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CLINICAL THERAPEUTICS

A Case Series and Literature Review of Isavuconazole Use in Pediatric Patients with Hemato-oncologic Diseases and Hematopoietic Stem Cell Transplantation

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ABSTRACT We analyzed the use of isavuconazole (ISA) as treatment or prophylaxis for invasive fungal disease (IFD) in children with hemato-oncologic diseases. A multicentric retrospective analysis was performed among centers belonging to the Italian Association for Pediatric Hematology and Oncology (AIEOP). Pharmacokinetic (PK) monitoring was applied by a high-performance liquid chromatography-tandem mass spectrometry (HLPC-MS/MS) assay. Twenty-nine patients were studied: 10 during chemotherapy and 19 after allogeneic hematopoietic stem cell transplantation (HSCT). The patients consisted of 20 males and 9 females with a median age of 14.5 years (age range, 3 to 18 years) and a median body weight of 47 kg (body weight range, 15 to 80 kg). ISA was used as prophylaxis in 5 patients and as treatment in 24 cases (20 after therapeutic failure, 4 as first-line therapy). According to European Organization for Research and Treatment of Cancer (EORTC) criteria, we registered 5 patients with proven IFD, 9 patients with probable IFD, and 10 patients with possible IFD. Patients with a body weight of <30 kg received half the ISA dose; the others received ISA on the adult schedule (a 200-mg loading dose every 8 h on days 1 and 2 and a 200-mg/day maintenance dose); for all but 10 patients, the route of administration switched from the intravenous route to the oral route during treatment. ISA was administered for a median of 75.5 days (range, 6 to 523 days). The overall response rate was 70.8%; 12 patients with IFD achieved complete remission, 5 achieved partial remission, 5 achieved progression, and 3 achieved stable IFD. No breakthrough infections were registered. PK monitoring of 17 patients revealed a median ISA steady-state trough concentration of 4.91 mg/liter (range, 2.15 to 8.54 mg/liter) and a concentration/dose (in kilograms) ratio of 1.13 (range, 0.47 to 3.42). Determination of the 12-h PK profile was performed in 6 cases. The median area under the concentration-time curve from 0 to 12 h was 153.16 mg·h/liter (range, 86.31 to 169.45 mg·h/liter). Common Terminology Criteria for Adverse Events grade 1 to 3 toxicity (increased transaminase and/or creatinine levels) was observed in 6 patients, with no drug-drug interactions being seen in patients re-

Citation Decembrino N, Perruccio K, Zecca M, Colombini A, Calore E, Muggeo P, Soncini E, Comelli A, Molinaro M, Goffredo BM, De Gregori S, Giardini I, Scudeller L, Cesaro S. 2020. A case series and literature review of isavuconazole use in pediatric patients with hemato-oncologic diseases and hematopoietic stem cell transplantation. Antimicrob Agents Chemother 64:e01783-19. https://doi.org/10.1128/AAC.01783-19.

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Received 31 August 2019
Returned for modification 21 October 2019
Accepted 10 December 2019

Accepted manuscript posted online 23 December 2019
Published 21 February 2020

ceiving immunosuppressants. Isavuconazole may be useful and safe in children with hemato-oncologic diseases, even in the HSCT setting. Prospective studies are warranted.

KEYWORDS hemato-oncologic disease, hematopoietic stem cell transplantation, isavuconazole, pediatric infectious disease

Invasive fungal disease (IFD) is a major complication in children with hematologic disease and in those who undergo hematopoietic stem cell transplantation (HSCT) (1–3). The treatment, especially for invasive aspergillosis (IA) and mucormycosis, can be challenging. Effective antifungal agents are limited, and polyene compounds have an unfavorable toxicity profile, whereas triazoles have an unpredictable pharmacokinetic (PK) profile and multiple drug-drug interactions (DDI), requiring therapeutic drug monitoring (TDM), especially in pediatric patients (4). The emergence of resistant strains also solicits the need for new antifungal agents (5).

