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BRIEF REPORT

Breakthrough Fungal Infections in Patients With Leukemia Receiving Isavuconazole

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We retrospectively assessed breakthrough invasive fungal infections (b-IFIs) in 100 consecutive patients with leukemia receiving single-agent isavuconazole; 13 had documented b-IFIs (candidiasis in 6, mucormycosis in 4). All b-IFIs were observed in patients with prolonged neutropenia and active leukemia.

Keywords: isavuconazole; breakthrough; invasive fungal infections; neutropenia; leukemia.

Isavuconazole (ISA), the most recently introduced triazole, is an appealing option for both treatment and prophylaxis of invasive fungal infections (IFIs) in patients with hematologic cancer due to its extended spectrum, tolerability, and the lack of requirement for therapeutic drug monitoring [1]. Breakthrough IFIs (b-IFIs) have been reported in high-risk patients receiving other mold-active triazoles, such as voriconazole and posaconazole, given for either primary treatment or prophylaxis [2–4]. Real-world data are lacking regarding b-IFIs in high-risk patients receiving ISA. Consequently, we reviewed our recent experience in patients with leukemia who received single-agent ISA.

METHODS

We reviewed the electronic medical records of all adult patients treated in the leukemia service who received ISA for the prevention or treatment of IFIs (from March 2015 to December 2016). All patients who received ≥7 days of ISA 372 mg daily, or ≥5 days of ISA 372 mg daily following a loading dose of 372 mg every 8 hours for the first 48 hours, were included. Patients may have received either intravenous or oral ISA. We excluded ISA-treated patients receiving a concomitant antifungal agent for IFI treatment. Demographic and clinical data were recorded, including age, sex, underlying disease and disease status, prior allogeneic stem cell transplantation (allo-SCT), laboratory data, and ISA formulation, indication, and duration of therapy.

Dichotomous variables were analyzed by means of χ^2 and Fisher exact test, continuous variables by means of Student *t* test, and nonparametric data by means of Mann-Whitney *U* test. IFIs (proven or probable) were defined according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria [5]. Breakthrough IFIs were defined as an occurrence of IFI due to an organism different from the organism originally detected before the initiation of ISA, or an occurrence of IFI after ≥7 days of continuous ISA use, or within 14 days of discontinuing ISA. In vitro susceptibility was performed on 6 available isolates, according to Clinical and Laboratory Standards Institute methods [6, 7]. The study was approved by our institutional review board and conducted in accordance with the Declaration of Helsinki.

RESULTS

We identified 100 patients. Their median age was 68 years (range, 24–91 years), and 73% were male; ISA was used most frequently for treatment of prior documented or presumed aspergillosis (n = 57; 57%), followed by primary (n = 27; 27%) and secondary (n = 16; 16%) prophylaxis. The oral dosage form was most commonly prescribed (n = 69; 69%); 3 patients received only the intravenous formulation, and 28 received both formulations at some point throughout treatment. Most patients (80%) had acute leukemia; 70% had acute myeloid leukemia, and 10% acute lymphoblastic leukemia. Two additional patients (2%) were in chronic myeloid leukemia blast crisis, and 6% had chronic lymphocytic leukemia. The remaining 12% had high-risk myelodysplastic syndrome, myeloproliferative neoplasm, aplastic anemia, or other T-cell leukemias.

All but 1 patient had received chemotherapy within the 3 months before initiation of the ISA regimen. Only 3 patients had leukemia in remission; the others had active hematologic disease and were receiving chemotherapy in either the frontline (25%) or relapsed/refractory setting (72%). In 18 patients, relapse after occurred after allo-SCT. At ISA initiation, 69% of patients were neutropenic (neutrophil count, <500/μL), and 61% had been neutropenic for >14 days. Thirty-nine patients were preexposed to posaconazole in the 3 months before ISA initiation.

In 13 patients, proven (n = 11) or probable (n = 2) b-IFIs developed while they were receiving ISA (Table 1). Another 7 patients had possible breakthrough fungal pneumonia while receiving ISA. These 13 b-IFIs occurred in the setting of primary prophylaxis (n = 5; 39%), secondary prophylaxis (n = 2; 15%), and treatment (n = 6’ 46%). Characteristics, including

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Table 1. Occurrence of Breakthrough Invasive Fungal Infections in 100 Patients With Leukemia Receiving Isavuconazole as a Single Agent

