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Amphotericin B or Ketoconazole Therapy of Fungal Infections in Neutropenic Cancer Patients

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Fungal infections in neutropenic cancer patients have increased in frequency and constitute an important cause of morbidity and mortality. Empiric antifungal therapy is often administered to those patients who have failed to respond to antibacterial antibiotics. We conducted a prospective, randomized trial of amphotericin B and ketoconazole for 172 neutropenic cancer patients with presumed or proven fungal infections. Overall, amphotericin B and ketoconazole were equally effective. Amphotericin B may have been more effective than ketoconazole for the treatment of pneumonia. Also, five of eight *Candida tropicalis* infections treated with amphotericin B responded, whereas all eight infections treated with ketoconazole failed to respond ($P = 0.03$). Response rates for localized fungal infections were similar with both drugs. Ketoconazole should not be used as empiric antifungal therapy at institutions where there is a high frequency of infections caused by *Aspergillus* spp. or *C. tropicalis* because this agent lacks activity in vitro against these species.

Fungal infections are increasing in frequency among neutropenic cancer patients (1, 4, 5, 7, 9). Many of these infections cannot be diagnosed antemortem; hence, the patients never receive antifungal therapy. For this reason, it has become accepted practice to administer antifungal agents empirically to neutropenic patients with persistent fever that is unresponsive to antibacterial agents.

Amphotericin B has been the mainstay of antifungal therapy. Unfortunately, it has many unpleasant side effects that make it an undesirable agent for empiric therapy. Ketoconazole, a new imidazole derivative, is an appealing substitute for amphotericin B because it is less toxic and is administered orally. However, its spectrum of antifungal activity does not include *Aspergillus* spp. and *Candida tropicalis*. We conducted the first prospective, randomized trial of amphotericin B and ketoconazole for the treatment of established or suspected fungal infections in neutropenic cancer patients.

MATERIALS AND METHODS

Patient eligibility. Between 1981 and 1983, neutropenic cancer patients having persistent fever (temperature > 38.3°C) after 72 to 96 h of therapy with antibacterial antibiotics were considered eligible for study participation. Patients with clinically suspected or microbiologically proven fungal disease were also included. Patients with significant hepatic impairment (bilirubin, >5 mg/dl) or renal insufficiency (creatinine, >2.5 mg/dl) were not included. All eligible patients had to be capable of taking oral medications or have functional nasogastric tubes. Initial therapy with antibacterial antibiotics was discontinued for all patients in this study. Cimetidine and antacids were discontinued before therapy was started in patients selected to receive ketoconazole. Patients who were receiving concomitant oral nystatin for thrush or esophagitis were not considered for evaluation. Leukocyte transfusions were given to those patients who had available donors and in whom a microbiologically proven infection had been documented but who yet remained febrile and clinically ill after institution of antifungal therapy.

Treatment regimens. Eligible patients were given either amphotericin B or ketoconazole as determined by a computer-generated randomization schedule. After allocation, all previous antibacterial antibiotics were discontinued. All patients in the study received trimethoprim-sulfamethoxazole if they had an undocumented bacterial infection. For the antifungal agents, the dosage schedules were as follows: ketoconazole was given orally at a dose of 200 mg every 6 h (1 h before or 2 h after meals); amphotericin B (1 mg) was given as a test dose on day 1, followed by 0.5 mg/kg intravenously (i.v.) on day 2 and 0.6 to 1.0 mg/kg on a daily basis thereafter. The dose of amphotericin B was reduced if the serum creatinine reached 2.5 mg/dl, and treatment was discontinued at levels greater than 4 mg/dl. Trimethoprim (480 mg/day) and sulfamethoxazole (2,400 mg/day) were given either orally or i.v. in divided doses once every 8 h. Patients were made aware of the investigational nature of the study and signed an informed-consent document according to institutional policies.

Patients were evaluated after they had received antifungal therapy for at least 4 days. In those patients responding to therapy, antifungal agents were continued for a minimum of 2 weeks. None of those eligible for evaluation had received trimethoprim-sulfamethoxazole or antifungal therapy before entering the study. Patients were considered cured when all clinical and microbiologic signs and symptoms of infection had been eradicated, and treatments were considered failures when those signs and symptoms persisted despite therapy for at least 7 days. The persistence of fever alone was defined as treatment failure only among patients with possible infections. In those patients with documented infections, persistence of fever was not considered a treatment failure if signs and symptoms of infection were resolved. Although crossover therapy was not included as part of this study, patients who failed to respond to their assigned regimens were occasionally treated subsequently with the other antifungal agent.