Isavuconazole (ISA) is a new extended-spectrum triazole with activity against yeasts, molds, and dimorphic fungi (including *Aspergillus* spp., Mucorales, *Candida* spp., and *Cryptococcus* spp.) (6), including those resistant to other azoles and with reduced DDI, even if it is metabolized by the cytochrome P450 (CYP450) 3A4/5.

ISA is formulated as a prodrug (isavuconazonium sulfate) without nephrotoxic excipients, such as β-cyclodextrin, and it is available in both oral and intravenous formulations. Two large multicenter clinical trials conducted in adults have demonstrated that the efficacy of ISA as the first-line treatment of invasive aspergillosis (SECURE trials [7]) and mucormycosis (VITAL study [8]) is similar to that of voriconazole (VRC) and liposomal amphotericin B (L-AMB), respectively. On the contrary, the ACTIVE trial did not demonstrate the noninferiority of ISA to caspofungin (CAS) against invasive candidiasis (9).

ISA is approved by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the treatment of adults (age, >18 years) with invasive aspergillosis (IA) and invasive mucormycosis (6–8, 10). ISA shows a favorable linear pharmacokinetic and safety profile with excellent bioavailability after oral administration with no relevant food or gastric pH effect, suggesting that TDM may not be necessary (11–13).

The efficacy and safety of ISA have not been tested in children, and the dosage and schedule have not been established. Notwithstanding these facts, some reports describe its compassionate use in pediatric patients with severe or resistant IFD.

We describe a cohort of pediatric patients with haemato-oncologic diseases who received off-label treatment with ISA along with a review of the recent literature.

RESULTS

Study population. During the study period, 29 pediatric patients were treated with ISA (Table 1). The median age at the time of ISA treatment was 14.5 years (interquartile range [IQR], 9 to 17 years; range, 3 to 18 years). Nine out of 29 patients were younger than 12 years old: 4 were <7 years old (range, 3 to 5 years) and 5 were >7 and <12 years old (range, 7.6 to 10 years). Ten patients were on chemotherapy alone, and 19 patients had received an allogeneic HSCT.

Among the patients who underwent HSCT, the source of the graft was a matched unrelated donor (MUD) in 5 cases, a haploidentical donor in 10 cases, and a matched sibling donor in 4 cases. Five patients received cyclosporine as prophylaxis for graft-versus-host disease (GVHD) during ISA treatment, whereas the remaining patients received sirolimus (2 patients), tacrolimus (1 patient), or methylprednisolone (2 patients). Acute GVHD was present in 6 patients, whereas chronic GVHD was present in 1 patient (Table 2).

Isavuconazole dosing regimen and pharmacokinetic monitoring. The median weight at the time of ISA treatment was 47 kg (IQR, 38 to 55 kg). Sixteen patients (55.2%) did not receive a loading dose, whereas 13 patients (44.8%) did. In patients who

TABLE 1 Main demographic and clinical characteristics of the study patients[a]

Characteristic	Value
Median (range) age (yr)	14.5 (3–18)
No. (%) of children ages:	
1 to <7 yr	4 (14)
7 to <12 yr	5 (17)
12 to <18 yr	20 (69)
No. (%) of male children	20 (70)
Median (range) wt (kg)	47 (15–80)
No. (%) of children who weighed:	
<30 kg	7 (24.1)
>30 kg	22 (75.9)
No. (%) of children who used ISA after:	
Chemotherapy	10 (34.4)
HSCT	19 (65.5)
No. (%) of children with the following underlying disease:	
Acute lymphoblastic leukemia	16 (55)
Acute myeloid leukemia	8 (27.6)
Lymphoma	3 (10.3)
Congenital bone marrow failure	1 (3.4)
MDS	1 (3.4)
No. (%) of children with the following underlying disease status at IFD diagnosis:	
First complete remission	17 (63)
Second complete remission or more	5 (18.5)
Relapse	5 (18.5)
No. (%) of children with the following outcome:	
Alive	25 (86.2)
Dead	4 (13.8)
No. (%) of children with the following cause of death:	
Relapse of underlying disease	2 (50)
PP-IFD	1 (25)
Other[b]	1 (25)

