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# International Retrospective Analysis of 73 Cases of Invasive Fusariosis Treated with Voriconazole▽

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**The outcomes for 73 invasive fusariosis patients treated with voriconazole were investigated. Patients with proven ($n = 67$) or probable ($n = 6$) infections were identified from the voriconazole clinical database ($n = 39$) and the French National Reference Center for Mycoses and Antifungals database ($n = 34$). Investigator-determined success was a complete or partial response. Survival was determined from day 1 of voriconazole therapy to the last day known alive. Patients were 2 to 79 years old (median, 43 years), and 66% were male. Identified *Fusarium* species (62%) were *F. solani*, *F. moniliforme*, *F. proliferatum*, and *F. oxysporum*. Underlying conditions analyzed included hematopoietic stem cell transplant (HSCT; 18%), hematologic malignancy (HM; 60%), chronic immunosuppression (CI; 12%), or other condition (OC; 10%). Infection sites were brain (5%), disseminated excluding brain (67%), lungs/sinus (15%), and other (12%). Most patients (64%) were or had recently been neutropenic (<500 cells/mm$^3$). Therapy duration was 1 to 480 days (median, 57 days), with a 47% success rate. Baseline neutropenia impacted success adversely ($P \leq 0.03$). Success varied by underlying condition (HSCT, 38%; HM, 45%; CI, 44%; OC, 71%) and infection site (brain, 0%; disseminated, 45%; other, 56%; lung/sinus, 64%) ($P > 0.05$). Combination therapy (13 patients) was no better than treatment with voriconazole alone. Overall, 59% of the patients died (49% died of fusariosis), and 90-day survival was 42%. Site of infection influenced survival ($P = 0.02$). Median survival (in days) by species was as follows: *F. solani*, 213; *F. oxysporum*, 112; *Fusarium* spp., 101; *F. proliferatum*, 84; *F. moniliforme*, 76. We conclude that voriconazole is a therapeutic option for invasive fusariosis.**

Species of the genus *Fusarium* are major plant pathogens with a global distribution and are responsible for billions of dollars of agricultural losses annually (27). The secondary metabolic products they produce can also cause significant toxicoses in animals and humans, necessitating costly monitoring of plant foodstuffs (10, 19). In addition, *Fusarium* species may cause allergic reactions in humans, while the major species (notably, *F. incarnatum*, *F. moniliforme*, *F. oxysporum*, and *F. solani*) are responsible for a range of superficial, subcutaneous, and invasive infections in immunocompetent or immunocompromised individuals (12).

The incidence of *Fusarium* infections in humans may be stable (11), or possibly rising slightly, particularly in patients with acute myeloid leukemia (15). This has stimulated the production of a number of literature reviews (8, 9, 12, 21, 22, 25). Clearly, *Fusarium* spp. are problematic human pathogens, with some species showing significant levels of apparent resistance to the common systemic antifungal agents (2, 7, 26). Consequently, in hematology and transplant patients, these organisms can cause invasive infections that are difficult to treat and for which the prognosis is poor (3, 14, 15).

The optimal therapy for invasive fusariosis remains unclear, although a lipid formulation of amphotericin B with or without an azole antifungal is commonly used (3, 5). Voriconazole was approved for the therapy of *Fusarium* infections in 2002, and although 34 cases reported in the literature were summarized by Stanzani et al. in 2007 (24), published clinical experience remains dispersed and limited. In the review by Stanzani et al. (24), 23 of the voriconazole-treated patients had invasive infections, and a successful response to voriconazole therapy was seen in 69% of these. In four of the patients voriconazole was used in combination with liposomal amphotericin B. In this international analysis we review the outcomes for 73 patients with invasive infection who were treated with voriconazole as initial or salvage therapy; the results for 9 of these patients were in part previously presented (17).

