Invasive Fusariosis in the Voriconazole Era: Single-Center 13-Year Experience

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Background. Invasive fusariosis remains an aggressive, albeit infrequent infection in immunocompromised patients.

Methods. We identified all cases of invasive fusariosis between January 2002 and December 2014. We recorded patient characteristics including clinical presentation, treatment, and outcomes at 6 and 12 weeks after diagnosis, as well as species identification and antifungal drug susceptibilities.

Results. Fifteen patients were diagnosed with proven (12, 80%) or probable (3, 20%) fusariosis. Median age was 60 years (range, 26–78), and 10 patients were male. Underlying conditions included hematological malignancies (13, 87%), juvenile idiopathic arthritis (1, 7%), and third-degree burns (1, 7%). Five patients underwent hematopoietic stem-cell transplantation before diagnosis. Six patients (40%) received systemic glucocorticoids, and 11 patients (73%) had prolonged neutropenia at the time of diagnosis. Clinical presentations included the following: skin/soft tissue infection (8, 53%), febrile neutropenia (4, 27%), respiratory tract infection (2, 13%), and septic arthritis (1, 7%). Twelve patients were treated with voriconazole: 6 (40%) with voriconazole alone, 4 (27%) with voriconazole and terbinafine, and 2 (13%) with voriconazole, terbinafine, and amphotericin. One patient (7%) was treated with terbinafine alone, and another with micafungin alone. Four patients underwent surgical debridement (4, 27%). Susceptibility testing was performed on 9 isolates; 8 demonstrated voriconazole minimum inhibitory concentrations ≥4 µg/mL. The cumulative probability of survival was 66.7% and 53.3% at 6 and 12 weeks after diagnosis.

Conclusions. Mortality associated with invasive fusariosis remains high. Cumulative mortality at our center was lower than previous reports despite elevated voriconazole minimum inhibitory concentrations. Combination therapy should be studied systematically for fusariosis.

Keywords. fungal disease; fusarium; invasive fusariosis; terbinafine; voriconazole.

Fusarium is a genus of widely distributed saprophytic molds capable of causing disease in plants, animals, and humans [1]. Invasive fusariosis (IF) is uncommon and predominately affects immunocompromised hosts, particularly those with underlying hematological malignancy (HM), neutropenia, and glucocorticoid exposure [2–4]. Disseminated fusariosis is the most challenging

and life-threatening manifestation with an estimated mortality rate between 66% and 75% [3, 5]. It is interesting to note that fungemia is a distinct feature of disseminated fusariosis relative to other opportunistic mold infections [3, 6]. Historically, amphotericin was used to treat IF. However, after voriconazole was approved by the US Food and Drug Administration in 2002, it has become the preferred treatment despite studies that have failed to demonstrate consistent in vitro activity [7–9]. Nonetheless, the therapeutic response to voriconazole in the clinical setting has been encouraging. Terbinafine use for invasive mold infections has increased; however, its reported use in cases of IF is limited [10, 11]. The aim of this study is to assess the clinical response of patients with IF to voriconazole—either as a single agent or as combination therapy. Furthermore, we document the use of terbinafine as a possible antifungal option for the treatment of IF, refractory to other antifungal classes.

METHODS

We retrospectively identified all cases of IF diagnosed and treated at Brigham and Women's Hospital and Dana-Farber Cancer Institute, in Boston, Massachusetts, between January 2002 and December 2014. The data were accrued by review of patient medical records and microbiology and pathology results. We collected baseline patient characteristics including age, gender, underlying conditions, presentation affected sites, and concomitant medications. All cases were classified according to the 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group criteria for invasive fungal disease (IFD) [12]. Possible cases of IF and noninvasive infections were excluded. Probable and proven cases were further reviewed to identify risk factors for IFD including prolonged neutropenia, recent glucocorticoid exposure, and transplant status, as well as survival at 6 and 12 weeks after diagnosis. Prolonged neutropenia was defined as an absolute neutrophil count ≤500 cells/μL for >10 continuous days. Disseminated fusariosis was confirmed by growth in blood cultures, or evidence of infection in multiple noncontiguous sites, confirmed on biopsy to be caused by *Fusarium*. Survival and responses were defined using the criteria of Segal et al [13] as (1) the time between the date of diagnosis and 6 and 12 weeks or (2) death from any cause. Survival was assessed by Kaplan–Meier analyses. Fungal species determination was made by morphological and phenotypic identification. Susceptibility and synergism testing were performed adhering to CLSI M38-A2 methods, with minor modifications to allow for combination testing, at The Fungus Testing Laboratory in San Antonio, Texas.

