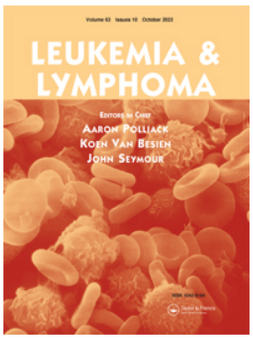

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ORIGINAL ARTICLE

Efficacy and safety of voriconazole as invasive fungal infection prophylaxis in patients with acute myeloid leukemia

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ABSTRACT

Invasive fungal infections (IFIs) are commonly observed in patients, who are at high risk of severe infections during the neutropenic phase. The aim of this retrospective single-center study was to evaluate the efficacy and safety of voriconazole as a fungal prophylaxis after induction chemotherapy for acute myeloid leukemia (AML) in adult patients. Six proven/probable IFIs were diagnosed in 213 patients with AML (median age 61 years, range 18–85), who received a total of 377 induction chemotherapies. This yielded an incidence rate of 1.6% based on all induction cycles administered. Voriconazole prophylaxis was administered as intended in 317 out of 377 (84%) induction cycles until the end of neutropenia with a median duration of 20 days (range: 2–101 days). In conclusion, voriconazole demonstrates efficacy and safety as a first-line IFI prophylaxis comparable to published data on posaconazole, which is the standard fungal prophylaxis recommendation for AML patients in international guidelines today.

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Myeloid leukemias and dysplasias; infectious complications; drug resistance

Introduction

Acute myeloid leukemia (AML) patients undergoing induction chemotherapy are at increased risk of invasive fungal infection (IFI) due to prolonged and severe neutropenia. In hematological population-based analyses, approximately two-thirds of these infections are caused by molds, mainly *Aspergillus* species, and one-third by yeasts, in most cases as candidemia [1]. These infections are a major cause of morbidity and mortality in patients with hematologic malignancies. Thus, international guidelines recommend antifungal prophylaxis during the induction phase of AML [2,3].

Since the early 1990s, first-generation triazoles, such as fluconazole and itraconazole, were used for primary antifungal prophylaxis, but they have known limitations in terms of their spectrum of antifungal activity, particularly against molds and due to limited tolerability for itraconazole.

In Austria, voriconazole was the first orally and intravenously available mold-active triazole approved for IFI therapy starting in 2002. Off-label use as antifungal prophylaxis was rapidly initiated to improve the outcome of AML patients at our hospital and with the oral administration, side effects were rarely observed. In 2005, posaconazole was licensed as another broad-spectrum triazole. Based on a large prospective randomized trial by Cornely et al. [4], comparing the efficacy of posaconazole vs. fluconazole or itraconazole, posaconazole received level AI recommendation for antifungal prophylaxis in AML patients and became the standard fungal prophylaxis recommendation for AML patients in international guidelines [5]. Yet until 2015 it was only available as an oral suspension with known concerns of inadequate absorption [6,7].

To our knowledge, there is currently no published prospective randomized controlled trial comparing the efficacy of both mold-active azoles for IFI prophylaxis. Retrospective analyses to date could not find any significant differences in the prophylactic effect of both drugs [8–10].

The aim of this study was to evaluate the efficacy and safety of voriconazole as first-line IFI prophylaxis in a cohort of consecutive patients with AML receiving induction chemotherapy.

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Table 1. Patient characteristics, induction therapies, and neutropenia.

Patients (*n*)	213
Age (years)	
≤60, *n* (%)	104 (49)
>60, *n* (%)	109 (51)
Median (range)	61 (18–85)
Gender	
Male, *n* (%)	102 (48)
Female, *n* (%)	111 (52)
Induction therapies (*n*)	377
First induction at initial diagnosis or at relapse or re-induction after failure/residual disease, *n* (%)	306 (81)
Subsequent inductions after achieving complete remission, *n* (%)	71 (19)
Induction therapy protocols	
3 + 7, *n* (%)	185 (49)
FLAG, *n* (%)	111 (29)
HAM, *n* (%)	78 (21)
Clofarabine, *n* (%)	3 (1)
Duration of grade IV neutropenia (days)	
Median (range)	17 (7–204)

