Original Report

Amphotericin B with and without Itraconazole for Invasive Aspergillosis: A Three-Year Retrospective Study

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ABSTRACT

Background: Treatment of invasive aspergillosis is frequently unsuccessful, so innovations in therapy are needed. Clinical studies demonstrate that itraconazole may be an effective alternative to amphotericin B. Itraconazole also has been combined with amphotericin B in animal models of aspergillosis, but this regimen produced antagonistic effects.

Objectives: To determine the role of itraconazole in the adjunctive treatment of invasive aspergillosis.

Methods: A review was conducted of all patients with definite or probable aspergillosis from January 1995 to December 1997 who were treated with conventional amphotericin B alone or in combination with itraconazole.

Results: Of 21 patients, 10 received amphotericin B and 11 received the combination. The two groups of patients were comparable clinically at baseline (including similar mean APACHE III scores). Both groups received similar doses and days of amphotericin B treatment. Of the patients who received combination therapy, nine (82%) were cured or improved, and of those who received only amphotericin B, five (50%) were cured or improved.

Conclusions: This study demonstrates that itraconazole and amphotericin B given together are not clinically antagonistic and that the promise of combination therapy for aspergillosis should be evaluated further in a randomized clinical trial.

Key Words: *amphotericin B, aspergillosis, combination, itraconazole*

Int J Infect Dis 1999; 3:157–160.

The risk for invasive aspergillosis is substantial among bone marrow transplant recipients, patients experiencing prolonged granulocytopenia due to intensive cytotoxic chemotherapy, and those with severe immunosuppression due to corticosteroids or human immunodeficiency virus (HIV) infection.[1,2] As these populations grow in number and as more potent cytotoxic regimens are administered, the incidence of aspergillosis also is expected to increase. For example, Wald et al recently reported that the incidence of invasive aspergillosis among bone marrow transplant recipients at their center increased from 5.7% in 1987 to 11.2% in 1993.[3]

Although early empirical treatment with high doses of amphotericin B (1.0–1.5 mg/kg/d) may improve survival among some patients with pulmonary aspergillosis,[4] the mortality from this infection remains unacceptably high. Mortality among patients with cerebral or pulmonary aspergillosis following allogeneic bone marrow transplantation has been reported to exceed 95%.[5,6] In a review of more than 2000 cases of aspergillosis, the overall response to therapy was only 30 to 35%, although this improved to 55% for patients who were able to tolerate at least 14 days of amphotericin B.[6]

Itraconazole is a broad-spectrum triazole antifungal agent that is available as a capsule or oral suspension. Its safety profile and therapeutic index are superior to those of amphotericin B. Itraconazole has fungicidal activity against *Aspergillus* species in vitro[7]; as a single agent in the treatment of invasive aspergillosis, it is effective in some patients.[8,9]

The efficacy and safety of combination or adjuvant therapy of aspergillosis have not been determined.[6] Studies in animal models yield conflicting results: amphotericin B and flucytosine have been observed to be synergistic or indifferent[10,11]; amphotericin B and rifampin were synergistic in animal and in vitro studies,[10] but in a study from the Memorial Sloan-Kettering Cancer Center, patients given combinations of amphotericin B and rifampin received no therapeutic benefit and experienced an increased risk of skin eruptions compared with patients treated with only amphotericin B.[12] Antagonism has been demonstrated with combined use of amphotericin B and ketoconazole,[11,13] and finally, amphotericin B and itraconazole have produced indifference or antagonism in animal models of aspergillosis.[11,14]

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Received: January 28, 1999; Accepted: May 7, 1999.

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In an effort to determine the clinical effect of itraconazole in combination with amphotericin B, a retrospective study of patients with invasive aspergillosis was undertaken.

METHODS

Patients at Memorial Sloan-Kettering Cancer Center, a 434-bed tertiary care cancer center in New York City, were identified through medical records and microbiology databases covering the period from January 1995 to December 1997. Information obtained from the pharmacy database identified all patients who received amphotericin B alone or in combination with itraconazole. Patients who received lipid formulations of amphotericin B were excluded.