RESULTS

Patient Characteristics

We identified 15 cases of IF during the study period. An additional 78 patients with non-IF were also identified—onychomycosis (36), skin or respiratory tract colonization (31), and noninvasive sinusitis (11)—and were excluded from this cohort. Twelve patients were diagnosed with proven IF and 3 with probable IF [12]. The baseline cohort characteristics are outlined in Table 1.

Individual clinical and microbiological details are delineated in Table 2. The most common underlying condition was HM in 13 (87%) of the patients. Of these 13 patients, 5 (33%) had undergone a hematopoietic stem-cell transplant (HSCT). The median time between HSCT and the diagnosis of IF was 166 days (range, 22–2709 days). The underlying conditions of the remaining 2 patients were severe third-degree burns over 80% body surface area and juvenile idiopathic arthritis (JIA) on chronic oral glucocorticoids. Eleven patients (73%) had prolonged

Table 1. Baseline Characteristics for 15 Patients With Invasive Fusariosis

Patient Characteristics	
N	15
Median age, years (range)	60 (26–78)
Male gender, number (%)	10 (67)
Underlying disease, number (%)	
Hematological malignancies	13 (87)
Others[a]	2 (13)
Immunologic risk factors for IFD, number (%)[b]	
Neutropenia	11 (73)
Exposure to glucocorticoids	6 (40)
Invasive Fusariosis, number (%)	
Proven	12 (80)
Probable	3 (20)
Clinical presentation, number (%)	
Cutaneous lesions	8 (53)
Febrile neutropenia	4 (27)
Respiratory symptoms	2 (13)
Septic arthritis	1 (7)
Positive fungal antigen testing, number (%)[c]	n = 11
1→3-β-D-glucan	4 (36%)
Galactomannan EIA	1 (9%)
Treatment, number (%)	
Voriconazole	6 (40)
Voriconazole, terbinafine	4 (27)
Voriconazole, terbinafine, amphotericin	2 (13)
Terbinafine	1 (7)
Micafungin	1 (7)
Surgical debridement[d]	4 (27)
Cumulative Probability of Survival, %[e]	
6-week survival	66.7
12-week survival	53.3

Abbreviations: EIA, enzyme immunoassay; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group; IFD, invasive fungal disease; JIA, juvenile idiopathic arthritis; OD, optical density.

[a] JIA, severe third-degree burns.

[b] Neutropenia and steroid exposure as defined by the EORTC/MSG criteria [12].

[c] Positive (1→3)-β-D-glucan: >80 pg/mL; positive galactomannan EIA: >0.5 OD.

[d] One patient underwent surgical debridement alone, whereas 3 received systemic antifungal therapy, concomitantly.

[e] Cumulative probability determined by Kaplan–Meier analysis.

neutropenia with a median of 32 days (range, 18–244 days). All patients with prolonged neutropenia had received recent chemotherapy. Six patients (40%) were receiving glucocorticoids during the month before or at the time of diagnosis.

Clinical Characteristics

Eight patients (53%) presented with skin lesions (local cutaneous or disseminated; see example in Figure 1), 4 (27%) with febrile neutropenia, 2 (13%) with respiratory symptoms, and 1 patient (7%) with septic arthritis of the knee. Disseminated

Table 2. Individual Patients With IFI Diagnosed Between January 2002 and December 2014