Methods

This single center analysis was conducted at the Ordensklinikum Linz Elisabethinen, Linz, Austria. Since 2002, all AML patients received voriconazole 200 mg orally twice daily as an IFI prophylaxis during the neutropenic phase of induction chemotherapy. Voriconazole was started as soon as the absolute neutrophil count (ANC) dropped below 0.5 G/l. In case of anthracycline therapy, voriconazole was paused during therapy and restarted 24 h after the last anthracycline dose. Prophylaxis was discontinued as the ANC recovered to more than 0.5 G/l and there was no evidence of persistent infection. Azole plasma level assays have only been available at our department since 2014 and were not routinely performed, but mostly on an individual basis only when clinical signs of toxicity occurred.

Complete patient data of consecutive AML patients were available from 2006 to the end of 2020 and analyzed retrospectively. Inclusion criteria were as follows: 18 years of age or older, newly diagnosed or relapsed AML, receiving induction chemotherapy and neutropenia with <500 neutrophils/μl for at least seven days. Except for patients with acute promyelocytic leukemia, there were no other exclusion criteria for this analysis. Induction therapy was based on a common 3 + 7, FLAG or HAM protocol combining cytarabine with an anthracycline or fludarabine. Three patients during the 15-year time period received clofarabine as relapse- or reinduction chemotherapy. For the treatment of leukemia patients, no HEPA filter rooms were available at our department.

Proven, probable, or possible fungal infections were classified in accordance with the revised consensus criteria of the EORTC/MSG published in 2008 [11]. All patients underwent daily clinical evaluations for the presence of an IFI. At the first suspicion of an IFI, at least one thoracic CT-imaging was performed. If accessible, a biopsy of a targetable lesion was attempted. Tissue specimens were processed and analyzed by conventional mycological culture, PCR and histology, blood samples and BAL-fluids by conventional mycological culture, galactomannan enzyme immunoassay or PCR. All microbiological analyses were performed at 'analyse BioLab', the certified laboratory partner for microbiology and/or at the Christian-Doppler Laboratory for Invasive Fungal Infections, Medical University of Innsbruck, Austria. The latter institution acts as the national reference center for molds in Austria.

Antifungal therapy with either (liposomal) amphotericin B or an echinocandin was initiated empirically in patients with imaging suspicious for IFI and in patients with persistent fever for more than 48 h after change of first-line antibiotic, as well as in all cases of confirmed fungal infection as specific therapy. All side effects reported in the medical record were collected and the Common Terminology Criteria of Adverse Events (CTCAE v5.0) defined by the National Cancer Institute, Bethesda, MD, was used to classify severity.

Results

Patient population and response to therapy

During the 15-year period, 213 patients met the inclusion criteria, receiving a total of 377 induction chemotherapies. Detailed patient characteristics and distribution of induction therapies are shown in Table 1, as well as the median time of neutropenia following all induction chemotherapies.

At initial diagnosis 110 out of 201 patients (51%) achieved complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) according to the European LeukemiaNet (ELN) 2017