[a]Data are for 29 patients. Abbreviations: MDS, myelodysplasia; HSCT, hematopoietic stem cell transplantation; PP-IFD, proven/probable invasive fungal disease.
[b]Transplant-related multiorgan failure.

weighed more than 30 kg, ISA was administered according to the adult schedule, which was 200 mg every 8 h for 2 days and then 200 mg/day; 7 out of 9 patients with a body weight of less than 30 kg and an age of <12 years received half of the adult dose (100 mg) with the same schedule and 2 received the adult dose.

TABLE 2 Main characteristics of patients who received an allogeneic stem cell transplant[a]

Characteristic	Value
No. (%) of patients with the following donor type:	
MFD	4 (21)
PMFD	10 (52.6)
MUD	5 (26.3)
No. (%) of patients with the following GVHD prophylaxis during ISA treatment:	10 (52.6)
Cyclosporine	5
Sirolimus	2
Tacrolimus	1
Methylprednisolone	2
No. (%) of patients with the following aGVHD grade:	
I-II	4
III-IV	2

[a]Abbreviations: MFD, matched family donor; PMFD, partially matched family donor; MUD, matched unrelated donor; aGVHD, acute graft-versus-host disease; GVHD, graft-versus-host disease.

TABLE 3 Isavuconazole dosage and PK data

Characteristic or parameter	Value
No. (%) of patients receiving an ISA loading dose	13 (44.8)
No. (%) of patients receiving the following ISA dose:	
100 mg/day	7 (24.1)
200 mg/day	22 (75.9)
Median (range) treatment duration (days) for those ages:	75.5 (6–523)
1 to <6 yr	46 (12–231)
6 to <12 yr	86 (6–153)
12 to <18 yr	80 (6–523)
Median (range) dose/kg/day (mg/kg) for patients with a body wt of:	4 (2.50–6.67)
<30 kg	4.55 (3.57–6.67)
>30 kg	4 (2.50–5.71)
Median (range) C_{trough} (mg/liter) for patients with a body wt of:	4.91 (2.15–8.54)
<30 kg	1.1 (0.73–2.15)
>30 kg	5 (2.48–8.54)
Median (range) concn/dose (in kg) for patients with a body wt of:	1.13 (0.47–3.42)
<30 kg	0.75 (0.47–1.38)
>30 kg	1.38 (0.71–3.42)
Median (range) AUC_{0-24} (mg·h/liter)	153.16 (86.31–169.45)

Ten patients received ISA orally; in the remaining patients, the route of administration shifted from the intravenous route to the oral route during the maintenance period.

The median duration of ISA administration was 75.5 days (range, 6 to 523 days; IQR, 24 to 175 days) and the median dose per day was 4 mg/kg of body weight, equivalent to 7.4 mg/kg of isavuconazonium sulfate.

The overall median steady-state trough concentration ($C_{trough,ss}$) of ISA observed in the 17 patients in which pharmacokinetic monitoring was performed was 4.91 mg/liter (range, 2.15 to 8.54 mg/liter), and their median concentration/dose (normalized for body weight [in kilograms]) (C/D) was 1.13 (range, 0.47 to 3.42) (Table 3).

A statistically significant relationship was observed between the individual trough concentration (C_{trough})/dose ratio and age in the range of 8 to 18 years: (C_{trough}/dose) = [ln(age) – 1.2] ($r = 0.81$, $P < 0.001$), where C_{trough} is in milligrams per liter, dose is in milligrams per kilogram, and age is in years. This relationship shows how much higher the ISA doses needed to be to obtain plasma concentrations comparable to those in adults.

In 6 cases, a 12-h PK profile was carried out, and a median area under the concentration-time curve from 0 to 12 h (AUC_{0-12}) of 153.16 mg·h/liter (range, 86.31 to 169.45 mg·h/liter) was obtained. These data seem to be in line with those previously reported for kinetic simulated profiles in the adult population (10, 11).