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TABLE 1. Distribution of patient characteristics

Characteristic	Amphotericin B	Ketoconazole
	No. of episodes (%)	No. of episodes (%)
Males	47 (57)	50 (67)
Females	36 (43)	25 (33)
Leukemia	79 (95)	71 (95)
Solid tumors	4 (5)	4 (5)
Severe neutropenia[a]	68 (82)	54 (72)
All	83 (53)	75 (47)

[a] <100 granulocytes per μl of blood.

Laboratory evaluation. Patients were monitored daily during their hospitalization by the investigators. Complete blood counts were performed daily. Evaluations of serum electrolytes, liver function, blood urea nitrogen, and creatinine, in addition to urinalysis, were performed before therapy and twice weekly thereafter. During the preceding days when patients were febrile, at least two blood cultures were done daily, and another specimen was obtained on day 1 of the study. Daily blood cultures were obtained for as long as the patients remained febrile. For the analyses, we used the BACTEC radiometric system (Johnston Laboratories, Inc., Towson, Md.); all specimens were subcultured after day 7. Other cultures and radiological studies were repeated as often as the attending physician believed necessary.

Definitions. Severe thrombocytopenia is common among patients with aplastic marrow and prevents the physician from performing those invasive procedures required for the definitive diagnosis of fungal infection. Because of these difficulties, we used the following definitions: documented fungal infection was indicated by clinical evidence of infection and fungus cultured or identified from tissue specimens; probable fungal infection was indicated by clinical documentation of infection, but no definitive evidence of fungal or bacterial organisms obtained from tissues (included in this category were patients with fungemia [catheter related; no evidence of tissue invasion]); possible fungal infection was characterized by febrile episodes, with no microbiological or radiological evidence of infection; localized fungal infection was confined to one specific anatomical area (e.g., esophagus, lungs, soft tissue, urinary tract, or oral cavity), and the blood cultures were negative; the presence of at least 100,000 colonies or more of the organism, in at least two separate specimens, with or without leukocytes in the sediment, denoted urinary tract infection; disseminated fungal infection was indicated by histologically documented fungal infection involving multiple organs; hepatic toxicity was defined as serum glutamic oxalacetic transaminase or alkaline phosphatase levels that were at least 30% higher than the initial values obtained at the onset of therapy; and renal toxicity was indicated by serum creatinine levels that were at least 25% higher than the initial value obtained at the onset of therapy.

RESULTS

Of the 192 febrile episodes that occurred in 172 patients studied, 34 episodes were excluded as responses that were not considered to be evaluatable (with 9, the patients were not neutropenic, with 17, the patients received inadequate trials of antifungal therapy [less than 4 days] or received other concurrent antifungal agents, and with 8, the patients had what proved to be bacterial infections).

Of the 158 episodes considered evaluatable, 97 occurred in males, and 61 occurred in females. The most common underlying malignancies were acute and chronic leukemias (144 and 6 patients, respectively); the remaining 8 patients had carcinomas of the lung or breast, sarcoma, or lymphoma. The outcome of the underlying malignancy was not examined in this investigation. The median age was 42 years, with a range of 16 to 76 years. Randomization resulted in treatment groups that had similar demographic and clinical characteristics (Table 1). All patients in the study had fever, which failed to respond to initial treatment with combinations of a cephalosporin plus aminoglycoside, an antipseudomonal penicillin plus aminoglycoside, or two β-lactam antibiotics. Evaluatable patients received antifungal therapy for an average of 9.3 days (range, 4 to 56 days). Among patients who received amphotericin B, the median total dose was 370 mg (range, 70 mg to 1 g). The median duration of therapy was similar for patients who received amphotericin B and ketoconazole (9.4 and 9.1 days, respectively).

Table 2 shows the overall results by treatment regimen. Fungal infection was documented in 29 episodes and was considered probable in 71. Without regard to therapy, the response rate was significantly lower among patients with documented fungal infection than among patients with probable fungal infection (21 versus 72%; $P < 0.0001$) and was lower among patients with disseminated rather than localized infection. The overall response rate in patients who received ketoconazole was slightly lower than that in patients who received amphotericin B (57 versus 66%), although this difference was not statistically significant.