Patient Age/Sex	Disease	Duration of Neutropenia, d[a]	ISA Indication	ANC, Cells/μL[b]	Duration of ISA, d	b-IFI	Breakthrough Pathogen	ISA MIC, mcg/mL[c]	Outcome[d]
45/F	R/R T-LGL	>14	Secondary prophylaxis	<100	146	Esophagitis[e]	*Candida albicans*	ND	Alive
71/M	R/R CLL	NA	Treatment[f]	500–1000	7	Fungemia[e]	*Candida parapsillosis*	ND	Deceased
52/M	R/R AML	7–14	Primary prophylaxis	<100	53	Fungemia[e]	*Trichosporon asahii*	0.5	Deceased
76/M	AML[g]	>14	Primary prophylaxis	500–1000	14	Disseminated[e]	*Rhizopus* spp.	2	Deceased
61/F	R/R AML	NA	Primary prophylaxis	<100	34[h]	Pneumonia[e]	*Mucorales* spp.	ND	Alive
30/M	R/R ALL	>14	Secondary prophylaxis	<100	63	Fungemia[e]	*Candida guilliermondii*	1	Deceased
76/F	R/R AML	>14	Treatment[f]	100–500	81	Pneumonia[e]	*Fusarium* spp.	ND	Alive
54/F	R/R AML	>14	Treatment[f]	<100	160	Disseminated[e]	*Candida krusei*	4	Alive
34/M	R/R AML[i]	>14	Primary prophylaxis	<10	24	Fungemia[e]	*Candida glabrata*	4	Deceased
51/F	R/R MDS[i]	7–14	Primary prophylaxis	>1000	41	Fungemia[e]	*Candida glabrata*	4	Alive
60/F	R/R ALL	NA	Treatment[f]	500–1000	157	Pneumonia; fungemia[e]	*Rhizopus* spp.*;* *C. glabrata*	ND	Deceased
61/M	R/R CLL	7–14	Treatment[f]	100–500	194	Pneumonia[j]	*Rhizomucor* spp.	ND	Deceased
78/F	R/R AML	>14	Treatment[f]	<100	26	Disseminated[j]	*Aspergillus* spp.	ND	Alive

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; b-IFI, breakthrough invasive fungal infection; CLL, chronic lymphocytic leukemia; ISA, isavuconazole; MDS, myelodysplastic syndrome; MIC, minimum inhibitory concentration; NA, nonapplicable; ND, not done; R/R, relapsed and/or refractory; T-LGL, T-cell large granular lymphocyte leukemia.

[a]At the time of ISA initiation.

[b]At the time of b-IFI diagnosis.

[c]Method according to the National Committee for Clinical Laboratory Standards.

[d]Outcome 42 days after diagnosis of the b-IFI.

[e]Proven b-IFI.

[f]Monotherapy for prior presumed (n = 4) or documented (n = 2) aspergillosis.

[g]Newly diagnosed.

[h]Discontinued 3 days before b-IFI diagnosis.

[i]History of allogeneic stem cell transplantation.

[j]Probable b-IFI.

underlying disease, history of allo-SCT, and duration and severity of neutropenia ,were similar between patients with documented b-IFIs and the rest of the cohort (Supplementary Table 1). No patient with documented b-IFIs had experienced remission of the hematologic malignancy, and only 1 (8%) was undergoing induction chemotherapy; the remaining 12 patients (92%) had relapsed/refractory leukemia. At the time of starting ISA, 10 patients (77%) who acquired b-IFIs were neutropenic, and all had been neutropenic for >7 days. At the time of the b-IFI, 9 (70%) were neutropenic.

The most common proven b-IFIs were fungemia (n = 5) due to *Candida glabrata* (n = 2), and 1 case each of *Candida parapsillosis*, *Candida guilliermondii*, and *Trichosporon asahii* infection. The other proven b-IFIs included 1 case of *Candida albicans* esophagitis, 2 disseminated infections (1 each due to *Rhizopus* spp. and *Candida krusei*), and 2 pneumonias (1 due to *Mucorales* spp. and 1 due to *Fusarium* spp.). Finally, 1 patient had both *Rhizopus* spp. pneumonia and *C. glabrata* fungemia. Probable b-IFIs included 1 case of pneumonia due to *Rhizomucor* spp. and 1 disseminated infection due to unidentified *Aspergillus* spp. The b-IFIs occurred after a median of 48 days of ISA use. The 42-day mortality rate for patients with a mold-causing b-IFI was 50% (death in 3 of 6 patients). In vitro susceptibility testing was performed on 6 identified breakthrough isolates (Supplementary Table 2).