## MATERIALS AND METHODS

**Data sources.** The Pfizer voriconazole clinical database was queried for invasive *Fusarium* infections from 1996 until 2002. In addition, invasive *Fusarium* infections reported to the French National Reference Center for Mycoses and

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TABLE 1. Demographic, clinical, and microbiological data for 73 patients with invasive fusariosis

| Data type and parameter | No. (%) of patients with trait |
|---|---|
| Demographic data | |
| Total patients | 73 (100) |
| Male | 48 (66) |
| Female | 25 (34) |
| Age (yr) | 43 (range, 2–79) |
| Clinical data | |
| Proven infection | 67 (92) |
| Probable infection | 6 |
| Prior therapy | |
| Yes | 57 (78) |
| No | 16 (22) |
| Neutropenia[a] | |
| Yes | 47 (64) |
| No or unknown | 7 or 19 (36 [both categories combined]) |
| *Fusarium* species | |
| All species | 28 (38) |
| *F. dimerum* | 4 |
| *F. incarnatum*[b] | 1 |
| *F. oxysporum* complex | 7 (10) |
| *F. moniliforme* complex | 8 (11) |
| *F. proliferatum* complex | 8 (11) |
| *F. solani* complex | 16 (22) |
| *F. subglutinans*[b] | 2 |

[a] Neutropenia was defined as a neutrophil count of less than 500/mm$^3$ at or immediately before start of voriconazole therapy.
[b] One dual infection with *F. incarnatum* and *F. subglutinans* was reported.

Antifungals (NRCMA), Institute Pasteur, Paris, France, from June 2002 to January 2009 were identified, and data for each patient were collected. Patient data were queried for sociodemographic features, predisposing factors, medical history, and therapy received prior to presentation, as well as the duration of any antifungal therapies and survival.

**Clinical review.** All cases were reviewed by three of us (O. Lortholary, G. Obenga, and P. Troke), and only those classified as proven or probable infections were included (4). The presence of neutropenia was assessed at baseline for all patients and at the end of therapy when available. Efficacy of therapy was based on investigator assessment at the end of therapy, and in line with current practice (23), a complete or partial response was classified as a success, while all other responses were classified as failures. Death caused by invasive fungal infection (IFI) was reviewed by our investigators and defined as follows: (i) any death considered by the investigator to be due to IFI; (ii) any death where fusariosis was microbiologically evolutive or where attribution was uncertain or not specified as clearly due to another cause by the investigator (with some supporting information for this conclusion).

Survival was defined throughout the study as the time from the first day of voriconazole therapy until death or the last day the patient was known to be alive.

**Statistical analysis.** For statistical analyses, the distributions of categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. All-cause mortality was assessed using the Kaplan-Meier curve. Subjects with missing death times were censored at their last known date of survival. Survival comparisons across strata were assessed using the log-rank test. Cause-specific mortality, due to IFI or due to other causes, was evaluated by using descriptive methods only. Analyses were conducted by using SAS, version 8.2.

## RESULTS

**Demography, *Fusarium* spp., and site of infection.** There were 73 patients in total, including 39 from the Pfizer database (11 from phase II/III protocols and 28 from named patient/compassionate studies) and 34 patients from the NRCMA (i.e., from 2002 onwards). Their median age was 43 years (range, 2 to 79 years), with 19 patients <18 years old (Table 1). Some 66% (48/73) of the patients were male, and 75% (53/73) were Caucasian. There were 67 (92%) proven and 6 probable infections.

The species of *Fusarium* was identified in the majority of patients (62%), with isolates from the *F. solani* complex predominating (Table 1). Most patients (73%, 53/73) had disseminated infections (to the brain in 4 and to more than one body site excluding the brain in 49 patients) or lung/sinus infections (15%, 11/73) (Table 2). Blood culture was positive for *Fusarium* in 26/73 (36%) overall and in 26/53 (49%) patients with disseminated infection.

**Prior therapy.** Most patients (57/73, 78%) had failed prior antifungal therapy and were receiving voriconazole as salvage therapy (Table 1). Prior therapies included any amphotericin B formulation (21/57, 37%), caspofungin (8/57, 14%), various azoles (fluconazole, 4; itraconazole, 4; posaconazole, 2; 18% combined), and micafungin (2/57, 3%). The specific therapy was unrecorded for 26 patients. In addition, 12/57 (21%) patients were known to have received more than one prior therapy, sometimes in combination.

**Underlying condition.** The majority of patients had hematologic malignancy (44 [60%]) or had undergone hematopoietic cell transplantation (13 [18%]) (Table 3). Those defined as having chronic immunosuppression included cases of lymphoma and aplastic anemia (Table 3). Consistent with these severe underlying conditions, 64% (47/73) of all patients were or had recently been neutropenic (Table 1). In the 19 patients for whom neutropenic status at baseline was unrecorded, 15 (79%) were recent transplants or had a hematologic malignancy.