The sites of infection and the response rates in patients with documented or probable fungal infection are shown in Table 3. The most common infections were fungemia, esophagitis, pneumonia, and disseminated disease. Patients with fungemia responded more frequently to amphotericin B

TABLE 2. Overall response rate by treatment arm

Infection	Amphotericin B		Ketoconazole		Total	
	No. of episodes	No. responding (%)	No. of episodes	No. Responding (%)	No. of episodes	No. responding (%)
Documented fungal	14	3 (21)	15	3 (20)	29	6 (21)
Localized	11	3 (27)	11	3 (27)	22	6 (27)
Disseminated	3	0 (0)	4	0 (0)	7	0 (0)
Probable fungal	37	28 (76)	34	23 (68)	71	5 (72)
Possible fungal	32	24 (75)	26	17 (65)	58	41 (71)
All	83	55 (66)	75	43 (57)	158	98 (62)

TABLE 3. Response by site of infection

Infection	Amphotericin B		Ketoconazole	
	Total	No. responding (%)	Total[a]	No. responding (%)
Disseminated	3	0 (0)	4	0 (0)
Fungemia	12	7 (58)	8	3 (38)
Pneumonia	20	13 (65)	15	7 (47)
Esophagitis	9	7 (78)	14	9 (64)
Soft tissue	3	2 (67)	1	1 (100)
Other localized[b]	4	2 (50)	7	6 (86)
All	51	31 (61)	49	26 (53)

[a] Eleven episodes subsequently responded to amphotericin B.
[b] Includes hepatitis, urinary tract infection, dental abscess, sinusitis, synovitis, osteomyelitis, and mucositis.

(58%) than to ketoconazole (38%); however, this difference was not statistically significant ($P = 0.61$). The difference in outcome was at least in part due to the poor response to ketoconazole for patients with fungemia caused by *C. tropicalis*. Three patients with fungemia who did not respond to ketoconazole subsequently responded to amphotericin B. The three disseminated infections treated with amphotericin B were caused by *Candida albicans*, *C. tropicalis*, and *Trichosporon cutaneum* in combination with *C. tropicalis*; treatment failed for these patients. The four disseminated infections treated with ketoconazole were all caused by *C. tropicalis*; treatment failed for all four patients, although two of them subsequently responded to amphotericin B. Response rates for pneumonia and esophagitis were lower among patients treated with ketoconazole than among those treated with amphotericin B; however, these differences were not statistically significant.

The response rates for infections caused by *C. albicans* and other *Candida* spp. were similar with both ketoconazole and amphotericin B (Table 4). However, a substantial difference in response rates was observed for patients infected with *C. tropicalis*, with five of eight episodes (63%) of infection responding to amphotericin B therapy, as opposed to none responding to ketoconazole therapy ($P = 0.03$). The few *Aspergillus* infections treated failed to respond to either drug.

The response to therapy was analyzed by changes in absolute neutrophil counts during therapy (Table 5). The response rate to amphotericin B was better overall for those patients whose neutrophil count increased than for those whose count decreased or remained unchanged during therapy ($P = 0.03$); the duration of neutropenia in these patients before initiation of antifungal therapy was not recorded. Amphotericin B was more effective than ketoconazole for those patients whose neutrophil count increased (81 versus 54%; $P = 0.06$). There was no difference in efficacy between the two drugs for patients whose neutrophil count decreased or remained unchanged.

TABLE 4. Response according to infecting fungal species

Organism	Amphotericin B		Ketoconazole	
	Total	No. responding (%)	Total	No. responding (%)
C. albicans	7	2 (29)	8	3 (38)
C. tropicalis	8	5 (63)[a]	8	0 (0)[a]
Candida	2	1 (50)	4	2 (50)
Aspergillus	4	0 (0)	2	0 (0)
Mucor	1	1 (100)		
Miscellaneous[b]	4	1 (25)	1	1 (100)

[a] $P = 0.03$.
[b] Includes *Trichosporon glabrata* (2 strains), *T. cutaneum* (1 strain), *Cryptococcus neoformans* (1 strain), and *T. cutaneum* plus *C. tropicalis* (1 strain).

TABLE 5. Response by neutrophil trend in documented infections

Initial neutrophil count/μl of blood	Change	Amphotericin B		Ketoconazole	
		No. of episodes	No. responding (%)	No. of episodes	No. responding (%)
<100	Total[a]	44	24 (55)	38	20 (53)
	Unchanged	27	11 (41)	17	9 (53)
	Increased	17	13 (76)	21	11 (52)
101–1,000	Total	6	6 (100)	8	3 (38)
	Decreased	2	2 (100)	5	1 (20)
	Unchanged	0		0	
	Increased	4	4 (100)	3	2 (67)
Total	Increased	21	17 (81)[b]	24	13 (54)[b]
	Decreased or unchanged	29	13 (45)	22	10 (45)

[a] Complete counts were not obtained for four episodes.
[b] $P = 0.06$.