Patient ID	IFD Classification[a]	*Fusarium* Species	Underlying Condition	Clinical Presentation	Disseminated IFD	Antifungal Treatment	Susceptibility Testing, MIC	Surgical Debridement	Response to Therapy[b]	Outcome, Survival
1	Probable	*Fusarium* NOS	Multiple myeloma, allogeneic HSCT	Pneumonia	No	Micafungin	N/A	–	Failed	Deceased, 38 days
2	Probable	*Fusarium* NOS	ALL	Localized skin infection	No	Voriconazole	N/A	Yes	Complete response	Alive, 4131 days
3	Probable	*Fusarium proliferatum*	NHL, allogeneic HSCT	Febrile neutropenia	No	Voriconazole	N/A	–	Failed	Deceased, 11 days
4	Proven	*Fusarium fujikuroi*	AML	Localized skin and intranasal lesion	No	Voriconazole	N/A	Yes	Complete response	Alive, 984 days
5	Proven	*Fusarium proliferatum*	AML/MDS	Skin nodules	Yes	Voriconazole, terbinafine	V: >8, P: >4, A: 2; V/T: 2, 0.125	–	Partial response	Alive, 368 days
6	Proven	*Fusarium* NOS	Third degree burns > 80% TBSA	Localized skin infection	No	–	N/A	Yes	Complete response	Alive, 2069 days
7	Proven	*Fusarium verticillioides*	AML/MDS	Sinusitis	Yes	Voriconazole	V: 2, C: >16	–	Complete response	Alive, 1865 days
8	Proven	*Fusarium solani*	Multiple myeloma, autologous HSCT	Skin nodules, fungemia	Yes	Voriconazole, terbinafine, amphotericin	V: 8, P: >8, A: 4, T: >2	–	Failed	Deceased, 64 days
9	Proven	*Fusarium proliferatum*	Juvenile idiopathic arthritis	Septic arthritis	No	Terbinafine	V: 8, A: 1, T: 1; M: >8	–	Complete response	Alive, 489 days
10	Proven	*Fusarium verticillioides*	ALL	Skin nodules	Yes	Voriconazole	V: 4, A: 8	–	Complete response	Alive, 3623 days
11	Proven	*Fusarium solani*	AML/MDS	Febrile neutropenia, fungemia	Yes	Voriconazole, terbinafine	V: >8, A: 4	–	Failed	Deceased, 13 days
12	Proven	*Fusarium solani*	AML/MDS, allogeneic HSCT	Localized skin infection	No	Voriconazole	N/A	Yes	Complete response	Deceased, 141 days
13	Proven	*Fusarium solani*	NHL, allogeneic HSCT	Febrile neutropenia, fungemia	Yes	Voriconazole, terbinafine, amphotericin	V: 16, P: >16, A: 4	–	Failed	Deceased, 18 days
14	Proven	*Fusarium* NOS	Hemophagocytic lymphohistiocytosis	Febrile neutropenia, fungemia	Yes	Voriconazole, terbinafine	V: 4, P: 1, M: >8, T: 1	–	Failed	Deceased, 12 days
15	Proven	*Fusarium solani*	AML	Skin infection, multiple sites	Yes	Voriconazole, terbinafine	V: 16, P: >16, A: 2; T: 2	–	Partial response	Deceased, 68 days

Abbreviations: A, amphotericin; AML, acute myeloid leukemia; C, caspofungin; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group; HSCT, hematopoietic stem-cell transplant; IFD, invasive fungal disease; IFI, invasive fungal infections; M, micafungin; MDS, myelodysplastic syndrome; MIC, minimum inhibitory concentration; N/A, not available; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; P, posaconazole; T, terbinafine; TBSA, total body surface area; V, voriconazole; V/T, voriconazole/terbinafine synergism.

[a] EORTC/MSG criteria [12].

[b] Treatment response based on Segal et al [13] consensus criteria.

Figure 1. Skin nodule, characteristic of disseminated invasive fusariosis.

fusariosis was confirmed in 8 patients (53%). Five patients had metastatic skin nodules, and 4 patients had positive blood cultures for *Fusarium* (1 patient had both disseminated skin nodules and fungemia).

Mycological Characteristics

The species identified in 11 patients were *Fusarium solani* (5, 33%), *Fusarium proliferatum* (3, 20%), *Fusarium verticillioides* (2, 13%), and *Fusarium fujikuroi* (1, 7%). Elongation factor-1α amplification and sequencing were also required for a single isolate for confirmation (*F fujikuroi*). Samples from 4 patients (27%) were not identified further than the genus. The median minimum inhibitory concentration (MIC) for voriconazole (9) was 8 μg/mL (1–16 μg/mL), median MIC for amphotericin (7) was 4 μg/mL (1–8 μg/mL), and median MIC for terbinafine (4) was 1 μg/mL (0.125–2 μg/mL). One patient had synergistic activity for voriconazole and terbinafine with a resulting MIC of 2 and 0.125 μg/mL, after initially demonstrating an MIC to voriconazole of >8 μg/mL.

Treatment and Outcome

Systemic antifungal therapy was administered to 14 of 15 patients for a median of 9 weeks (range, 1–182 weeks). The patient with severe third-degree burns underwent surgical debridement alone. Three patients who received systemic therapy also underwent surgical debridement of the affected areas (fungating skin lesion, nasal mass, septic arthritis). One patient with proven fusariosis was receiving posaconazole prophylaxis at the time of diagnosis.

Voriconazole was administered to 12 patients (80%) in the cohort. Six patients received voriconazole alone, and 6 patients were treated with combination therapy—4 patients (27%) received voriconazole and terbinafine, and 2 patients (13%) received voriconazole, terbinafine, and amphotericin. The 2

patients who received the latter therapy had disseminated IF and a greater number of comorbidities. Three patients did not receive long-term voriconazole: 1 was treated with surgery alone, 1 received micafungin as a single agent, and 1 patient with fusarial septic arthritis was treated with high-dose terbinafine (2000 mg/day).