Isavuconazole efficacy and safety. ISA was administered as prophylaxis in 5 cases (as primary prophylaxis in 2 cases and as secondary prophylaxis in 3 cases). By 90 days of follow-up from the end of treatment, none of them developed a breakthrough IFD.

Twenty-four patients received ISA for treatment; in 4 patients ISA was used as first-line therapy, and in the others it was used as rescue therapy: in 2 cases because of the toxicity of the first-line antifungal drugs (1 L-AMB and 1 VRC) and in the remaining 18 cases because of treatment failure. According to European Organization for Research and Treatment of Cancer (EORTC) criteria, 10 patients had possible IFD, 9 had probable IFD (8 with aspergillosis, 1 with candidiasis), and 5 had proven IFD (caused by an *Aspergillus* sp., *Aspergillus flavus*, *Aspergillus fumigatus*, a *Penicillium* sp., and a *Mucor* sp. in 1 patient each). Seven patients had already received L-AMB, 3 patients had already received CAS, 1 patient had already received posaconazole, and 4 patients had already received VRC; 5 patients were on combination therapy (L-AMB plus VRC in 2 cases, L-AMB plus CAS in 1 patient, and VRC plus CAS in 2 patients).

TABLE 4 Isavuconazole treatment indication and outcome

Characteristic	Value
No. (%) of patients with the following indication to use ISA:	
Prophylaxis	5 (17.2)
First-line therapy	4 (13.8)
Rescue treatment	20 (69)
No. (%) of patients with IFD	
Possible	10 (41.7)
Probable	9 (37.5)
Proven	5 (20.8)
No. (%) of patients with the following IFD outcome:	
Complete remission	12 (50)
Partial remission	5 (20.8)
Stable disease	2 (8.3)
Progression	5 (20.8)
No. (%) of patients with IFD-attributable mortality	1 (3.4)
% of patients with breakthrough infections	0

The main infection site was the lungs (18 patients), followed by the liver (2 cases) and sinuses (3 patients). Two patients had central nervous system (CNS) involvement due to mucormycosis and aspergillosis, respectively. One patient had a disseminated infection of the skin, legs, arms, lungs, and kidneys.

ISA was used in combination with other antifungals in 7 patients: in 5/7, ISA was added to the ongoing therapy (3 patients were already being treated with L-AMB, 1 patient was already being treated with CAS, and 1 patient was already being treated with posaconazole), and the combined therapy was effective in 4/5 cases. In the remaining 2 patients (1 with disseminated proven aspergillosis and 1 with probable pulmonary aspergillosis), both of whom had already been treated with VRC, a rescue treatment with ISA plus CAS was administered, and it was effective in 1 patient.

Among the patients who received ISA for IFD treatment, after a follow-up of 90 days from the beginning of ISA treatment, 12 patients (50%) had a complete response (CR) and 5 patients (20.8%) had a partial response (PR), for an overall treatment success rate of 70.8%. There were no differences in the treatment success rate according to an age younger than or older than 12 years (among 5/7 children $<$12 years of age, 5 had a CR and 1 had a PR, whereas among 12/17 children $>$12 years of age, 8 had a CR and 4 had a PR).

Considering the 14 patients with probable and proven IFD, the treatment success rate was 64.3%, whereas it was 60% in the subgroup of 5 patients with proven IFD (2 had a CR and 1 had a PR). Among the patients who used ISA as first-line treatment, the response rate was 50%.

The overall treatment failure rate was 29.1%: 2 patients (8.3%) had stable disease, and 5 patients (20.8%) experienced disease progression (2 patients had possible pulmonary fungal infection, 2 had probable pulmonary aspergillosis [in 1 of these 2 patients it was associated with sinus involvement], and 1 patient had proven pneumonitis due to a *Penicillium* sp. that was sensitive to VRC) (Table 4).