Only patients with definite or probable aspergillosis were included. Definite aspergillosis was defined as (a) tissue histopathology showing acute branching septate hyphae with or without isolation of *Aspergillus* species from the same site or (b) isolation of *Aspergillus* species from an otherwise sterile tissue or body fluid obtained by an invasive diagnostic procedure, such as transbronchial biopsy or percutaneous or fine needle aspiration.[15] Probable aspergillosis was defined as (a) neutropenic patients undergoing allogeneic bone marrow transplantation or peripheral stem-cell transplant or with a diagnosis of hematologic malignancy, aplastic anemia, or myelodysplastic disorder who developed a positive bronchoalveolar lavage or sputum specimen for *Aspergillus* with no other clinically significant pulmonary pathogen identified and a compatible radiologic picture or (b) patients with HIV disease or acquired immunodeficiency syndrome (AIDS) with new infiltrates or nodules on chest x-ray or chest computed tomography (CT) and a bronchoalveolar lavage positive for *Aspergillus* and no other clinically significant pulmonary pathogen. Patients with aspergilloma or allergic bronchopulmonary aspergillosis were excluded.

Baseline and follow-up clinical, radiologic, histopathologic, and mycologic data, as well as medication history were collected through May 1998. Baseline APACHE III score (an assessment of severity of illness and prediction of outcome) was calculated for each patient.[16]

Patients were classified into two groups: (1) patients who received only amphotericin B during their entire episode of aspergillosis and (2) patients who received amphotericin B and itraconazole (400 mg/day) as follows: (a) amphotericin B and itraconazole simultaneously throughout the duration of treatment or (b) amphotericin B followed by amphotericin B and itraconazole and then itraconazole to complete therapy. No patients were given itraconazole alone at the initiation of treatment (Figure 1). For patients who received combination therapy, the choice and timing for use of itraconazole appeared to be dependent on (1) the ability of the patient to take

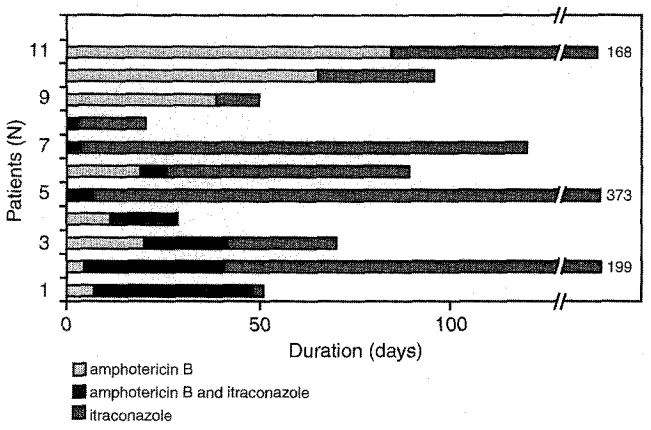

Figure 1. Treatment regimens for patients who received amphotericin B and itraconazole.

medication orally, (2) the severity of the patient's medical status, (3) concerns about amphotericin B intolerance, and (4) the preference of the primary attending physician, although the reasons were not always stated in the medical record. The baseline characteristics of the two groups were compared and P-values calculated using the Student's t-test.

Response at the end of treatment was categorized as follows: (1) cured: resolution of all attributable symptoms, signs, and radiologic abnormalities due to aspergillosis present at baseline; (2) improved: major improvement in all attributable baseline features; (3) unchanged: minor or no improvement in abnormalities due to aspergillosis; and (4) failure: deterioration in attributable clinical and radiologic abnormalities or resulting in death due to aspergillosis.

Mortality was assessed at completion of therapy for aspergillosis. Safety assessments were based on the known adverse event profiles of amphotericin B and itraconazole.[8,17]

RESULTS

The baseline characteristics of 21 patients with invasive aspergillosis are shown in Table 1. The two groups had comparable baseline characteristics, including mean APACHE III score at diagnosis (47 in the combination therapy group vs. 51 in the amphotericin B group). All patients received amphotericin B (1 mg/kg/d) and/or itraconazole (400 mg/d) (capsules or suspension, depending on the clinical situation).

