

# Efficacy of posaconazole prophylaxis in acute myeloid leukemia and myelodysplastic syndrome patients treated with hypomethylating agents

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## Abstract

**Background:** Although many acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients have been treated with hypomethylating agents (HMAs) as a substitute for intensive chemotherapy in recent years, the incidence of invasive fungal infections (IFIs) and the efficacy of posaconazole as antifungal prophylaxis in these patients are not well known to date.

**Methods:** We retrospectively analyzed 280 AML and MDS patients treated with HMAs to identify IFI incidence and posaconazole efficacy as antifungal prophylaxis in these patients.

**Results:** The overall incidence of probable or proven IFIs was 7.9% (22/280 patients): 11.5% in the no-use group (17/148 patients) and 3.8% in the posaconazole group (5/132 patients). Most IFIs occurred during the early cycles of the HMAs (median: 3 cycles; range: 1–8 cycles), especially in patients who had neutropenia or did not respond to HMAs. Posaconazole significantly lowered IFI incidence compared with that in the no-use group in univariate and multivariate analyses. Moreover, patients who had reduced liver function at HMA initiation, were treated with decitabine therapy, and did not respond to HMA chemotherapy were independently associated with a higher IFI risk. In subgroup analysis, posaconazole appeared to be more beneficial for patients with good Eastern Cooperative Oncology Group performance score or liver function at HMA initiation.

**Conclusion:** Thus, in AML and MDS patients receiving HMAs, IFI risk may be high during the early cycles, especially when the underlying disease is not controlled. Posaconazole could represent antifungal prophylaxis in these patients; further studies are needed for its appropriate indications.

**Keywords:** antifungal prophylaxis, hypomethylating agent, invasive fungal infection, posaconazole

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## Introduction

Invasive fungal infection (IFI) is a major cause of non-relapse mortality during the treatment of hematologic malignancy. The incidence of IFIs has been reported to be approximately 5–20% in acute myeloid leukemia (AML)<sup>1–5</sup> and 2–10% in myelodysplastic syndrome (MDS),<sup>6–9</sup> but the mortality rate has been reported to be as high as 70%.<sup>6,10–13</sup> For this reason, the current guidelines

recommend the use of antifungal prophylaxis during the treatment of patients with AML or MDS, especially in high-risk patients undergoing intensive chemotherapy or in cases of anticipated prolonged and profound neutropenia.<sup>14–17</sup>

In recent years, an increasing number of AML and MDS patients were treated with hypomethylating agents (HMAs) as a substitute for best

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supportive care or even conventional intensive chemotherapy.<sup>18</sup> Although the incidence of prolonged severe neutropenia is not as high as that of intensive chemotherapy, HMAs may cause cytopenia, including neutropenia, and increase transfusion demand.<sup>19,20</sup> In addition, considering that AML and MDS themselves are risk factors for febrile neutropenia,<sup>15</sup> the use of antimicrobial prophylaxis during HMA treatment needs to be discussed. However, unfortunately, there is a lack of information on the risk of infection, including IFI, and the use of antifungal prophylaxis in patients treated with HMAs for AML and MDS.

Posaconazole is an oral azole with a wide spectrum, including species of *Candida*, *Aspergillus*, *Fusarium*, and *Zygomycetes*.<sup>21</sup> Cornely *et al.* reported that posaconazole prevented IFIs and improved survival more effectively than fluconazole or itraconazole in patients receiving chemotherapy for AML or MDS.<sup>22</sup> Since then, several guidelines have recommended the use of posaconazole as antifungal prophylaxis in these patients.<sup>14,16</sup> However, this study was conducted mainly in AML and MDS patients who received intensive chemotherapy; therefore, the effect of posaconazole on patients receiving HMAs is unclear. Thus, the present study was conducted retrospectively to identify the incidence of IFIs in AML and MDS patients treated with HMAs and confirm the efficacy of posaconazole as antifungal prophylaxis in these patients.

## Methods

### *Study design and patients*

This was a non-interventional comparative cohort study, in which we retrospectively analyzed the data of patients who were consecutively enrolled in the AML and MDS Registry from January 2006 to April 2020. Three affiliated tertiary hospitals (Anam, Guro, and Ansan hospitals) located in the metropolitan area participated in the registry. The study was approved by the institutional review board, and all data were fully anonymized (IRB No. 2020AN0211, 2020GR0237, and 2020AS0137).

Patients who met the following inclusion criteria were selected: (1) patients with a diagnosis of AML or MDS according to the World Health Organization classification;<sup>23</sup> (2) patients first exposed to HMAs (azacitidine or decitabine) as

first-line chemotherapy; and (3) patients who received at least one full cycle of either drug. Azacitidine and decitabine were administered at the recommended dose of 75 mg/m<sup>2</sup> subcutaneously or intravenously (IV) daily for 7 days every 4 weeks and 20 mg/m<sup>2</sup> IV daily for 5 days every 4 weeks, respectively. The use of posaconazole was determined at the discretion of the participating physicians according to the patients' insurance coverage and the risk of IFI as judged by a physician, and posaconazole was administered at the recommended dose of 300 mg once a day (maintenance dose) after 300 mg twice a day (loading dose) from chemotherapy day 1 until neutropenia recovery.

