B 500 mg tds plus nystatin 2 MU qds. Overall, 65% of itraconazole-treated patients were considered to have had successful prophylaxis, compared with 53% in the polyene group. Proven deep fungal infections occurred in 5% of patients in each group. Fewer patients receiving itraconazole than amphotericin plus nystatin had superficial infections (3 versus 8%; $P = 0.066$). This trend in favour of itraconazole was seen in patients with profound neutropenia (neutrophil count $<0.1 \times 10^9$ cells/L at least once) or prolonged neutropenia (neutrophil count $<1.0 \times 10^9$ cells/L for >14 days). The median time to prophylactic failure was longer in the itraconazole group (37 days) than in the polyene group (34 days). The number of patients with fungal colonization (nose, sputum, stool) changed more favourably from baseline to endpoint in the itraconazole group than in the polyene group. Both treatments were safe and well tolerated; however, patients receiving amphotericin plus nystatin had a higher incidence of nausea and rash. In conclusion, itraconazole oral solution at doses of 100 mg bd and oral amphotericin B plus nystatin have similar prophylactic efficacy against fungal infections in neutropenic patients. On the basis of reduced incidence of superficial fungal infections, fungal colonization and specific adverse events, itraconazole may be the preferred treatment.

Introduction

Invasive fungal infections are a major cause of morbidity and mortality in neutropenic cancer patients. All too often, acute leukaemia or bone marrow transplant patients die from disseminated candidosis or aspergillosis, despite having a good prognosis for their underlying disease.[1] In addition, an increasing number of new opportunistic fungi are being observed in these immunosuppressed patients. Establishing optimal prophylactic strategies is therefore vital to prevent these invasive fungal infections in high-risk populations.

The usefulness of intravenous amphotericin B as a prophylactic agent is limited by its lack of absorption and poor compliance when used orally and by its nephrotoxicity when used intravenously.[2] The antifungal azoles ketoconazole and fluconazole are orally absorbed and systemically active agents; however, they are not effective against *Aspergillus* spp., and some non-*albicans* species of *Candida* are resistant to fluconazole.[3–5] An effective, broad-spectrum, non-toxic, orally active agent may therefore be required for prophylaxis in severely immunocompromised patients.

Itraconazole is an orally active broad-spectrum triazole derivative that exhibits pronounced antifungal activity against a wide range of pathogenic fungi, such as *Candida* and *Aspergillus* spp., and *Cryptococcus neoformans*.[5–7]

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Initial studies have indicated that fungal infections occur less often in neutropenic patients with plasma itraconazole concentrations of >250 ng/mL than in those with lower concentrations.[8] However, the bioavailability of itraconazole from the traditional capsule formulation can be variable in neutropenic patients. In the light of these observations, a new formulation of itraconazole with improved bioavailability has been developed, namely itraconazole oral solution containing hydroxypropyl-β-cyclodextrin.[9] This has been developed primarily for use in neutropenic patients, who should benefit not only from the improved bioavailability, but also from the easy administration of the oral solution, even if they have mucositis and swallowing problems; this may help to promote compliance.

The present study was performed to compare the efficacy and safety of itraconazole oral solution 100 mg bd with the non-absorbable combination of oral amphotericin B plus nystatin in the prevention of fungal infections in neutropenic patients. These non-absorbable drugs were, at the time of study initiation, still considered to be state-of-the-art prophylactic treatment. Amphotericin B was chosen because of its wide antifungal spectrum, and nystatin to treat mucosal colonization, an event frequently preceding invasive infection.

Patients and methods

This open, parallel-group, multicentre trial was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committees (institutional review boards). All patients provided informed consent to participate.

Patients

Patients were eligible for the trial if they were aged at least 16 years, had leukaemia or aplastic anaemia or had undergone bone marrow transplantation, and/or were due to receive remission induction or consolidation therapy likely to produce neutropenia (neutrophil count $<0.5 \times 10^9$ cells/L) lasting at least 10 days. The same patient could be included more than once if more than 3 months had elapsed since the previous neutropenic episode and no breakthrough fungal infection was observed in the previous treatment period.

Patients were excluded if they were hospitalized for fewer than 7 days or if they were receiving other antifungal agents, rifampicin or phenytoin. Other exclusion criteria were known hypersensitivity to azole antifungal agents, evidence of fungal infection at the start of the study, and possible pregnancy or lactation.

Treatment

Eligible patients were randomized to receive either itraconazole oral solution 100 mg bd or a combination of amphotericin B capsules 500 mg tds plus nystatin oral suspension 2 MU qds. Itraconazole was given as a 10 mg/mL oral solution immediately after a meal; the solution had to be swallowed with water after a contact time with the oral mucosa of about 10 s. Treatment was started either 3–4 days before or at the same time as cytostatic therapy and was continued until the neutrophil count was restored to $>1.0 \times 10^9$ cells/L.