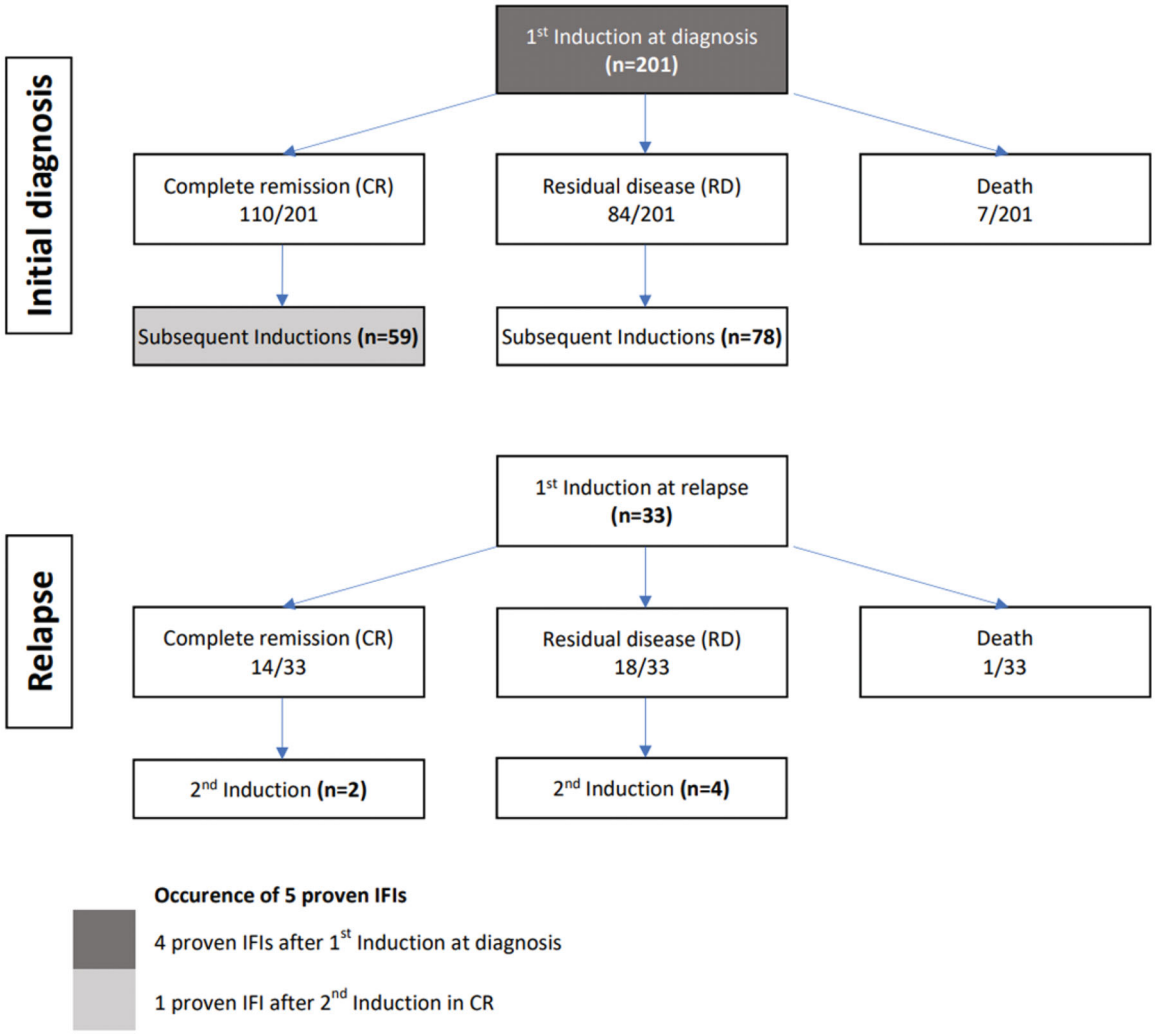

Figure 1. Distribution of induction therapies in hospitalized patients with AML. IFIs: invasive fungal infections.

recommendations [12], whereas 84 patients showed resistant or residual disease. Seven patients died during the first induction chemotherapy cycle, the majority from bacterial sepsis, cardiac death, or hemorrhage.

Patients in CR received either subsequent induction therapy ($n = 59$), followed mainly by four consolidation therapies or allogeneic stem cell therapy, depending on age, general condition and molecular/cytogenetic risk profile. A total of 55 patients with residual or resistant disease after first induction were eligible for subsequent induction cycles ($n = 78$). Thirty-three patients developed one or more relapses and received a total of 39 induction cycles. The distribution of all 377 induction therapies is shown in Figure 1.

Efficacy and safety of voriconazole prophylaxis

The median duration of voriconazole prophylaxis was 20 days with a range of 2–101 days. During 317 induction cycles (84%), voriconazole prophylaxis was administered as scheduled until the end of neutropenia. Reasons for early drug discontinuation were adverse events (5.3%), proven or suspected IFI (5.6%), persistent fever (4.8%) and other, for example, physician's choice (0.3%). As shown in Table 2, a total of five proven and one probable IFI were detected during voriconazole prophylaxis yielding an incidence rate of 1.6% based on all induction cycles administered. Additionally, we observed 18 possible cases (4.8% of all induction cycles). None of these developed proven IFI during the further course of treatment. Empirical antimycotic therapy was administered in 37 cases (9.9%, including persistent fever, probable and possible IFI). Autopsies performed in selected patients (in 33 out of 110 who died during the observation period) did not reveal additional fungal infections.