### *Clinical endpoints*

The primary endpoints were the incidence of IFIs in the AML and MDS patients treated with the HMAs and the efficacy of posaconazole as antifungal prophylaxis. We counted probable or proven IFIs that occurred during treatment with the HMAs (from the time of HMA initiation to before second-line chemotherapy or allogeneic hematopoietic stem cell transplantation), and each IFI was defined according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria.<sup>24</sup> In brief, a proven IFI was defined as a case that satisfied any one of the following criteria: (1) identification of fungal elements (molds or yeasts) through microscopic analysis with sterile material; (2) the detection of fungal elements (molds or yeasts) through culture with sterile material or blood; and (3) identification of fungal elements (applies only to yeasts) through serological analysis of cerebrospinal fluid. A probable IFI was defined as a case that satisfied all three of the following conditions: the presence of a host factor, a clinical criterion, and a mycological criterion. Details are presented in Supplemental Material Table 1 online.

The secondary endpoint was the characteristics of patients who would benefit from posaconazole use. The following data were collected: age, diagnosis of AML or MDS, cytogenetics–molecular risk stratification of AML classified according to the 2017 European LeukemiaNet criteria,<sup>25</sup> prognosis risk groups of MDS divided according to the revised international prognostic scoring

system,<sup>26</sup> Eastern Cooperative Oncology Group performance score (ECOG PS),<sup>27</sup> absolute neutrophil count (ANC), Child–Pugh score (CPS),<sup>28</sup> chronic kidney disease (CKD) stage<sup>29</sup> based on estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation at the initiation of HMAs,<sup>30,31</sup> type of HMAs, use of antibacterial prophylaxis, and treatment responses to HMAs. Responses to the HMAs were evaluated according to the International Working Group.<sup>32–34</sup> Patients who responded to treatment were defined as achieving a complete response (CR) or partial response (PR) in AML and CR or PR or hematologic improvement in MDS.

### Statistical analysis

Baseline characteristics were compared between the groups using the Mann–Whitney *U* test or chi-squared test, as appropriate. Factors affecting the incidence of IFIs were assessed using univariate and multivariate logistic regression analyses with the following variables for identifying the overall condition of the patient: age, diagnosis of AML or MDS, ECOG PS, characteristics at the initiation of HMAs (ANC, CPS, and CKD stage), type of HMAs, use of antibacterial prophylaxis, and treatment responses to HMAs. The IBM Statistical Package for Social Sciences version 21.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. A *p* value <0.05 was considered statistically significant.

## Results

### Patient characteristics

In total, 280 AML or MDS patients treated with HMAs were analyzed in this study (no-use group: *n* = 148; posaconazole group: *n* = 132). In the case of MDS patients (total, 198 patients), the median ANC at diagnosis was 1096/μL with a range of 33 to 63,909/μL [no use: 969/μL (median), 91–29,856/μL (range); posaconazole: 1276/μL, 33–63,909/μL] and the median time to treatment from diagnosis was 0.50 months with a range of 0.03 to 80.67 months (no use: 0.47 months, 0.07–80.67 months; posaconazole: 0.59 months, 0.03–75.90 months). The baseline characteristics at HMA initiation of each group are summarized in Table 1. The posaconazole group showed a higher median age than the no-use group [no use:

70.5 years (median), 31.0–86.0 years (range); posaconazole: 74.0 years, 21.0–87.0 years; *p* = 0.009]. The posaconazole group also showed a higher proportion of patients with AML diagnosis (no use: 30/148 patients, 20.3%; posaconazole: 52/132 patients, 39.4%; *p* = 0.001), decreased liver function (defined as having CPS more than 7; no use: 12/148 patients, 8.1%; posaconazole: 27/132 patients, 20.5%; *p* = 0.003), decreased kidney function (defined as having CKD stage 3, 4, or 5; no use: 46/148 patients, 31.1%; posaconazole: 75/132 patients, 56.8%; *p* < 0.001), and decitabine use (no use: 91/148 patients, 61.5%; posaconazole: 99/132 patients, 75.0%; *p* = 0.021). In contrast, the proportion of antibacterial prophylaxis use was higher in the posaconazole group than in the no-use group (no use: 77/148 patients, 52.0%; posaconazole: 95/132 patients, 72.0%; *p* = 0.001). However, there were no significant differences in the other characteristics between the groups, including sex, proportion of patients with poor prognostic risk, ECOG PS, proportion of neutropenia, and responses during treatment.