Data detailing the actual durations of neutropenia were not available. However, of the 47 patients known to be neutropenic at baseline, 19 (40%) were still so at the end of therapy (EOT).

**Response to therapy.** A complete or partial response to voriconazole therapy was achieved in 47% (34/73) of patients (Table 2), with a median therapy duration of 57 days (range, 1

TABLE 2. Outcome and survival of fusariosis patients treated with voriconazole, by site of infection

| Site of infection (no. of patients) | Median (range) duration of voriconazole therapy (days) | No. (%) with clinical response | Median (range) survival[a] (days) | No. that died (no. that died due to IFI) |
|---|---|---|---|---|
| Brain (4) | 37 (1–75) | 0 (0) | 40 (5–75) | 4 (4) |
| Disseminated (49) | 33 (3–480) | 22 (45) | 84 (4–808) | 30 (16) |
| Lung/sinus (11) | 90 (24–379) | 7 (64) | 329 (29–435) | 5 (1) |
| Other[b] (9) | 57 (2–259) | 5 (56) | 202 (19–365) | 4 (1) |
| Total (73) | 57 (1–480) | 34 (47) | 120 (4–808) | 43 (22) |

[a] Significant ($P = 0.02$) for all survival comparisons, based on the log-rank test.
[b] Other infection sites were bone (4 patients), gallbladder (1), and superficial (4).

TABLE 3. Outcome and survival of fusariosis patients treated with voriconazole, by underlying condition

| Underlying condition (no. of patients) | Median (range) duration of voriconazole therapy (days) | No. (%) with clinical response | Median (range) survival (days) | No. that died (no. that died due to IFI) |
|---|---|---|---|---|
| HSCT (13) | 18 (3–182) | 5 (38) | 27 (6–202) | 9 (4) |
| HM[a] (44) | 61 (1–480) | 20 (45) | 112 (4–808) | 27 (15) |
| Chronic[b] (9) | 57 (3–267) | 4 (44) | 200 (6–435) | 5 (3) |
| Other[c] (7) | 30 (19–259) | 5 (71) | Not reached (19–365) | 2 (0) |
| Total (73) | 57 (1–480) | 34 (47) | 120 (4–808) | 43 (22) |

[a] HM, hematologic malignancy.
[b] Chronic conditions included lymphoma (3 patients), aplastic anemia (3), tumor lysis syndrome (1), neuroblastoma (1), and kidney transplant (1).
[c] Other conditions were immunocompetence (4 patients), diabetes mellitus (2), paralytic ileus (1), and burns (1).

to 480 days). When the 66 (90%) patients receiving at least 5 days of voriconazole therapy were assessed separately, their response rate was 34/66 (52%). In 13 (18%) patients, caspofungin (2), liposomal amphotericin B (8), terbinafine (1), posaconazole (4), or white blood cell transfusion (1) was administered simultaneously or immediately after voriconazole treatment (Table 4). However, there was no significant difference in response rates between these patients and those receiving voriconazole alone (Table 4).

There was also no significant difference in response rates by gender between patients receiving primary or salvage therapy, between those with proven or probable infections, or between those in the voriconazole database or NRCMA (Table 4). In contrast, patients with current or recent baseline neutropenia exhibited a significantly worse response to voriconazole therapy than nonneutropenic patients ($P \leq 0.03$). However, 17/47 (36%) patients who were neutropenic at baseline responded to therapy (Table 4).

The neutropenia status of patients at EOT, their voriconazole median therapy duration, and clinical response rate were as follows: for neutropenic patients (19/73 [26%]), median duration of therapy was 7 days and response rate was 5%; for nonneutropenic patients (24/73 [33%]), median duration of therapy was 101 days and response rate was 63%; and for patients with unknown neutropenia status (30/73 [41%]), median duration of therapy was 57 days and response rate was 60%.