Species diagnosis revealed infections with Zygomycetes (*Mucor*, *Lichtheimia corymbifera*, *Rhizopus*

Table 2. Voriconazole prophylaxis and adverse events.

	n (%)
Days of voriconazole prophylaxis	
Median	20
Range	2–101
Invasive fungal infections	
Proven	5 (1.3)
Probable	1 (0.3)
Possible	18 (4.8)
Inductions with voriconazole prophylaxis as scheduled	317/377 (84)
Reasons for early drug discontinuation	60/377 (16)
Adverse events	20 (5.3)
Proven IFI	5 (1.3)
Probable IFI	1 (0.3)
Possible IFI	15 (4)
Persistent fever	18 (4.8)
Others (Physician's decision)	1 (0.3)
Adverse events	
Increase of cholestasis parameters/transaminases	27 (7.1)
Skin reactions (exanthema/rash)	2 (0.5)
Sleep disturbance	1 (0.3)
Optical hallucination	1 (0.3)
Neuropathy	1 (0.3)
Bradycardia	1 (0.3)

oryzae), *Aspergillus fumigatus* and *Fusarium* spp. No candidemia was detected during our observation. As shown in Figure 1 in four of five patients, IFI was detected during the 1st induction at initial diagnosis. In the fifth patient, this occurred in CR during the 2nd induction, albeit in this case voriconazole prophylaxis was interrupted due to an increase of transaminases for three days. Details of patients with proven IFI are shown in Table 3.

Voriconazole was switched to another class of antifungal agents, preferably (liposomal) amphotericin B empirically or after fungal confirmation. One patient died from fungal infection and another other four patients died by the end of the observation period in refractory relapse from bleeding or non-fungal infections. No IFI-related death was observed.

Possible drug related adverse events were detected in 33 cases (8.8%) during all induction therapies. Most commonly observed as an increase of cholestasis parameters/transaminases (7.1%), followed by skin reactions (0.5%), sleep disturbances, optical hallucination, neuropathy, and bradycardia (each 0.3%).

Discussion

Antifungal prophylaxis is currently recommended by various national and international guidelines for the prevention of IFI in patients during remission induction chemotherapy of AML and high-risk myelodysplastic syndrome, as well as allogeneic stem cell transplantation [3].

In a 15-year timeframe, our retrospective analysis assessed the efficacy and safety of voriconazole in a real-life AML population. We observed a very low rate (1.3%) of proven IFIs and probable IFIs (0.3%) in 213 patients with 377 induction cycles. Compared to published trials of prophylactic voriconazole [13–15] or posaconazole [4,16–19], this represents a similar rate of breakthrough infections. The probability of developing an IFI is usually highest within the first 100 days following diagnosis of AML, especially in patients who did not achieve remission after the first course of induction chemotherapy [20]. Despite the number of detected infections in this analysis being very low, all five patients with proven IFIs were detected within 17–44 days after AML diagnosis and almost all during the first induction therapy. A limitation of our study, as well as other retrospective analyses of leukemia patients, might be an underestimation of possible fungal infections, since invasive diagnostic procedures were not performed in all cases of neutropenic fever due to bleeding risks and unavailability of 24/7 access.

The fact that no IFI occurred after treatment of the recurrent disease was probably a coincidence due to the small number of patients. With a median age of 61 years and the oldest patient being 85 years undergoing intensive induction chemotherapy, our cohort is rather old compared to most AML studies investigating intensive therapy. This may explain the low CR rate, but did not seem to have an impact on the occurrence of IFI. Of note, most patients were treated before the availability of hypomethylating agents.