### IFIs

The median number of HMA chemotherapy cycles was five cycles (range: 1–72 cycles) in the no-use group and four cycles (range: 1–28 cycles) in the posaconazole group. In total, 22 out of 280 patients were identified with probable or proven IFIs (overall incidence of IFIs: 7.9%) and the details of each IFI are summarized in Tables 2 and 3. The overall incidence of probable or proven IFIs was 11.5% in the no-use group (17/148 patients) and 3.8% in the posaconazole group (5/132 patients); of these, the incidence of invasive mold infections was 8.1% in the no-use group (12/148 patients) and 3.8% in the posaconazole group (5/132 patients). The patients with probable or proven IFIs showed a median age of 69.5 years (range: 21–82 years) and 27.3% of the patients had AML. The median values of the HMA chemotherapy cycle and ANC at the time of IFI diagnosis were 3 (range: 1–6 cycles) and 100/μL (range: 0–2700/μL), respectively. The changes in the ANCs of each patient at the time of diagnosis, the start of HMA treatment, the time of IFI diagnosis, and over the 14 days before IFI diagnosis are summarized in Supplemental Figure 1, as is febrile neutropenia. At the time of IFI diagnosis, the proportion of patients who did not respond to HMAs and the

**Table 1.** Baseline characteristics at the initiation of hypomethylating agents.

Baseline characteristics	Antifungal prophylaxis		p value
	No use n = 148	Antifungal prophylaxis using posaconazole n = 132	
Median age, years (range)	70.5 (31.0–86.0)	74.0 (21.0–87.0)	<b>0.009</b>
<70 years, n (%)	68 (45.9)	40 (30.3)	<b>0.010</b>
≥70 years, n (%)	80 (54.1)	92 (81.1)	
Male:female ratio	1.85	1.59	0.620
Primary diagnosis, n (%)			<b>0.001</b>
Acute myelogenous leukemia <sup>†</sup>	30 (20.3)	52 (39.4)	0.287
Favorable risk	2 (6.7)	5 (9.6)	
Intermediate risk	19 (63.3)	39 (75.0)	
Poor risk	9 (30.0)	8 (15.4)	
Myelodysplastic syndrome <sup>‡</sup>	118 (79.7)	80 (60.6)	0.884
Very low, low, and intermediate risk	66 (55.9)	46 (57.5)	
More than high risk	52 (44.1)	34 (42.5)	
ECOG PS, n (%)			0.791
0–1	141 (95.3)	124 (93.9)	
≥2	7 (4.7)	8 (6.1)	
Neutropenia (absolute neutrophil count <1000 cells/μL), n (%)	76 (51.4)	53 (40.2)	0.072
Child–Pugh score, n (%)			<b>0.003</b>
5–6	136 (91.9)	105 (79.5)	
≥7	12 (8.1)	27 (20.5)	
CKD stage, n (%) <sup>*</sup>			<b>&lt;0.001</b>
Stage 1 and 2: eGFR ≥60	102 (68.9)	57 (43.2)	
Stages 3 and 4: 15 ≤ eGFR <60	43 (29.1)	70 (53.0)	
Stage 5: eGFR <15	3 (2.0)	5 (3.8)	
Type of hypomethylating agent, n (%)			<b>0.021</b>
Azacytidine	57 (38.5)	33 (25.0)	
Decitabine	91 (61.5)	99 (75.0)	
Antibacterial prophylaxis, n (%)			<b>0.001</b>
No use	71 (48.0)	37 (28.0)	

(Continued)

**Table 1.** (Continued)

Baseline characteristics	Antifungal prophylaxis		<i>p</i> value
	No use <i>n</i> = 148	Antifungal prophylaxis using posaconazole <i>n</i> = 132	
Levofloxacin or ciprofloxacin	77 (52.0)	95 (72.0)	
Best response during treatment, <i>n</i> (%)**			0.454
Response	74 (53.6)	70 (58.3)	
No response	64 (46.4)	50 (41.7)	

Bold indicates statistical significance.  
†Cytogenetics-molecular risk stratification of acute myelogenous leukemia was classified according to the 2017 European LeukemiaNet criteria.  
‡Prognosis risk groups of myelodysplastic syndrome were divided according to the revised international prognostic scoring system.  
\*Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.  
\*\*The analysis was conducted except for the missing value of 7.9% (total 22/280 patients, no use: *n* = 10, and posaconazole: *n* = 12).  
CKD, chronic kidney disease; ECOG PS, Eastern Cooperative Oncology Group performance score; eGFR, estimated glomerular filtration rate.

incidence of IFI-related death were 72.7% and 50%, respectively.

In the univariate analysis, the posaconazole group showed a significantly lower incidence of IFIs than the no-use group [no use *versus* posaconazole, odds ratio (OR): 3.296, 95% confidence interval (CI): 1.181–9.201, *p* = 0.023]. In the multivariate analysis of IFI incidence, the use of posaconazole as antifungal prophylaxis led to a significant reduction of IFI incidence (no use *versus* posaconazole, OR: 3.921, 95% CI: 1.964–7.826, *p* < 0.001). In addition, patients who had reduced liver function at HMA initiation, were treated with decitabine therapy, and did not respond to HMA chemotherapy were independently associated with a higher risk of IFIs (OR: 2.775, 95% CI: 1.161–6.632, *p* = 0.022; OR: 3.237, 95% CI: 1.633–6.418, *p* < 0.001; and OR: 7.227, 95% CI: 3.849–13.567, *p* < 0.001, respectively) (Table 4). Receiver operating characteristic (ROC) curve analysis was conducted to assess the predictability potential of the four variables for IFIs, and the resultant ROC curve is shown in Figure 1. The area under the curve (AUC) value for this ROC curve was 0.780. The ROC curve displayed a sensitivity of 0.80 and a specificity of 0.64 for predicting IFIs in AML or MDS patients treated with HMAs. Cross validation

was performed to test the predictability potential of the four variables. The AUC value for the ROC curve of the cross-validation model was 0.703. The sensitivity and specificity for this validation model were 0.80 and 0.63, respectively.