In 39 patients, ISA was initiated owing to poor tolerance of posaconazole or failure to achieve therapeutic posaconazole serum levels. Overall, 30 patients had documented serum posaconazole levels. Similar numbers of patients with a prior posaconazole level <700 ng/mL were observed in the b-IFI group (n = 2; 15%) and the rest of the cohort (n = 6; 8%); therefore, no association with prior low posaconazole levels and b-IFI during ISA treatment was observed. ISA was well tolerated; only 5 patients (5%) discontinued ISA owing to elevated liver enzyme levels (n = 3), nausea plus elevated liver enzyme levels (n = 1), or hallucinations (n = 1). Three of the 4 liver toxicity associated discontinuations were in the setting of concomitant chemotherapy known to be hepatotoxic.

DISCUSSION

This report is one of the first published real-world data on ISA use, as well as the incidence and characteristics of b-IFIs in patients with leukemia receiving this agent [8]. The landscape of b-IFIs among patients receiving antifungal therapy has begun to shift away from *Aspergillus*. Among our 13 patients with probable or proven b-IFI, only 1 infection was due to a likely *Aspergillus* spp., whereas 38% (n = 5) were due to other non-*Aspergillus* molds, mainly *Mucorales*, adding to the evidence supporting this epidemiological shift. Clinicians should be vigilant of the potential for non-*Aspergillus* spp. infections to occur in the era of broad-spectrum triazole antifungal therapy. Although ISA has been successfully used as primary treatment of mucormycosis [9], the agent exhibits modest in vitro activity against most *Mucorales*, with 90% minimum inhibitory concentration values of 4–16 μg/mL against the 5 most common genera of *Mucorales* [10].

Whether the relative frequency of mucormycosis as b-IFI seen in our series reflects a selection of innately ISA resistant *Mucorales* by the frequent prior (posaconazole) or continuous (ISA) triazoles in the setting of profound immunosuppression and suboptimal ISA pharmacokinetic exposure requires further study. Susceptibility testing may be useful when using ISA for mucormycosis treatment in this setting. In the VITAL study [9], only 28% of patients with mucormycosis (9 of 32) were neutropenic at the onset of ISA ,and no data were provided on the evolution of the infection in the setting of profound neutropenia, active hematologic disease, and continuous ISA.

In addition to the occurrence of uncommon mold infections, breakthrough candidiasis, namely candidemia, made up a sizable proportion of our b-IFIs. More than half (54%) of the proven or probable b-IFIs identified were due to *Candida* spp. infections, with 5 cases of candidemia, 1 of esophagitis, and 1 of disseminated infection. All candidemias were caused by a species other than *C. albicans*, a pattern previously observed in patients receiving broad-spectrum antifungal therapy [11, 12]. Of the limited number of *Candida* isolates tested, elevated minimum inhibitory concentration values similar to those seen with other azoles tested were noted (Supplementary Table 2). Of note, there are no established clinical break points for in vitro nonsusceptibility of yeasts and molds to ISA. Whether the candidiasis cases observed in our cohort were due to resistance, suboptimal ISA pharmacokinetics, or any combination of these merits further study.

The rate of 13% proven/probable b-IFIs seems higher than what has been reported in patients receiving primary posaconazole prophylaxis during remission induction chemotherapy at our institution [13] and could be explained by the inclusion of patients receiving ISA as primary treatment and secondary prophylaxis. Notably, a minority of patients (25%; n = 25) receiving ISA during first induction chemotherapy were included in this cohort; the majority of our patients had relapsed/refractory leukemia and prolonged cytopenia. Prolonged and profound neutropenia has been associated with poor outcomes in patients undergoing treatment, including ISA, for invasive aspergillosis [14]. Finally, ISA was well tolerated in our ill patient population, in accordance with early reports regarding the real-life use of this agent [15].

Our relatively small, retrospective, single-institution, observational study had several limitations. Therapeutic drug monitoring for ISA was not performed; therefore, there are no ISA serum levels to evaluate in patients with or without b-IFIs, although ISA serum levels have yet to be associated with clinical outcomes. In addition, in vitro susceptibility testing was performed in only 6 of 13 fungal isolates.

In conclusion, in our preliminary experience, we found that b-IFIs were observed in 13% of high-risk patients receiving single-agent ISA. The spectrum of b-IFIs included mostly non–*Aspergillus* spp. Molds, such as *Mucorales*, as well as *Candida* spp. infections due to species other than *C. albicans*. Currently, ISA is being evaluated in the primary prophylaxis setting for patients with acute myeloid leukemia/myelodysplastic syndrome (NCT03019939) and patients undergoing allo-SCT (NCT03149055).

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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