Forty-six patients received leukocyte transfusions during the course of infection. Of the 46, 34 patients received from one to four transfusions; 12 of 20 transfusion recipients treated with amphotericin B responded (60%), and 5 of 14 recipients treated with ketoconazole responded (36%). Twelve more patients received from 5 to 12 transfusions: three of eight treated with amphotericin B responded (38%), and two of four treated with ketoconazole responded (50%).

Eight patients developed nausea and vomiting attributed to ketoconazole, which was severe enough to prompt discontinuation of the drug. In seven patients, fever and bronchospasm induced by amphotericin B were so severe that they became dose-limiting factors. Adequate liver and renal function tests were available for analysis during eval-

TABLE 6. Renal and hepatic toxicity related to therapeutic regimens and duration of therapy

Duration of therapy (days)	Amphotericin B		Ketoconazole	
	No. of episodes	No. abnormal (%)	No. of episodes	No. abnormal (%)
Alkaline phosphatase	83	36 (43)[a]	75	16 (21)[a]
4–14	19	9 (47)	13	2 (15)
≥15	64	27 (42)	62	14 (23)
SGOT[b]	83	24 (29)	75	26 (35)
4–14	19	10 (53)	13	2 (15)[c]
≥15	64	14 (22)	62	24 (39)[c]
Creatinine	83	34 (41)[d]	75	7 (9)[d]
4–14	19	9 (47)	13	4 (31)[e]
≥15	64	25 (39)	62	3 (5)[e]

[a] $P = 0.06$.
[b] SGOT, Serum glutamic oxalacetic transaminase.
[c] $P = 0.10$.
[d] $P = 0.000003$.
[e] $P = 0.02$.

uation of the 158 episodes of fungal infection (Table 6). Increases in alkaline phosphatase occurred more frequently among patients receiving amphotericin B (43 versus 21%; $P = 0.06$). Although elevations of serum glutamic oxalacetic transaminase occurred with similar frequency in both treatment groups, patients receiving ketoconazole for more than 2 weeks experienced toxicity more frequently than did those treated with shorter courses (39 versus 15%; $P = 0.11$).

Renal toxicity was detected in 41 patients. A statistically significant difference was observed between those who received amphotericin B and those who received ketoconazole (41 versus 9%; $P = <0.001$). There was no relation between dosage of amphotericin B and the incidence of nephrotoxicity. For those patients with amphotericin B-induced renal insufficiency, the median dose administered was 330 mg (range, 100 mg to 1 g), and for those without toxicity, the median dose was 380 mg (range, 70 mg to 1 g). The frequency of renal toxicity was also unrelated to the duration of therapy (Table 6). A significant difference in nephrotoxicity was observed among patients receiving ketoconazole for less than 14 days versus those receiving longer therapy. The elevations of creatinine values for these patients probably were not related to the drug, since all patients demonstrating renal toxicity also exhibited some degree of liver dysfunction, perhaps as a result of the infectious and neoplastic processes.

DISCUSSION

There are several difficulties in designing a prospective study to evaluate therapy of fungal infections in neutropenic patients. Clinicians who care for these individuals are familiar with many of these frustrating problems; perhaps that is why no large studies comparing amphotericin B with ketoconazole have been conducted. The frequency of proven fungal infections is low, and invasive diagnostic procedures seldom can be performed for documentation without subjecting the patient to substantial risks. Antibacterial regimens induce changes in normal flora, resulting in fungal overgrowth, and so add to the diagnostic uncertainties (2, 3, 13). Finally, there are few therapeutic alternatives, and toxicity and mortality rates are often high. Because of these adverse circumstances, management strategies vary from institution to institution, and many therapeutic regimens are instituted on an empiric basis.

The difficulty in documenting fungal infections was again encountered during this study. Of 158 evaluatable episodes, fungal infection was documented in only 29 (18%), a proportion which closely resembles previously reported figures (4). Interestingly, a better response rate was obtained with patients whose fungal infection could not be documented than in those with histologically proven infection. These response rates could reflect either the treatment effect before substantial tissue invasion or the absence of fungal infection.