#### *Subgroup analysis for the incidence of IFIs according to the use of posaconazole as antifungal prophylaxis*

To further investigate which subgroups would benefit from the use of posaconazole as antifungal prophylaxis, subgroup analysis of the following factors was performed: age, diagnosis, characteristics at HMA initiation (ECOG PS, ANC, CPS, and eGFR), type of HMA, use of antibacterial prophylaxis, and treatment responses to HMAs (Figure 2). In the subgroup analysis, the use of posaconazole significantly decreased the incidence of IFIs in the groups with 0–1 ECOG PS and in the groups with 5–6 CPS (OR: 0.230, 95% CI: 0.061–0.866, *p* = 0.030 and OR: 0.254, 95% CI: 0.064–1.001, *p* = 0.050, respectively). No other subgroups benefited from the use of posaconazole as antifungal prophylaxis.

In addition, we further analyzed whether there was medical history that could increase the risk of IFI in patients with AML and MDS. In the

**Table 2.** Cases of IFIs during treatment with HMAs.

Case	Age (years)	Sex	WHO diagnosis	Antifungal prophylaxis	HMA cycle at IFI diagnosis	HMA cycle with febrile neutropenia	ANC at IFI diagnosis (/ $\mu$ L)	Response to HMAs	Category of IFI per EORTC/MSG	Host factor	Clinical criteria	Mycological criteria	Treatment outcome of IFI
1	53	Male	MDS	No use	1	1	812	SD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	Resolved
2	52	Female	MDS	No use	2	-	1771	HI	Proven	-	Lower respiratory tract fungal disease	Mucormycosis (lung biopsy)	IFI-related death
3	56	Male	MDS	No use	2	1, 2	Not detectable	PD	Proven	Recent history of neutropenia	Lower respiratory tract fungal disease	<i>Candida tropicalis</i> (blood culture)	IFI-related death
4	80	Female	AML	No use	5	1, 2, 3, 4	19	CR	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	Resolved
5	76	Female	AML	No use	2	1	1800 (IC 92%)	NA	Proven	-	Lower respiratory tract fungal disease	<i>Candida glabrata</i> (blood culture)	IFI-related death
6	81	Male	AML	No use	2	1, 2	875	PD	Proven	Recent history of neutropenia	-	<i>Candida parapsilosis</i> (blood culture)	IFI-related death
7	49	Male	MDS	No use	3	1, 2, 3	211	PD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	Resolved
8	81	Male	AML	No use	3	1, 3	864	PD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	$\beta$ -D-glucan (+)	IFI-related death
9	68	Male	MDS	No use	3	1, 2, 3	1190	PR	Proven	-	Sinonasal infection, lower respiratory tract fungal disease	<i>Aspergillus flavus</i> (sputum culture, nasopharyngeal biopsy)	Resolved
10	75	Male	MDS	No use	6	1, 2	2700 (IC 20%)	PD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	$\beta$ -D-glucan (+)	IFI-related death
11	52	Female	MDS	No use	1	1	68	SD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	Resolved
12	63	Male	MDS	No use	4	1, 2, 3, 4	13	SD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	IFI-related death

(Continued)

Table 2. (Continued)

Case	Age (years)	Sex	WHO diagnosis	Antifungal prophylaxis	HMA cycle at IFI diagnosis	HMA cycle with febrile neutropenia	ANC at IFI diagnosis (/ $\mu$ L)	Response to HMAs	Category of IFI per EORTC/MSG	Host factor	Clinical criteria	Mycological criteria	Treatment outcome of IFI
13	75	Female	MDS	No use	2	1, 2	78 (LIC 32%)	PD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	IFI-related dead
14	41	Male	MDS	No use	1	1	380	PD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	Resolved
15	48	Male	MDS	No use	4	1, 3, 4	Not detectable	PD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	IFI-related dead
16	73	Female	MDS	No use	3	1, 2, 3	123	PD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	Resolved
17	63	Male	MDS	No use	2	2	33	NA	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	IFI-related dead
18	71	Male	AML	Posaconazole	3	3	20	SD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	Resolved
19	82	Female	AML	Posaconazole	2	1	36	SD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	IFI-related dead
20	80	Male	MDS	Posaconazole	3	1, 2, 3	350	PR	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	Resolved
21	21	Male	MDS	Posaconazole	4	1, 2, 4	50	SD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	Resolved
22	78	Male	MDS	Posaconazole	5	5	25	SD	Probable	Recent history of neutropenia	Lower respiratory tract fungal disease	Aspergillosis Ag (+)	Resolved

Febrile neutropenia was defined according to the National Comprehensive Cancer Network guidelines (prevention and treatment of cancer-related infections, version 2.2020). Microbiologic criteria for probable infection with *Aspergillus* species included a positive test for the aspergillus galactomannan antigen ( $\geq 0.5$  on the galactomannan index) and  $\beta$ -D-glucan ( $\geq 80$  pg/mL) in serum.