Drugs affecting gastric acid secretion, such as H_2 receptor antagonists, antacids or anticholinergic agents, were not permitted within 2 h of administration of itraconazole. Standard chemotherapeutic, antibiotic and disinfectant regimens were maintained at each centre. Topical antifungal agents applied to the skin were permitted for patients with positive skin cultures.

Assessments and endpoints

Routine specimens from the mouth, nose, stools and catheter exit site were taken before starting prophylaxis, before initiating chemotherapy or radiotherapy, and twice weekly during the period of neutropenia. If a patient became febrile, further samples were taken from the same sites and from other appropriate locations (e.g. biopsy sites, drainage fluid, suspected lesions).

The primary endpoint was prophylactic failure, defined as breakthrough of proven or suspected deep fungal infection, superficial fungal infection, or fever of unknown origin despite the use of broad-spectrum antibiotics. The criteria for these endpoints are summarized in Table I.

Patients were reviewed every 3–4 days until 56 days after the start of treatment. Any abnormal symptoms and adverse events were recorded. The onset and duration, intensity (mild, moderate or severe), frequency, drug-relatedness, action taken and outcome of all adverse events were recorded. Symptoms associated with a proven or suspected fungal infection (cough, wheezing, headache) were rated as absent, mild, moderate or severe.

During the 24 h period before prophylaxis was started, blood was collected for routine haematological and biochemical investigations. These investigations were repeated at least once a week during treatment. In addition, in itraconazole-treated patients, plasma concentrations of itraconazole were measured by high performance liquid chromatography 2 h after administration on days 3, 7, 14, 21 and 28. In all patients, heart rate, blood pressure and body temperature were measured at each assessment.

Statistics

Data were analysed on an intention-to-treat basis; thus, the analysis included all patients randomized to treatment, regardless of protocol violations. Differences in trial endpoints between and within groups were analysed by the Mann–Whitney *U*-test. In patients who withdrew from the trial because of prophylactic failure, the mean time to failure was calculated by the Kaplan–Meier technique.

Table I. Definitions of breakthrough of fungal infection[a]

Endpoint	Definition
Proven deep fungal infection	positive histology on biopsy from deep tissue *or* clinical signs and radiographic lesions with the presence of *Aspergillus* spp. or other filamentous fungi in bronchoalveolar lavage fluid
Suspected deep fungal infection	clinical signs and symptoms (with or without radiographic lesions) with fever of unknown origin unresponsive to broad-spectrum antibiotics *or* highly suggestive radiographic lesions without mycological evidence *or* clinical signs and symptoms (with or without radiographic lesions) associated with suggestive fungal isolation
Superficial fungal infection	clinical signs and symptoms of oral, oesophageal or vaginal candidosis, combined with positive mycological evidence at the site of infection
Fever of unknown origin	oral or axillary temperature >38°C or rectal temperature >38.5°C for at least 48 h during broad-spectrum antibiotic treatment covering Gram-negative and -positive bacteria (including a glycopeptide antibiotic) without clinical signs and symptoms

[a]Current definitions are made by the Mycoses Study Group and/or the Invasive Fungal Infection Group of the EORTC.

Results

A total of 277 patients were randomized to treatment, of whom 144 received itraconazole and 133 received amphotericin B plus nystatin. The patient and disease characteristics are shown in Table II. The two patient groups were well balanced, except that the proportion of women was significantly higher in the group receiving amphotericin B plus nystatin ($P = 0.04$).

A total of 205 patients (104 in the itraconazole group, 101 in the amphotericin B plus nystatin group) withdrew from the trial (Table III). Of the 98 failures in the itraconazole group, 53 were prophylactic failures, 23 had adverse events, 13 had intercurrent events, one had abnormal laboratory values and eight died. Of the 101 failures in the amphotericin B plus nystatin group, 60 were prophylactic failures, 23 had adverse events, 11 had intercurrent events and seven died.

Efficacy

In both groups, the mean neutrophil count decreased from $>3.0 \times 10^9$ cells/L to $<0.2 \times 10^9$ cells/L after approximately 2 weeks. The mean time during which patients had a neutrophil count of $<0.1 \times 10^9$ cells/L was 13.9 days in the itraconazole group and 14.7 days in the amphotericin B plus nystatin group. The mean duration of neutrophil counts of 0.1–0.5 $\times$ 10^9 cells/L was 14.3 days in the itraconazole group and 14.5 days in the amphotericin B plus nystatin group. For counts of 0.5–1.0 $\times$ 10^9 cells/L, the mean duration was 17.1 days and 15.7 days, respectively. In the itraconazole group, 121 patients (84.0%) were neutropenic for at least 10 days, compared with 115 (86.5%) in the group treated with amphotericin B plus nystatin. No significant differences in neutrophil count were seen between the two groups at any time.