Fungemia without clinical evidence of tissue invasion was considered a probable fungal infection as defined in this study. All of these patients had intravascular catheters at the time the fungus was cultured from their blood. Although we recommend removal of catheters under these circumstances, this was done with only three of the patients. The usual practice at most institutions is to remove the catheter without administering antifungal therapy. However, Rose reported that 9 of 35 patients with catheter-associated candidemia had persistent positive blood cultures after the catheter was removed and thus required antifungal therapy (11). In a study of 82 cancer patients with candidemia, the mortality was 77%; of those who underwent autopsy examination, 71% had histological evidence of candidiasis. Furthermore, some patients whose catheters had been removed but who received no antifungal therapy returned at a later date with documentable fungal infection. Hence, it is likely that some of our patients may also have had undetected disseminated candidiasis.

Candida spp. still remain the most common causes of fungal infection at our institution. The ratio of *C. tropicalis* to *C. albicans* infections has increased in recent years (6, 12). Of interest is the fact that there were equal numbers of major infections caused by the two species. While the response rate for *C. albicans* was similar in both arms of the study, a striking difference was noted in those patients infected with *C. tropicalis*. None of the patients treated with ketoconazole responded, whereas five of eight who had received amphotericin B responded. Moody et al. have previously reported the suboptimal in vitro activity of ketoconazole against *C. tropicalis* (8). At our institution, *C. albicans* was the predominant fungal pathogen in neutropenic patients prior to the initiation of this study; this was one of the reasons that our comparative trial of amphotericin B and ketoconazole was conducted. However, in institutions where *Aspergillus* spp., *C. tropicalis*, and *Mucor* spp. are common pathogens, ketoconazole should not be used since this compound has minimal therapeutic activity against these species.

The proper treatment for a neutropenic patient who has no focal signs of infection and yet remains febrile despite broad-spectrum antibiotic therapy remains uncertain. We have used antifungal therapy empirically for many of these patients since 1966. However, there are many possible causes of persistent fever in these patients (e.g., drugs, resistant bacterial infections, and the malignant process itself). Pizzo et al. (10) conducted a prospective, randomized study among patients who failed to respond to carbenicillin, cephalothin, and gentamicin. Patients continued the same therapy, discontinued antimicrobial therapy, or received amphotericin B in addition. The best results were obtained when amphotericin B was added (10).

Trimethoprim-sulfamethoxazole was given to all of the patients in our study because we recognized that persistent fever could be due to bacterial infections. Although we were able to prove the presence of bacterial infection in only eight patients, it is possible that some of the responses attributed to the antifungal agent were really due to trimethoprim-sulfamethoxazole. Furthermore, we were concerned that some patients might develop bacterial superinfections during antifungal therapy if all antibacterial therapy was discontinued. In our previous experience, patients have died unexpectedly as a result of an unrecognized bacterial infection during treatment of a proven fungal infection. Consequently, we believed that it was inappropriate to discontinue all antibacterial treatment in these patients, despite possible complications for interpretation of the results. In any case, there is no evidence that a systematic bias influenced the comparison of amphotericin B and ketoconazole.

The most important toxic effect of amphotericin B was renal insufficiency, which developed in 34 patients treated with this drug. The renal abnormalities found in patients treated with ketoconazole were probably the result of disseminated infection, renal involvement, septic shock, or poor renal perfusion (which many of these patients developed), rather than true drug-induced nephrotoxicity. Until better diagnostic procedures become available or new, less toxic antifungal agents are discovered, many patients with

suspected fungal infection will be exposed to amphotericin B on an empiric basis, thereby risking undesirable side effects.

We used a higher dose of ketoconazole than is usual to make sure that we achieved adequate and useful therapeutic levels. The major toxic effect among patients treated with ketoconazole in this study was an asymptomatic increase in serum glutamic oxalacetic transaminase. Liver function test abnormalities are common findings in these acutely ill patients. Sometimes it is extremely difficult to distinguish the cause of these abnormalities since they can be related to the underlying malignancy, toxicity of antimicrobial agents, septicemia, or fungal involvement of the liver.

This study failed to detect significant therapeutic differences between amphotericin B and ketoconazole except for infections caused by *C. tropicalis*. Neither agent was effective against disseminated fungal infection. This confirms our previous observation that the most critical factor in response to fungal infection is recovery of the neutrophil count. Because of the limitations of ketoconazole, amphotericin B was more useful for empiric therapy of suspected fungal infection.

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