AML, acute myeloid leukemia; ANC, absolute neutrophil count; CR, complete remission; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group; HI, hematological improvement; HMA, hypomethylating agent; IC, immature cell in peripheral blood; IFI, invasive fungal infection; MDS, myelodysplastic syndrome; NA, not applicable; PD, progressive disease; PR, partial remission; SD, stable disease; WHO, World Health Organization.

**Table 3.** Patient characteristics at the time of IFI diagnosis.

Characteristics	No use <i>n</i> = 17	Antifungal prophylaxis using posaconazole <i>n</i> = 5	Total <i>N</i> = 22
Median age, years (range)	63.0 (41–82)	78.0 (21–82)	69.5 (21–82)
Primary diagnosis, <i>n</i> (%)			
Acute myelogenous leukemia <sup>†</sup>	4 (23.5)	2 (40)	6 (27.3)
Favorable risk	0 (0)	0 (0)	0 (0)
Intermediate risk	2 (50)	2 (100)	4 (66.7)
Poor risk	2 (50)	0 (0)	2 (33.3)
Myelodysplastic syndrome <sup>‡</sup>	13 (76.5)	3 (60)	16 (72.7)
Very low, low, and intermediate risk	10 (76.9)	3 (100)	13 (81.2)
More than high risk	3 (23.1)	0 (0)	3 (18.8)
HMA cycle at IFI diagnosis (range)	2 (1–6)	3 (2–5)	3 (1–6)
ANC at IFI diagnosis, / $\mu$ L (range)	211 (0–2700)	36 (20–350)	100 (0–2700)
No response to HMAs, <i>n</i> (%) <sup>*</sup>	12 (70.6)	4 (80.0)	16 (72.7)
IFI-related death, <i>n</i> (%)	10 (59)	1 (20)	11 (50)

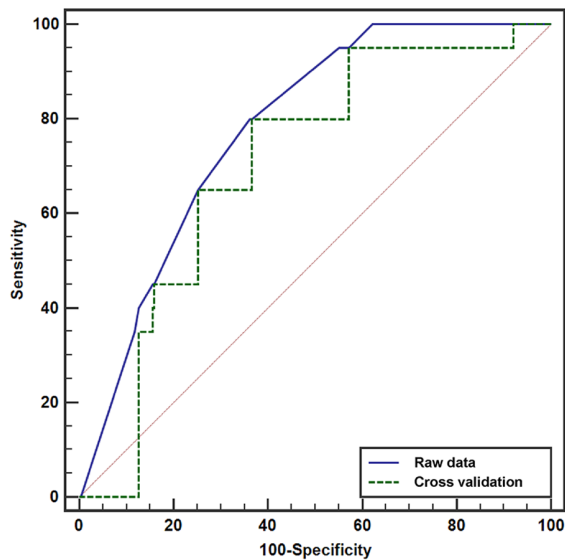
<sup>†</sup>Cytogenetics-molecular risk stratification of acute myelogenous leukemia was classified according to the 2017 European LeukemiaNet criteria.  
<sup>‡</sup>Prognosis risk groups of myelodysplastic syndrome were divided according to the revised international prognostic scoring system.  
<sup>\*</sup>The analysis was conducted except for the missing value of 9.1% (total 2/22 patients, no use: *n* = 2, and posaconazole: *n* = 0).  
ANC, absolute neutrophil count; HMA, hypomethylating agent; IFI, invasive fungal infection.

**Table 4.** Univariate and multivariate analyses of the incidence of invasive fungal infections.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
No use <i>versus</i> posaconazole	3.296 (1.181–9.201)	0.023	4.483 (2.280–8.813)	<0.001
Age $\geq$ 70 years <i>versus</i> <70 years	0.602 (0.252–1.442)	0.255	–	–
Acute myeloid leukemia <i>versus</i> myelodysplastic syndrome	0.933 (0.374–2.327)	0.882	–	–
ECOG PS $\geq$ 2 <i>versus</i> ECOG PS 0–1 <sup>†</sup>	0.717 (0.090–5.694)	0.753	–	–
ANC <1000/ $\mu$ L <i>versus</i> ANC $\geq$ 1000/ $\mu$ L <sup>†</sup>	1.855 (0.803–4.286)	0.148	–	–
Child–Pugh score $\geq$ 7 <i>versus</i> 5–6 <sup>†</sup>	1.197 (0.388–3.696)	0.754	2.775 (1.161–6.632)	0.022
15 $\leq$ eGFR <60 <i>versus</i> eGFR $\geq$ 60 <sup>†,*</sup>	1.006 (0.430–2.352)	0.99	–	–
eGFR <15 <i>versus</i> eGFR $\geq$ 60 <sup>†,*</sup>	1.480 (0.17–12.906)	0.723	–	–
Decitabine <i>versus</i> azacytidine	1.556 (0.599–4.039)	0.364	3.237 (1.633–6.418)	<0.001
Antibacterial prophylaxis <i>versus</i> no use <sup>†</sup>	0.654 (0.287–1.492)	0.313	–	–
Treatment response (–) <i>versus</i> response (+)	6.562 (2.154–19.995)	0.001	7.227 (3.849–13.567)	<0.001

<sup>†</sup>These characteristics were measured at the initiation of hypomethylating agents.  
<sup>\*</sup>eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.  
ANC, absolute neutrophil count; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; eGFR, estimated glomerular filtration rate; OR, odds ratio.