The incidence of breakthrough fungal infections in the two groups is summarized in Table IV. Overall, 93 patients (64.6%) in the itraconazole group were considered to have had successful prophylaxis, compared with 71 (53.4%) in the group receiving amphotericin B plus nystatin ($P = 0.066$). The estimated time to prophylactic failure was 37 days in patients treated with itraconazole and 34 days in patients receiving amphotericin B plus nystatin. In most patients requiring rescue antifungal medication (itraconazole group $n = 50$, amphotericin B plus nystatin group $n = 52$), the rescue medication consisted of intravenous amphotericin B, with or without another antifungal agent.

Trends in favour of itraconazole were seen in subgroups of patients with severe neutropenia or prolonged neutropenia. In the itraconazole group, 76/120 (63.3%) patients with severe neutropenia were considered to have had successful prophylaxis, five (4.1%) had proven deep fungal infection and three (2.5%) had suspected infection. In the amphotericin B plus nystatin group, 54/106 (50.9%) patients with severe neutropenia were considered to have had successful prophylaxis, six (5.7%) had proven deep fungal infection and four (3.8%) had suspected infection. Overall, the difference between the groups almost reached statistical significance ($P = 0.054$).

In the itraconazole group, 69/111 (62.2%) patients with prolonged neutropenia were considered to have had successful prophylaxis, four (3.6%) had proven deep fungal infection and four (3.6%) had suspected infection. In the

amphotericin B plus nystatin group, 52/109 (47.7%) patients with prolonged neutropenia were considered to have had successful prophylaxis, six (5.5%) had proven deep fungal infection and four (3.7%) had suspected infection. The difference between the treatment groups was statistically significant ($P = 0.031$).

The number of patients with fungal colonization of the nose and sputum decreased from baseline to endpoint (from 5 to 3 and 7 to 4, respectively) in the itraconazole group. In the amphotericin B plus nystatin group only the number of patients with colonization of the nose decreased (from 1 to 0). The number of patients with colonization of

Table II. Patient and disease characteristics of randomized patients

	Treatment group	
	itraconazole	amphotericin B plus nystatin
Patients		
randomized	144	133
male:female ratio	88:56	64:69
age[a]	45	49
Underlying disease		
acute myeloid leukaemia	87	94
acute myeloid leukaemia + other	1	1
bone marrow transplantation	8	3
bone marrow transplantation + other	7	7
other	41	28
Episode		
first	133	123
second	11	28
Severe neutropenia (at least one neutrophil count $< 0.1 \times 10^9$/L)	120	106
Prolonged neutropenia (neutrophil count $< 1.0 \times 10^9$/L for >14 days)	111	109

Data are numbers of patients, except [a]age, where data are mean years.

Table III. Reasons for withdrawal from the study

	Treatment group	
	itraconazole	amphotericin B plus nystatin
Failure		
prophylactic failure	53	60
adverse events	23	23
intercurrent events	13	11
abnormal laboratory values	1	0
death	8	7
Ineligibility	5	2
Treatment deviations		
non-compliance	1	1
patient's decision	3	1
withdrawal of consent	0	1
Loss to follow-up	1	2
Total[a]	104 (72%)	101 (76%)

Data are numbers of patients.
[a]Some patients withdrew for more than one reason.

Table IV. Incidence of breakthrough fungal infections and requirement for rescue medication

	Treatment group	
	itraconazole	amphotericin B plus nystatin
Deep fungal infection		
proven	7 (5)	7 (5)
suspected	4 (3)	5 (4)
Superficial fungal infection	4 (3)	11 (8)
Fever of unknown origin	21 (15)	18 (14)
Pneumonia of unknown origin	11 (8)	14 (11)
Rescue medication required (intravenous amphotericin B with or without another antifungal agent)	50 (35)	52 (39)

Data are numbers of patients, with percentages in parentheses.

stool increased in both groups (from 22 to 33 in the itraconazole group and from 6 to 24 in the amphotericin B plus nystatin group) and, in the amphotericin B plus nystatin group, colonization of the sputum was recorded in one patient at baseline and in 12 at endpoint. No correlation was seen between colonization at baseline or endpoint and subsequent proven or suspected fungal infection.

Plasma concentrations of itraconazole

The mean plasma concentrations of itraconazole were 383 ng/mL (range 2–1666 ng/mL) on day 7, 372 ng/mL (range 1–1605 ng/mL) on day 14 and 460 ng/mL (range 1–1443 ng/mL) on day 28. The low extreme values may have been caused by non-compliance.