TABLE 4. Comparisons of outcomes for invasive fusariosis cases treated with voriconazole

| Comparison (statistical method)[a] | No. with clinical response/ total no. of patients (%) | *P* value |
|---|---|---|
| Male vs female (C) | 21/48 (44) vs 13/25 (52) | NS[b] |
| Proven vs probable infection (C) | 31/67 (46) vs 4/6 (67) | NS |
| Primary vs salvage/unknown therapy (C) | 7/16 (44) vs 27/57 (47) | NS |
| Combination vs voriconazole alone/unknown (C) | 6/13 (46) vs 28/60 (47) | NS |
| Voriconazole database vs NRCMA (C) | 20/39 (51) vs 14/34 (41) | NS |
| Neutropenia (F) | | ≤0.03[c] |
| Recent | 17/47 (36) | |
| None | 5/7 (71) | |
| Status unknown | 12/19 (63) | |
| *Fusarium* species (F) | | NS |
| *F. solani* complex | 9/16 (56) | |
| *F. moniliforme* complex | 2/8 (25) | |
| *F. proliferatum* complex | 4/8 (50) | |
| *F. oxysporum* complex | 6/7 (86) | |
| All other *Fusarium* spp. | 13/34 (38) | |

[a] C, chi-square test; F, Fisher's exact test.
[b] NS, not significant.
[c] *P* value for outcome in patients with neutropenia versus patients without neutropenia or with neutropenia status unknown.

Although response rates by *Fusarium* species varied from 38% to 86%, these differences were not statistically significantly different (Table 4). Clinical response by site of infection (Table 2) varied from 0% (brain) to 64% (lung/sinus) and by underlying condition (Table 3) from 38% (HSCT) to 71% (other), but none of the differences in responses between these groups was statistically significant.

**Survival.** A total of 43 (59%) patients died, and a further 30 (41%) had their survival censored on the last day they were known to be alive (range, >18 days to >808 days). When the 66 patients receiving at least 5 days of voriconazole therapy were assessed separately, 36/66 (55%) had died. Only 12% of patients were known to have survived for >365 days. Of those who died, 51% (22/43) had progressive invasive fungal infection and 13/22 (59%) were still neutropenic (Table 2). For patients who were neutropenic at baseline, all-cause mortality was 68% (32/47), compared with 42% (11/26) for all other patients. However, 19/43 (44%) patients who were neutropenic at baseline were still neutropenic at EOT and had an all-cause mortality of 100%.

More patients with hematologic malignancy and hematopoietic cell transplant died (36/57 [63%], with 53% experiencing progressive fungal infection), compared with all other patients (7/16 [44%], with 43% experiencing progressive fungal infection). More patients with disseminated infection and central nervous system (CNS) disease died (34/53, 64%) than all others (9/20, 45%).

Overall median survival was 120 days (range, 4 to 808 days). Median failure time for death due to invasive fungal infection was not reached (range, 4 to 135 days), while the median failure time for death due to other causes was 431 days (range, 11 to 461 days).

Hematopoietic cell transplant patients had the shortest median survival time (27 days; range, 6 to 202 days), and patients without notable immune suppression ("other") survived the longest (range, 19 to 365 days), although a median survival time was not reached for this group (Fig. 1). However, none of these survival differences was statistically significant. There was also no significant difference in survival times by *Fusarium* spp. However, differences in survival times by site of infection were significant ($P = 0.02$), with

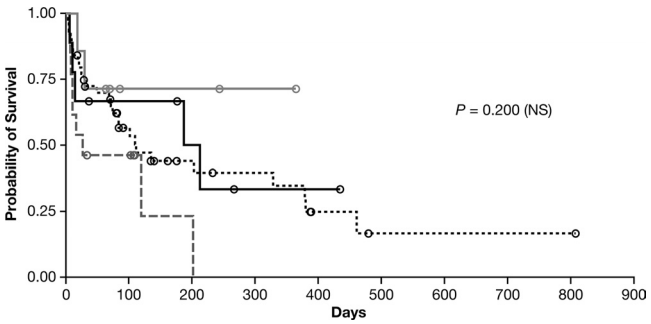


FIG. 1. Kaplan-Meier curves of patient survival, by underlying condition. Differences between groups were not significant ($P = 0.2$). Hematopoietic stem cell transplant, gray dashed line; hematologic condition, black dotted line; chronic immune suppression, solid black line; other underlying condition, solid gray line; censored patients, black or gray circles.