**Figure 1.** Receiver operating characteristic curve for the raw data and cross validation based on the logistic regression model.

univariate logistic regression analyses, there were no histories that raised the risk of IFI, including hypertension (yes: 108 *versus* no: 172, OR 0.725, 95% CI 0.286–1.841,  $p=0.499$ ), diabetes (yes: 70 *versus* no: 210, OR 1.145, 95% CI 0.406–3.227,  $p=0.798$ ), cardiovascular diseases (including angina, arrhythmia, valvular heart disease, and heart failure; yes: 17 *versus* no: 263, OR 0.720, 95% CI 0.091–5.701,  $p=0.756$ ) and cerebral diseases (including cerebral infarction and Parkinson's disease; yes: 10 *versus* no: 270, OR 1.317, 95% CI 0.159–10.904,  $p=0.798$ ). Cases of pulmonary diseases, autoimmune diseases, preceding hematologic diseases, previous history of solid cancer diagnosis, and occupational exposure could not be analyzed because of small sample sizes or insufficient data.

#### *Adverse events leading to the discontinuation of posaconazole*

There were no reports of grade 3 or higher adverse events requiring the interruption or discontinuation of posaconazole treatment.

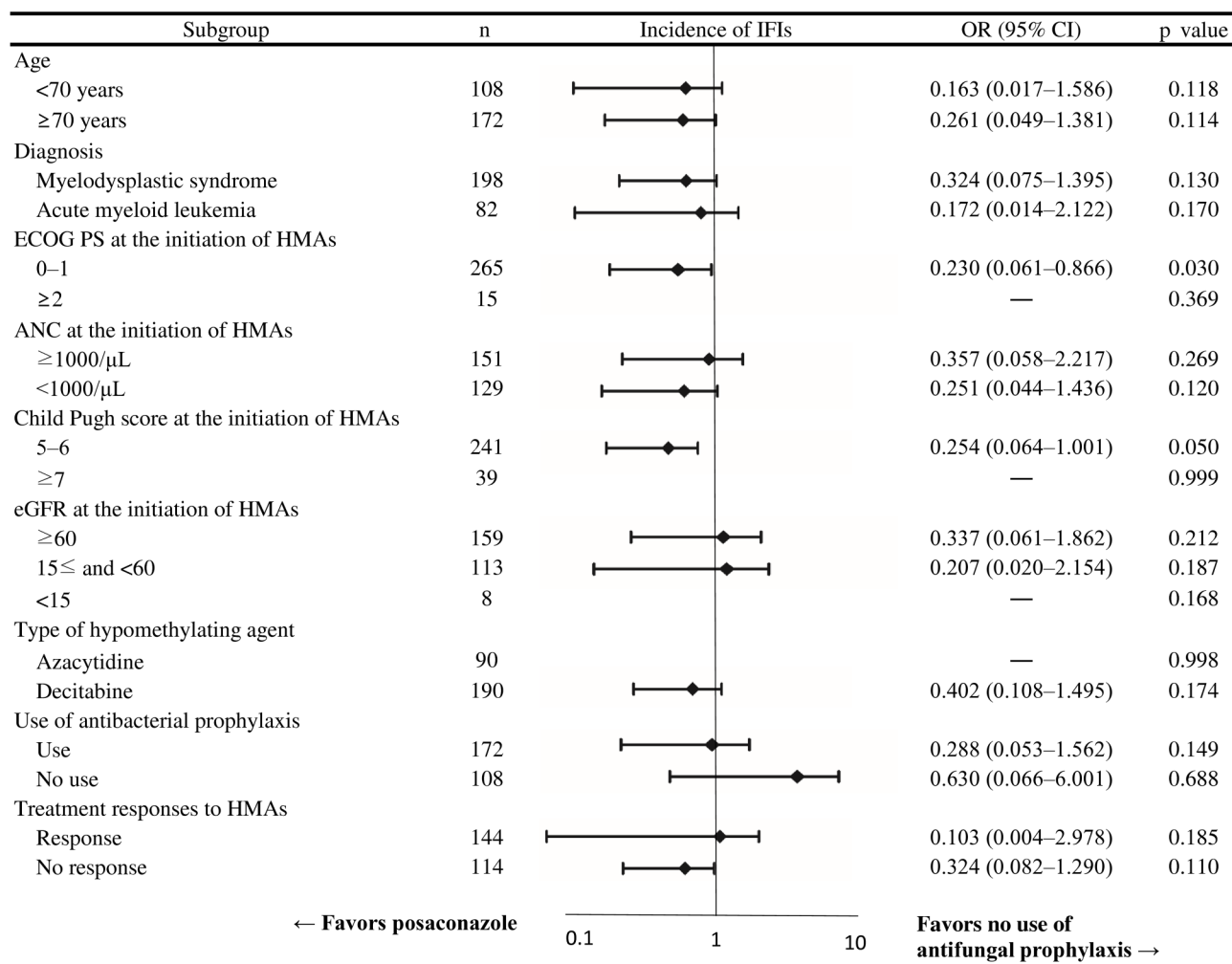
#### **Discussion**

In this study, the overall incidence of probable or proven IFIs in AML and MDS patients treated with HMAs as first-line chemotherapy was 7.9%:

11.5% in the no-use group and 3.8% in the posaconazole group. Among the IFIs, the overall incidence of invasive mold infection was 6.1%: 8.1% in the no-use group and 3.8% in the posaconazole group. Although the posaconazole group had a higher median age and proportion of patients with AML diagnosis and lower liver or kidney function at HMA initiation than the no-use group, the use of posaconazole as antifungal prophylaxis during HMA treatment significantly reduced the incidence of IFIs. In the subgroup analysis, this advantage of posaconazole appeared to be greater in patients with good ECOG PS or liver function at HMA initiation. Moreover, this study suggested other factors associated with a higher risk of IFIs, including reduced liver function at HMA initiation, the use of decitabine, and a poor response to HMAs.

Previous studies on the incidence of IFIs in patients treated with HMAs are summarized in Table 5.<sup>6,35–37</sup> In these studies, the incidence of IFIs ranged from 3.3% to 12.5%, which is consistent with the incidence range obtained in the present study (overall incidence: 7.9%). As most previous studies did not provide information on the use of antifungal prophylaxis or used antifungal prophylaxis in less than 30% of patients, it is difficult to directly compare the efficacy of posaconazole as antifungal prophylaxis. However, considering