Six patients (20.7%) experienced adverse events during ISA treatment: one patient had a grade 1 bilirubin increase, two patients had a grade 2 elevation of transaminase levels, and three patients had elevated creatinine levels (of grade 2 in two patients and of grade 3 in one patient). One patient with an elevated creatinine level interrupted ISA for 7 days with rapid normalization of his renal function, so that he was able to start again ISA at the same dose, without other adverse events. All the other patients continued ISA at the same dose without further problems. No differences in adverse events were registered when patients younger than or older than 12 years of age were compared. Abnormalities in biochemical liver and renal parameters during ISA treatment were reported in 1 out of 9 patients $<$12 years of age and 5 out of 20 patients $>$12 years of age.

Notably, among the patients receiving chemotherapy, one received vincristine during ISA treatment (which is contraindicated with VRC), without adverse events.

Outcomes. After a median follow-up of 239 days, 4 patients (13.8%) died. The interval between the start of ISA treatment and death in these 4 patients was 104, 11, 198, and 311 days, respectively. The first patient died because of the development of an IFD with pulmonary and sinus involvement after haplo-HSCT, the second one died because of a relapse of acute lymphoblastic leukemia (ALL) with IFD, the third one died of multiorgan failure secondary to haplo-HSCT without IFD, and the last one died because of an ALL relapse without IFD.

DISCUSSION

In this paper, we describe a cohort of pediatric patients with hemato-oncologic diseases treated with ISA as treatment or prophylaxis for IFD. To our knowledge, our work is the first to present data on the use of ISA in pediatric patients affected not only by mucormycosis but also by aspergillosis, and it is the first to report on the use of ISA as primary or secondary prophylaxis in pediatric patients. Moreover, this paper describes the largest cohort of pediatric patients with hemato-oncologic diseases, including those treated with HSCT, in which IFD is even more aggressive and difficult to treat, treated with ISA to be evaluated.

Four papers described 6 pediatric cases successfully treated with ISA for proven mucormycosis (14–17). In the studies described in the literature, as summarized in Table 5, ISA was used as a rescue treatment in 4/6 patients, and in two-thirds of the cases, ISA was used as part of combination therapy; most patients also underwent surgical debridement. All patients but one showed a complete regression of the infection. No adverse events were recorded, except in patient 3, who complained of nausea and vomiting during the first 2 months after ISA initiation (16). No suspension of drug treatment was necessary, and in no case was the scheduled chemotherapy suspended because of ISA interactions.

In our study, the majority of patients (20/24) were affected by aspergillosis (only 1 patient had proven mucormycosis), and ISA was used as rescue therapy because of the failure of treatment with other antifungal drugs (18 patients) or intolerance of other antifungal drugs (2 patients). Our data showed that the overall response rate in patients with proven/probable IFD was high (64.3%), suggesting that ISA may also be an effective salvage therapy for patients with aspergillosis and for those who have already been treated with azoles or combined therapy and that it may also be useful as a first-line therapy when other options are contraindicated.

The efficacy of ISA as primary or secondary prophylaxis was also excellent, as no patient developed breakthrough IFD, but too few patients ($n = 5$) were evaluated to permit a conclusion to be made.

Currently, the need for a TDM-based guided therapy is controversial.

The target plasma trough level reported in adult studies ranges from 2 to 4 mg/liter (7, 8), but no relationship between drug exposure and efficacy or safety endpoints beyond this range of values has been identified by the analysis of data from clinical trials, so TDM is not mandatory, even if some authors suggest that it could be indicated in special cases (18).

The pharmacokinetic profile of ISA was investigated in three pediatric cases reported by Barg et al. (15), Cornu et al. (16), and Pomorska et al. (17).

In two reports, ISA was initially administered at the adult dose with a subsequent dose adjustment based on TDM (15, 17), while in the case described by Cornu et al. (16), the initial dosage of 70 mg/day was estimated via an extrapolation approach based on pharmacokinetic-pharmacodynamic modeling and on body surface area.