Table 2 compares the response to therapy for the two groups of patients. Nine (82%) of 11 patients who received amphotericin B and itraconazole were cured or improved versus 5 (50%) of 10 patients who received amphotericin B alone (P = 0.12). Two (18%) patients failed therapy or had unchanged clinical and radiologic

Table 1. Baseline Characteristics of 21 Patients with Invasive Aspergillosis

Characteristic	*Treatment Group*		*P-Value*
	Amphotericin B and Itraconazole	*Amphotericin B*	
Patients (n)	11	10	
Mean age (y)	41.2	48.7	0.28
Male	7	6	>0.50
Hematologic malignancy	7	9	0.33
Solid tumor	4	1	0.15
Immunosuppressive therapy*	6	5	>0.50
Neutropenic at diagnosis (≤500/mm^3)	1	2	0.47
Allogeneic bone marrow transplant recipient	4	3	>0.50
HIV disease	2	0	0.15
Mean APACHE III score at diagnosis	47	51	>0.50
Aspergillosis diagnosis:			
Definite/probable	8/3	8/2	
Pulmonary	9	7	
Sinus	1	3	
Other	1	0	
Mean treatment duration (d)	34/95	33	>0.50

*Defined as steroid treatment, antithymocyte globulin and/or cyclosporine prior to diagnosis of invasive aspergillosis.

conditions in the amphotericin B and itraconazole group compared with 5 (50%) patients in the amphotericin B group. Mortality in the combination group was 27% (3 patients) versus 50% (5 patients) in the amphotericin B group.

Among patients with invasive pulmonary aspergillosis, six of eight patients in the amphotericin B and itraconazole group were cured or improved versus four of seven who were cured or improved in the amphotericin B group.

No patients who received combination therapy required drug discontinuation due to side effects. However, three patients who received amphotericin B and itraconazole had mild elevations of total bilirubin, and two additional patients had a rise in alkaline phosphatase. No changes in total bilirubin or alkaline phosphatase were noted in patients treated with amphotericin B alone. The incidence and severity of renal insufficiency was similar for both groups (two patients in each group had reversible rises in serum creatinine to 2.4 mg/dL from normal baseline values).

CONCLUSION

Itraconazole and amphotericin B used in combination resulted in higher rates of cure or improvement than did amphotericin B alone, among comparable groups of patients with invasive aspergillosis. Furthermore, the combination of itraconazole and amphotericin B was not clinically antagonistic, in contrast to the finding of antagonism in some animal studies.[14] Although the improvement in outcome among patients who received itraconazole and amphotericin B was not statistically significant, this retrospective study suggests that the addition of itraconazole to amphotericin B in the management of aspergillosis may be a useful therapeutic measure. A power analysis suggests that it would be necessary to include twice as many patients in each arm, at the same distribution, to achieve statistical significance.

In this series, most patients who received combination therapy (10 of 11 patients) completed therapy with itraconazole alone. Despite the apparent "monotherapy" of this treatment, patients who receive itraconazole

Table 2. Outcome and Mortality among Patients Receiving Amphotericin B with Itraconazole or Amphotericin B Alone for Invasive Aspergillosis

Outcome	*Treatment Group*	
	Amphotericin B and Itraconazole n = 11 (%)	*Amphotericin B n = 10 (%)*
Cured	3 (27)	2 (20)
Improved	6 (54)	3 (30)
Unchanged	0	1 (10)
Failed	2 (18)	4 (40)
Death*	3 (27)	5 (50)
Death due to aspergillosis	2 (18)	4 (40)
Death due to underlying disease	1 (9)	1 (10)
Alive at end of therapy	7 (63)	5 (50)

*Defined as mortality during treatment; 10 of 11 patients received combination therapy.

following amphotericin B are, in reality, receiving combination treatment for several days to weeks. This supposition is based on the pharmacodynamics of amphotericin B, levels of which may be detected 3 to 6 weeks after the last dose,[17,18] an effect that may be prolonged, depending on the total dose given and degree of renal insufficiency. The "effective" continuation of combination therapy results in treatment with both drugs, not with itraconazole alone.