that the median value of IFI incidence in the previous studies was 8.8% (range: 3.3–12.5%), the 3.8% IFI incidence in the posaconazole group in the present study was considered relatively lower than that in the previous studies. In addition, in the present study, the overall incidence of invasive mold infections in the no-use group was 8.1% (12/148 patients), which exceeds the 8% threshold of the incidence of invasive mold infections set by the European Conference on Infections for the recommendation of antifungal prophylaxis.<sup>17</sup> Collectively, the results of the present study suggest that the use of antifungal prophylaxis in AML or MDS patients treated with HMAs is reasonable, and one of the options could be posaconazole.

In this study, the characteristics at the time of IFI diagnosis were further summarized to identify patients with a risk of IFIs (Table 3). First, the proportion of AML patients was 27.3% (no-use group: 23.5%, posaconazole group: 40%), suggesting that the risk of developing IFIs could be considered even in MDS patients treated with



**Figure 2.** Subgroup analysis of IFI incidence according to posaconazole use as antifungal prophylaxis. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation. ANC, absolute neutrophil count; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; eGFR, estimated glomerular filtration rate; HMA, hypomethylating agent; IFI, invasive fungal infection; OR, odds ratio.

HMAs. Second, most cases of IFIs in the present study occurred during the early cycles of HMA treatment (median: 3 cycles; range: 1–6 cycles), consistent with previously published results (Table 5). Third, in most cases, ANC was less than 1000/μL at the time of IFI diagnosis. In half of the cases with ANC more than 1000/μL, immature cells were observed in peripheral blood. Neutropenia or immature cells could indicate that the underlying disease was not controlled at the time of IFI diagnosis. In addition, the response to HMA treatment was independently associated with a risk of IFIs in the present study (Table 4). Based on these results, during the early cycles of

HMAs, especially until the confirmation of the improvement of cytopenia or response to treatment, the risk of IFIs may be high and the possibility of IFIs among causes of infections should be considered even in MDS patients treated with HMAs.

Posaconazole use as antifungal prophylaxis should be limited to well-accepted indications to avoid excessive cost, toxicity, and antimicrobial resistance.<sup>38</sup> To find the patient groups that benefit more from posaconazole, we conducted a subgroup analysis. In the present study, posaconazole as antifungal prophylaxis significantly decreased