In all these 4 cases, initial plasma levels were lower than the reference values, and dose adjustments were required to achieve exposure levels similar to those in adults, suggesting a higher drug clearance rate and a shorter half-life in children than in adults (19). For this reason, it seems appropriate to evaluate TDM in the pediatric setting, where no dose per kilogram of body weight is currently available (20).

TABLE 5 Literature review of isavuconazole treatment in children[a]

Case no.	Age (y)	Sex	Disease	Proven IFD	Pathogen	First-line therapy	Reason to switch	Salvage treatment	ISA dose (mg/day)	IFD outcome	AE	Authors (reference)
1	4.5	M	ALL	Mucormycosis (orbital sinus)	*Rhizopus oryzae*	L-AMB + CAS	IFD progression	L-AMB + ISA	80–160 (i.v.), 100–200 (p.o.)	CR	None	Barg et al. (15)
2	5	M	ALL	Mucormycosis (hard palate, skull, conchae)	Negative culture	L-AMB	IFD progression	L-AMB + ISA	150–200 (i.v.), 100–200 (p.o.)	CR	None	Barg et al. (15)
3	3	F	ALL	Mucormycosis (disseminated)	*Lichtheimia* spp.	VRC	Renal impairment	ISA monotherapy	70–180 (i.v.), 200 (p.o.)	PR	Nausea, vomiting	Cornu et al. (16)
4	13.8	NI	HM	Mucormycosis		L-AMB	IFD progression	L-AMB + ISA	4 mg/kg/day (i.v.-p.o.)	CR	None	Muggeo et al. (14)
5	16	NI	HM	Mucormycosis		L-AMB	Maintenance therapy	ISA monotherapy	4 mg/kg/day (p.o.)	CR	None	Muggeo et al. (14)
6	7	F	ALL	Mucormycosis	*Cunninghamella*	ABLC + CAS	IFD progression	ABLC + ISA + CAS	200–400 (i.v.-p.o.)	CR	None	Pomorska et al. (17)

[a]Abbreviations: AE, adverse events; ALL, acute lymphoblastic leukemia; CR, complete resolution; F, female; HM, hematologic malignancy; i.v., intravenous; M, male; NI, not indicated; p.o., oral; PR, partial resolution.

A trial on the use of isavuconazole in children 1 to 17 years old for the intravenous regimen and 6 to 17 years old for the oral regimen is ongoing (ClinicalTrials.gov identifier NCT03241550). Waiting for its results, Desai and colleagues presented some data on the best pediatric ISA dosage predicted by using allometric scaling for children >2 years old (21) and by physiologically based pharmacokinetic modeling for children <2 years old (22). The authors concluded that an isavuconazonium sulfate dose of 10 mg/kg (maximum dose, 372 mg for all subjects) every 8 h for the first 48 h and once daily thereafter would result in effective and safe drug concentrations in patients aged 2 to 17 years. Conversely, for children aged 6 months to 1 year, they recommended a dose of 6 mg/kg. These data have recently been validated in a cohort of children by Arrieta et al. (23).

We analyzed the PK data in 17 of the patients in our study. All patients received a median ISA dose of 4 mg/kg/day, equivalent to 7.4 mg/kg of isavuconazonium sulfate. The median $C_{trough,ss}$ level achieved by patients with a body weight of >30 kg, who received the adult scheduled dosage, was in line with the target value reported in adults, while younger patients did not achieve the threshold desired, confirming that ISA clearance is faster in younger patients and that a higher dose of the drug may be necessary in these patients. According to the relationship observed between the individual C_{trough}/dose ratio and age for the age range of 8 to 18 years, to achieve a C_{trough} in a patient 8 years old comparable to that in a patient 16 years old, the daily ISA dose (in milligrams per kilogram) needs to be essentially doubled for the 8-year-old patient.