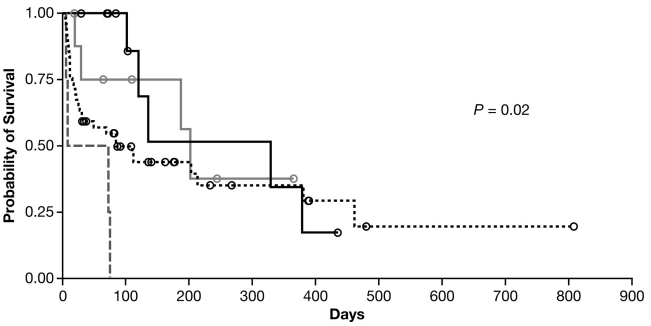


FIG. 2. Kaplan-Meier curves of patient survival, by site of infection. Differences between groups were significant ($P = 0.02$). Brain, gray dashed line; disseminated (excluding brain), black dotted line; lung/sinus, solid black line; other, solid gray line; censored patients, black or gray open circles.

those patients with CNS or disseminated infection exhibiting the worst survival (Table 2 and Fig. 2).

## DISCUSSION

We have not presented the susceptibility data for the *Fusarium* isolates in this analysis, although voriconazole MICs for isolates from 15 patients in the Pfizer database have been published and range from 1.0 μg/ml to 16.0 μg/ml (6). However, the results of antifungal susceptibility testing of *Fusarium* spp. reveal a wide susceptibility range, with *F. solani* apparently resistant to most antifungals, thus making such testing of low clinical value for any therapeutic decision (1, 2, 18). In addition, it should be noted that no *in vitro*/*in vivo* correlation has yet been demonstrated for the antifungal management of fusariosis.

Consistent with observations in the literature (3, 12, 15), most patients in this analysis had hematologic malignancy or a hematopoietic cell transplant as their underlying condition. Consequently, the majority had disseminated fusariosis and presented with recent or current neutropenia (3, 12, 15). *Fusarium* infections in such patients result in a poor prognosis, with death rates of up to 75%, as opposed to 36% in patients where infection is not disseminated (3, 12). In the current study, despite 73% of patients having disseminated/CNS disease and 78% experiencing hematologic malignancy or a recent hematopoietic cell transplant, the overall response rate was 47% and the 3-month survival was 42%. Survival rates at 3 months, specifically in hematologic malignancy or hematopoietic cell transplant patients, were 38% and 39%, respectively, compared to 21% and 13%, respectively, in recent studies of patients not treated with voriconazole (13, 14). However, it is clear that a subset of patients did not recover from their neutropenia, rapidly failed therapy, and died. Others have also shown that neutropenia status impacts survival significantly (3).

There have been no formal clinical trials for fusariosis. Consequently, estimates of efficacy for any antifungal agent depend on case studies or small retrospective analyses. A combination of a lipid amphotericin derivative with voriconazole or another azole is currently considered the best therapy (3, 5). In our study, the outcome of the 13 patients receiving combination therapy was no better than with voriconazole alone, despite 8/13 patients having received liposomal amphotericin B with their voriconazole. Clearly, the value of combination versus monotherapy for fusariosis requires further exploration with a much larger sample of patients (3).

For amphotericin derivatives in general, published efficacy rates range from 32% for amphotericin B to 46% for amphotericin B lipid complex (ABLC) (total cumulative dose, 5 g) and other lipid formulations (13, 14, 16). Preliminary data obtained with voriconazole in nine patients with intolerance to therapy or invasive infections refractory to primary therapy showed a 44% response rate with a 3-month survival of 71% (17). Posaconazole has also been studied as salvage therapy in 21 patients, including almost one-third who were neutropenic, with an overall success rate of 48% (20). However, in all these publications, the response rates were heavily dependent on persistence of underlying immunosuppression and dissemination of infection. The presence of neutropenia has a critical role in the outcome (3, 12). Consequently, the results obtained here with voriconazole in a high-risk population (64% were confirmed to have recent or current neutropenia) are encouraging. However, 40% of the patients who were neutropenic at baseline still succumbed rapidly and died.

Finally, voriconazole given as primary therapy (in 22% of patients, with 75% of these having a hematologic malignancy or a hematopoietic cell transplant) or in patients failing initial therapy was associated with a similar outcome. In conclusion, the results of this large, retrospective international study show the potential efficacy of voriconazole in the management of disseminated fusariosis in heavily immunocompromised hosts.

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