Safety

Adverse events were reported by 63 patients (43.8%) in the itraconazole group and by 61 patients (45.9%) in the amphotericin B plus nystatin group. The most frequent events were vomiting (itraconazole group $n = 14$, amphotericin B plus nystatin group $n = 12$), diarrhoea ($n = 12$ and 9, respectively), nausea ($n = 5$ and 12, respectively) and rash ($n = 2$ and 13, respectively).

Most adverse events were mild or moderate; severe adverse events were reported by 23 itraconazole-treated patients and by 26 patients receiving amphotericin B plus nystatin. Seventeen patients in each group died during the trial or within 30 days after the last dose of trial medication (six died in each group with suspected or proven fungal infection); death was recorded as an adverse event in 13 patients in the itraconazole group and in nine patients in the amphotericin B plus nystatin group. Discontinuation of treatment because of adverse events (including death) was necessary in 34 itraconazole-treated patients and in 33 patients who received amphotericin B plus nystatin.

A high incidence of laboratory abnormalities was to be expected in this group of neutropenic patients, given the serious nature of their underlying disorders and concomitant medications, but no significant difference was found between the two groups. Liver function tests showed a similar number of patients reporting 'code-4' important abnormalities in each group. Pathological grade 1, code-4, important abnormalities were reported in 36 patients in each group. Pathological grade 2, 3 and 4, code-4, important abnormalities were reported in 20, nine and two patients, respectively, in the itraconazole group, and in 17, five and three patients in the amphotericin B plus nystatin group.

Discussion

The results of the present study indicate that itraconazole oral solution may be effective in the prophylaxis of fungal infections in neutropenic patients with severe or prolonged neutropenia.

The incidence of proven or suspected deep fungal infections was similar in itraconazole-treated patients and in those treated with amphotericin B plus nystatin. The number of deaths from proven or suspected deep fungal infections was also similar in the two groups. The prominent causative organism in both groups at baseline and endpoint was *Candida albicans*. Superficial infections were less frequent in patients receiving itraconazole, the change in the number of patients with a colonized site (which can lead to systemic infection[10]) at endpoint was more favourable in the itraconazole group, and a larger proportion of itraconazole-treated patients remained free from fungal infection, indicating a trend in favour of itraconazole. A trend in favour of itraconazole was also detected in subgroups of patients with severe or prolonged neutropenia, who are at particular risk of infection, although these findings may be attributable to the higher incidence of superficial infections in patients treated with amphotericin B plus nystatin. Both treatments were well tolerated, but the considerably higher

incidence of nausea and rash in patients treated with amphotericin B plus nystatin may indicate a further advantage of itraconazole.

In other recent trials of the efficacy and tolerability of itraconazole oral solution, a dosage of 5 mg/kg/day, given in two doses, was used;[11–13] this resulted in a lower incidence of fungal infections in neutropenic patients than with placebo, fluconazole or amphotericin B. The death rate with proven fungal infection was lower in the itraconazole arm of each trial. Moreover, a lower rate of suspected deep fungal infections requiring empirical intravenous amphotericin B rescue therapy occurred in itraconazole recipients. These superior results with itraconazole suggest that a dosage of 5 mg/kg/day is preferable to the 100 mg bd used in the present study. However, the potential for itraconazole oral solution to be more effective than other oral antifungals at preventing aspergillosis has not been conclusively demonstrated in clinical trials, possibly because they have not included enough patients who are at high risk of aspergillosis (such as allogeneic transplant recipients with chronic extensive or severe acute graft versus host disease).[11–14]

Recent pharmacokinetic data indicate that the bioavailability of the oral solution is 60% higher when taken under fasting conditions than when taken with food.[15,16] The mean plasma itraconazole concentrations in the present study might therefore have been increased further if the oral solution had been taken on an empty stomach. Nevertheless, even though itraconazole was taken after meals, the mean plasma itraconazole concentrations exceeded the 250 ng/mL needed to maintain prophylactic efficacy.[17] This indicates that absorption of the oral solution is not dependent on an acid pH in the stomach. In addition, the absorption of the itraconazole oral solution is not impaired by coadministration with an antacid;[18] the restriction on the use of gastric acid suppressing drugs in the protocol of this study was therefore unnecessary.

Overall conclusions from this pilot open study are limited, because no placebo group was included, and neither treatment was shown to be clearly more effective than the other. Future comparative studies should confirm the important role of the itraconazole oral solution in not only primary, but also secondary prophylaxis, and in the early empirical treatment of systemic fungal infections in neutropenic patients.

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