Potential flaws of this study are similar to those of most retrospective studies: patients were not randomized and treatment was unblinded. The choice of therapy for each patient was based on physician preference, best judgment, and ability of patients to take oral medications or discontinue concomitant medications contraindicated with itraconazole use. Unfortunately, the number of patients was not sufficient to detect statistical significance or to assess the true therapeutic benefit of the combination regimen.

In earlier animal models, the evidence that suggested mycologic antagonism from combinations of amphotericin B and itraconazole was based only on a mortality assessment.[14] In the uncontrolled environment of the clinical setting, a similar assessment is more difficult to make, as many other factors may have obscured antifungal antagonism. It is therefore possible that antagonism due to combined polyene-triazole therapy may have been missed.

The data presented in this study suggest that the addition of itraconazole to amphotericin B was well tolerated and produces no obvious mycologic antagonism with amphotericin B. A prospective, randomized, controlled study is needed to determine the true benefit of combined itraconazole and amphotericin B in the treatment of invasive aspergillosis.

REFERENCES

1. Bodey GP, Vartivarian S. Aspergillosis. Eur J Clin Microbiol Infect Dis 1989; 8:413-437.
2. Denning DW, Follansbee S, Scolaro M, Norris S, Edelstein H, Stevens DA. Pulmonary aspergillosis in acquired immunodeficiency syndrome. N Engl J Med 1991; 324:654-662.
3. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis 1997; 175:1459-1466.
4. Burch PA, Karp JE, Merz WG, Kullman JE, Fishman EK. Favorable outcome of invasive aspergillosis in patients with acute leukemia. J Clin Oncol 1987; 5:1985-1993.
5. Denning DW. Therapeutic outcome in invasive aspergillosis. Clin Infect Dis 1996; 23:608-615.
6. Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2121 published cases. Rev Infect Dis 1990; 12:1147-1201.
7. Chryssanthou E. In vitro susceptibility of respiratory isolates of *Aspergillus* species to itraconazole and amphotericin B. Acquired resistance to itraconazole. Scand J Infect Dis 1997; 29:509-512.
8. Stevens DA, Lee JY, Hostetler JS, et al. Analysis of compassionate use of itraconazole therapy for invasive aspergillosis by the NIAID Mycoses Study Group criteria. Arch Int Med 1997; 157:1857-1862.
9. Lebeau B, Pelloux H, Pinel C, et al. Itraconazole in the treatment of aspergillosis: a study of 16 cases. Mycoses 1994; 37:171-179.
10. Arroyo J, Medoff G, Kobayashi GS. Therapy of murine aspergillosis with amphotericin B in combination with rifampin or 5-fluorocytosine. Antimicrob Agents Chemother 1977; 11:21-25.
11. Polak A. Combination therapy of experimental candidiasis, cryptococcosis, aspergillosis, and wangiellosis in mice. Chemotherapy 1987; 33:381-395.
12. Chitkara N, White M, Rosenberg A, Sun M, Armstrong D. Retrospective comparison of treatment with amphotericin B versus amphotericin B and rifampin for invasive aspergillosis. Presented at the Ninth International Symposium on Infections in the Immunocompromised Host, Assisi, Italy, June 23-26, 1996.
13. Schaffner A, Frick P. The effect of ketoconazole on amphotericin B in a model of disseminated aspergillosis. J Infect Dis 1985; 151:902-910.
14. Schaffner A, Bohler A. Amphotericin B refractory aspergillosis after itraconazole: evidence of significant antagonism. Mycoses 1993; 36:421-424.
15. Denning D, Lee J, Hostetler JS, et al. NIAID Mycoses Study Group multicenter trial of oral itraconazole therapy for invasive aspergillosis. Am J Med 1994; 97:135-144.
16. Sirio CA, Knaus WA. Triage and assessment of severity of illness. In: Hall J, Schmidt G, Wood L, eds. Principles of critical care. New York: McGraw-Hill, 1992:551-557.
17. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. Rev Infect Dis 1990; 12:308-329.
18. Daneshmend TK, Warnoch DW. Clinical pharmacokinetics of systemic antifungal drugs. Clin Pharmacokinet 1983; 8:17-42.