**Table 5.** Previous studies on the incidence of IFIs in patients treated with HMAs.

Study	Subjects	No.	Use of antifungal prophylaxis	Category of IFIs	Incidence of IFIs	HMA cycle at IFIs	High-risk patients of IFIs
Merkel <i>et al.</i> <sup>35</sup>	AML or high-risk MDS patients treated with AZA	184	UK; 10.9% of patients were prescribed prophylactic antibiotics	UK	6/184 patients (3.3%)	UK; infections were more common during the first two cycles of HMAs	UK; the risk of infection was higher in patients with poor cytogenetics, PLT <20 × 10 <sup>9</sup> /L and ANC <0.5 × 10 <sup>9</sup> /L
Falantes <i>et al.</i> <sup>36</sup>	AML or MDS patients treated with AZA	64	No use	Six cases of invasive aspergillosis were probable; in the other two cases, no information was presented	8/64 patients (12.5%)	UK; febrile episodes mainly occurred during the first three cycles of HMAs	Patients who received prior IC had more febrile episodes; the incidence of infection reached a plateau after 4–6 cycles of AZA among patients with <10% blasts and less severe cytopenia
Pomares <i>et al.</i> <sup>6</sup>	AML or MDS patients treated with AZA	121	No use	One proven, one probable, and two possible	4/121 patients (3.3%)	All IFI cases occurred within the second cycle of HMAs	Only two IFIs occurred in the context of severe neutropenia (ANC <0.1 × 10 <sup>9</sup> /L)
Trubiano <i>et al.</i> <sup>37</sup>	AML or MDS patients treated with AZA	68	Antifungal prophylaxis in 30% of AZA cycles (268/884 cycles); no information was given on the number of patients	All cases of IFIs were classified as the proven category	6/68 patients (8.8%)	All IFI cases occurred within the second cycle of HMAs	UK; the risk of infection increased in patients with a very high risk of IPSS-R category
Kim <i>et al.</i> <sup>7</sup>	AML or MDS patients treated with AZA or DAC	203	Fluconazole prophylaxis was administered to 11% of patients; patients receiving mold-active antifungal prophylaxis were excluded	Proven, probable, and possible IFIs were three, four, and 13 cases, respectively	20/203 patients (9.6%)	The median number of cycles at the diagnosis of IFI was 3; only three cases occurred in the fifth cycle and beyond	The risk of IFIs increased in patients with therapy-related MDS or those who were neutropenic on the first day of the first cycle of HMA
The present study	AML or MDS patients treated with AZA or DAC	280	No use: 148 patients; posaconazole: 132 patients	The proven and probable IFIs were five and 17 cases, respectively	22/280 patients (7.9%)	The median number of cycles at the diagnosis of IFI was 3 (range: 1–6 cycles)	Posaconazole as antifungal prophylaxis led to a lower risk of IFIs; patients who had reduced liver function at HMA initiation, were treated with DAC therapy, and did not respond to HMA chemotherapy were independently associated with a higher risk of IFIs

AML, acute myeloid leukemia; ANC, absolute neutrophil count; AZA, azacytidine; DAC, decitabine; HMA, hypomethylating agent; IFI, invasive fungal infection; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; PLT, platelet; UK, unknown.

the incidence of IFIs in the groups with 0–1 ECOG PS and groups with 5–6 CPS at the initiation of HMAs. As posaconazole is an oral medication partly metabolized in the liver, it may lead to hepatotoxicity.<sup>39,40</sup> Thus, posaconazole might not be beneficial for patients with poor compliance or reduced liver function. However, there was no definitive evidence supporting these hypotheses. Rather, considering that the risk of invasive infection is generally high when the performance status is poor<sup>41–43</sup> and that delayed diagnosis and treatment are commonly caused by insufficient clinical symptoms in patients with reduced liver function,<sup>44,45</sup> antifungal prophylaxis alone may not lower the risk of IFIs in patients with poor ECOG PS or reduced liver function at HMA initiation. The finding that reduced liver function at HMA initiation was an independent risk factor for IFIs in the present study may also support this hypothesis. However, the results of the present study alone are not enough to identify a subgroup that will obtain greater benefit from posaconazole; therefore, further studies are warranted.

The present study was conducted retrospectively with a small number of patients. Thus, the results of this study alone are insufficient to conclude whether the use of posaconazole as antifungal prophylaxis is recommended in AML or MDS patients treated with HMAs or to suggest a subgroup that will obtain greater benefit from posaconazole. In addition, as posaconazole was not compared with fluconazole or itraconazole, which can be generally used as a prophylactic antifungal agent, it is necessary to verify the cost-effectiveness of posaconazole compared with other antifungal agents. Nevertheless, this study provided meaningful insights into the incidence and characteristics of IFIs as well as the efficacy of posaconazole as antifungal prophylaxis in AML or MDS patients treated with HMAs.

### Conclusion

In conclusion, in AML or MDS patients receiving treatment with HMAs, the risk of IFIs may be high during the early cycles of HMA treatment, especially when the underlying disease is not controlled. Posaconazole could be an option for antifungal prophylaxis in these patients, and further studies are needed to determine its appropriate indications.

### Author contributions

BSK and KWK designed the study. KWK analyzed the registry, summarized the results, and wrote the manuscript. KWK, BHL, MJJ, ESY, DSK, SRL, HJS, CWC, YP, and BSK performed patient management and maintained the registry. All authors approved the final version of the manuscript.

### Conflict of interest statement

The authors declare that there is no conflict of interest.

### Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

### Ethics approval

The study was approved by the institutional review board, and all data were fully anonymized (IRB No. 2020AN0211, 2020GR0237, and 2020AS0137).

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### Informed consent statement

Informed consent was waived by the institutional review board because of the retrospective nature of the study and because the analysis used anonymous clinical data.

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### Supplemental material

Supplemental material for this article is available online.

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