Voriconazole is known for its limited activity against atypical mold infections. It is therefore not surprising that in four out of the five patients a breakthrough infection with Zygomycetes or Fusarium was detected. Three of four patients with break through IFI could be rescued by switching antimycotic therapy to either (liposomal) amphotericin B or caspofungin or by additional surgery. Only one patient with IFI showed fulminant infection and died from fungal sepsis within two weeks after first induction therapy. However, at institutions with a known higher incidence of atypical mold infections, voriconazole should not be considered as preferentially used IFI prophylaxis. Serological tests, such as the galactomannan antigen were initially not available and were later only performed at irregular intervals. The importance of routine galactomannan antigen testing during mold-active prophylaxis is discussed controversially, but the lack of its routine use may have led to underdiagnosis of 'probable IFI' and is a limitation of this analysis that should be emphasized. On the other hand, especially in leukemia patients a risk of drug interaction-related false-positive galactomannan results exists, which is why now testing should be done by PCR anyway.

Table 3. Cases with proven invasive fungal infections (IFI).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	50	45	64	74	72
Sex	M	F	F	F	F
Onset of proven IFI	ID[a]	ID[a]	ID[a]	ID[a]	ID[a]
1st or subsequent induction	Induction I	Induction I	Induction II	Induction I	Induction I
Induction regimen	HAM	FLAG	FLAG	3 + 7	3 + 7
Response to therapy	CR[b]	Failure	CR[b] (after 1st ind.)	CR[b]	Induction death
Grade 4 neutropenia (d)	15	29	7	24	10
Days from ID[a] to IFI	18	30	44	21	17
Prophylaxis interrupted	No	No	Yes	No	No
Fungal species detected	*Mucor*	*Fusarium* spp.	*Rhizopus oryzae*	*Aspergillus fumigatus*	*Lichtheimia corymbifera*
IFI organ involvement	Lung	Maxillary sinus	Paranasal sinuses Orbital, cerebral	Lung	Lung Fungemia
Diagnostic procedures	CT, PCR, microscopy	CT Culture	CT/MRI Histology, PCR	CT Culture	CT Histology, PCR
IFI Therapy (combination or subsequent)	Amphotericin B Caspofungin posaconazole	Amphotericin B	Lip. amphotericin B Posaconazole	Amphotericin B	Amphotericin B
IFI outcome	Remission after surgery	Remission	Regressive under therapy	Remission	Death from fungal septicemia
Further AML therapy	Chemotherapy Allo-SCT	Chemotherapy	Azacitidine	Chemotherapy Azacitidine	–
AML outcome	Death in refractory relapse	Death in refractory relapse	Death in refractory relapse	Death in refractory relapse	–

[a]ID: initial diagnosis.
[b]CR: complete remission.

Voriconazole prophylaxis was associated with a low number of adverse events, observed in 33 cases of all induction therapies (8.8%) and resulted in premature discontinuation in 20 cases (5.3%). This is comparable with adverse events related drop-out rates reported in other voriconazole studies (range 4–18%), but might be slightly lower observed when using posaconazole [9,10,13,14]. However, there may have been an underestimation of adverse events due to the retrospective recording by chart review.

Regarding costs, it should be mentioned that until 2018 both azole preparations were still available in Austria as original products with a cost difference in favor of voriconazole of 40 euros per day.

In conclusion, the efficacy and safety profile of voriconazole as first-line IFI prophylaxis was comparable to published data on prophylaxis with posaconazole. When considering fungal prophylaxis in patients with AML, the adverse event related discontinuation and atypical mold breakthrough rates must be carefully weighed against the lower costs of voriconazole when selecting a triazole antifungal agent.

Author contributions

S.M.S., T.V., and M.G. wrote the manuscript; S.M.S., T.V., and M.B. performed the administration of data; S.M.S., M.B., A.W., and M.G. provided patient samples and clinical information; T.V. performed the statistical analyses; C.L.F. and P.A. performed the microbiological analysis and contributed to the manuscript, M.G. and T.V. analyzed and interpreted the data. All authors have read and agreed to the published version of the manuscript.

Disclosure statement

The authors declare that they have no conflict of interest to disclose in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author [SMS], upon reasonable request.

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