Our pharmacokinetic data were examined retrospectively, so the patients continued to receive the same ISA dose throughout the treatment period; given the lack of PK/PD data and the good efficacy rate obtained in the children in our study, we speculate that ISA may be effective even at lower $C_{trough,ss}$ levels or that by increasing the dose in younger patients, as Desai and colleagues suggest (22), we could have further ameliorated the response rate, but the limited sample size of our study did not permit any final conclusion to be made. However, we agree with Darnaud and coworkers (13), who suggest that at least one blood sample be collected just before the first maintenance ISA dose to make an early estimation of the patient's most likely pharmacokinetic profile. If the kinetic profile is outside the expected range, an individualized dose adjustment, together with screening for CYP450 3A4 and 3A5 genetic polymorphisms to explain the aberrant profiles, particularly in patients in whom immunosuppressive drugs are coadministered, may be proposed.

The safety data for our patients are encouraging, as no one either in the group of HSCT patients contemporaneously receiving immunosuppressants or among those patients that received ISA in combination with other antifungal drugs had to stop treatment because of severe adverse events.

In conclusion, our data suggest that ISA may be a safe and effective treatment as first-line or salvage therapy for both mucormycosis and aspergillosis in pediatric immunosuppressed children in the particular setting of HSCT, in which the need for multidrug chemotherapy protocols and the use of immunosuppressants make the use of other antifungals challenging. The major advantages of ISA in this particular setting of patients are the extended antifungal spectrum of activity, good tolerability and limited drug-to-drug interactions, the possibility to shift from the intravenous to the oral route, and the once-daily frequency of administration. Moreover, it has been reported that an ISA capsule has been opened and its contents dissolved in an acidic beverage or administered via a gastrojejunum tube, in the case of patients with swallowing difficulties (16, 24). This could facilitate treatment compliance even in the youngest patients and could be helpful in the setting of a prophylaxis strategy. The range of C_{trough}/dose ratios seen in our patients suggests that one treatment strategy cannot fit all pediatric patients, stressing the need for pharmacokinetic monitoring to identify individualized treatment strategies, particularly in younger patients.

MATERIALS AND METHODS

Data collection. This retrospective study involved six centers of the Italian Association for Pediatric Hematology and Oncology (AIEOP) that reported all cases of IFD treated with ISA in patients aged 0 to 18 years between January 2017 and February 2018. Ethics Committee approval and written informed consent were obtained on a single-patient basis for the off-label use of the drug. Data collection and processing were according to Italian law for patient confidentiality and good clinical practice. Informed consent to use the data was obtained from the parents or legal guardian.

IFD was defined as possible, proven, or probable according to internationally accepted criteria (25). The data collected concerned patient characteristics, underlying disease, type of HSCT, graft-versus-host disease (GVHD) incidence and prophylaxis, antifungal prophylaxis and/or treatment, and IFD characteristics. Information on ISA treatment and adverse effects (ranked according to Common Terminology Criteria for Adverse Events, version 5.0) was collected for all patients. The response to ISA administration was defined as a complete or partial response, stable disease, or disease progression (26).

Pharmacokinetic (PK) sampling and analysis. Plasma ISA concentrations were monitored by a high-performance liquid chromatography-tandem mass spectrometry (HLPC-MS/MS) assay technique by using a deuterated internal standard. This method was validated according to EMA/FDA guidelines before its introduction in the diagnostic service. The steady-state isavuconazole plasma concentration was determined as the trough level (C_{trough}), but in some patients, sampling was carried out at additional times (at 1, 2, 3, 4, 6, 8, and 12 h postdose) according to their clinical needs (27).

Statistical analysis. Patient demographics and clinical characteristics were described as percentages or as medians and ranges. The 90-day overall survival was estimated using the Kaplan-Meier method. Death was attributed to IFD in the case of clinical and radiological evidence of IFD progression. All analyses were performed using the statistical software STATA (version 15.0; Stata Corporation, College Station, TX, USA).

ACKNOWLEDGMENTS

We thank Mario Regazzi for scientific advice and comments on the manuscript.

This was a spontaneous study that received no funding.

We have no conflicts of interest to declare.

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