Treatment success was seen in 9 of 15 patients (60%) by week 12. Complete resolution of IF was seen in 6 patients by 6 weeks and in 1 patient by 12 weeks of initiating therapy. Two patients had a partial response to systemic antifungal agents by the final day of observation. Six patients (40%) failed to respond to therapy. The overall cumulative probability of survival in the cohort was 66.7% at 6 weeks and 53.3% at 12 weeks after diagnosis. The median overall survival was 141 days (range, 11–4131 days). The median survival of patients with disseminated fusariosis was 53 days (range, 12–3623 days). Among HSCT recipients, the median survival was 35 days (range, 11–141 days) after presentation. Only 1 patient with acute myelogenous leukemia in this subgroup survived beyond 12 weeks after IF diagnosis.

DISCUSSION

The cumulative incidence of IF in the immunocompromised population is universally low [5, 14]. Invasive fusariosis typically presents as fever, skin, and soft tissue infection, respiratory tract infection, or disseminated disease. Fungemia is a distinct feature of IF and reflects a more critical presentation of this IFD [2, 5].

Our cohort included 15 patients with IF diagnosed over a 13-year period. Similar to the published literature, HM was the predominant underlying condition, and *F solani* was the most common species identified in this study [5, 14–16]. It is interesting to note that *F fujikuroi* was isolated from a fungating necrotic intranasal mass in 1 patient with proven IF. To our knowledge, *F fujikuroi* has seldom been reported as a cause of human disease [17–19]. The infection resolved after surgical resection of the nasal mass and 12 weeks of systemic voriconazole.

Most data on human fusariosis are available as retrospective analyses and case reports. The aggressiveness and low incidence of IF hinders the execution of randomized controlled trials. Reports displaying clinical improvement and tolerable side-effect profiles support the use of newer antifungal drugs, such as posaconazole and voriconazole, over amphotericin [20–22]. Nevertheless, their in vitro activity against *Fusarium* species is not predictable. The unsatisfactory susceptibility profiles can be attributed to several factors, including the species of *Fusarium* causing disease and the inoculate size and incubation period during susceptibility testing [23, 24]. Therefore, the choice of antifungal should be determined on a case-by-case basis, depending on the species and susceptibilities performed at an experienced center, whenever feasible to obtain.

It is worth noting that we report a patient with joint infection who responded to treatment with terbinafine alone. The patient

had a long-term history of JIA and presented with fusarial septic arthritis of the knee secondary to numerous arthrocenteses for joint effusion and pain relief. Because the patient remained culture-positive and without clinical improvement despite treatment with amphotericin, amphotericin joint washouts, and multiple surgical explorations, empiric voriconazole in combination with terbinafine was initiated. Once the species (F proliferatum) and antifungal sensitivity data were available, voriconazole was discontinued due to an elevated MIC of 8 μg/mL and no synergism with terbinafine. The patient remains on high-dose oral terbinafine. Regular liver function surveillance consistently demonstrated normal hepatic function during the pre-established observation period, although the patient reported intermittent nausea at the time of initiation. Terbinafine levels were not performed.

Fusarium is an uncommon cause of septic arthritis and represents a therapeutic challenge [25]. In immunocompromised hosts, this manifestation can arise secondary to fungemia or from direct inoculation [1, 26]. Amphotericin has reportedly been the preferred antifungal drug in this setting. Terbinafine is a fungicidal allylamine approved for systemic treatment of dermatophytic infections. Because of its marked lipophilic properties, terbinafine has excellent tissue penetration, which makes it an optimal agent for skin and soft tissue disease [27]. A high percentage of the drug binds to plasma proteins once in the bloodstream, limiting the amount available for tissue distribution. For this reason, higher doses of terbinafine were required for our patient to guarantee delivery to the involved site. This unique presentation of *Fusarium* causing persistent septic arthritis, refractory to multiple antifungals and therapeutic approaches, suggests that the use of high-dose terbinafine may be a viable alternative for treatment of joint IF. To our knowledge, this is the first report of the use of high-dose systemic terbinafine as a single agent for the treatment of fusarial arthritis.

Several in vitro studies have demonstrated that combination therapy with terbinafine and azole antifungal drugs results in increased synergistic effects [28–30]. However, data supporting the clinical efficacy of these combinations are underwhelming [11, 28, 31]. For this reason, this therapeutic modality should be evaluated to better understand the possible antifungal synergistic activity against IF.

CONCLUSIONS

In conclusion, 60% of patients in this cohort responded to therapy. In addition, the observed 6- and 12-week survival rates in this cohort was higher than that observed in previous studies and case series [5, 32, 33]. However, the small number of cases in this single-center study and the significant competing risk of death related to underling HM in many cases in the cohort limit our ability to draw conclusions about the impact of combination antifungal therapy for IF. The use of terbinafine, either alone or combined with another agent, should be studied systematically for the treatment of fusariosis, including refractory IF and fusarial arthritis.

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