Supportive Care in Cancer (2019) 27:3613–3622
https://doi.org/10.1007/s00520-019-04720-5

ORIGINAL ARTICLE

High incidence of invasive fungal infection during acute myeloid leukemia treatment in a resource-limited country: clinical risk factors and treatment outcomes

Variya Nganthavee[1] · Woraphun Phutthasakda[1] · Kawita Atipas[1] · Sirikul Tanpong[1] · Teeramet Pungprasert[1] · Dhanach Dhirachaikulpanich[1] · Saran Krithin[1] · Supang Tanglitanon[1] · Warissara Jutidamronphang[1] · Weerapat Owattanapanich[2] · Methee Chayakulkeeree[3] · Ployploen Phikulsod[2]

Received: 7 September 2018 / Accepted: 26 February 2019 / Published online: 5 June 2019

Abstract

Background Invasive fungal infection (IFI) causes high morbidity and mortality during acute myeloid leukemia (AML) treatment. Interventions to prevent fungal infection, including air filtration systems and antifungal prophylaxis, may improve outcomes in this group of patients. However, they are expensive and therefore inapplicable in resource-limited countries. The benefit of antifungal therapy is also dependent on the local epidemiology. That led us to conduct the study to evaluate the characteristics and impact of IFI in AML patients without prophylaxis in our setting.

Methods Clinical data from patients with AML who have been treated with chemotherapy without antifungal prophylaxis were retrieved during a 5-year period at Thailand's hematology referral center. Incidence and risk factors of IFI and outcomes of patients were evaluated.

Results Among 292 chemotherapy courses, there were 65 (22.3%) episodes of IFI. Of those, 10 (15.4%) were proven, 19 (29.2%) were probable, and 36 (55.4%) were categorized as being possible IFI. Molds were the most commonly observed causative pathogens (93.1%). The incidence of probable/proven IFI was highest during first induction (20.5%), followed by second induction (6.1%), and consolidation (2.7%). A long duration of neutropenia, old age, and low serum albumin were the strongest predictors of IFI. Compared with patients who had no IFI, patients with probable/proven IFI had a longer length of hospital stay and higher in-hospital mortality. Patients with proven IFI had a significantly worse outcome at 1 year.

Conclusions These results suggest the change in health policy to implement IFI preventive measures to improve outcomes of AML treatment.

Keywords Invasive fungal infection · Acute myeloid leukemia · Asian · Limited-resource · Without prophylaxis

Introduction

Invasive fungal infection (IFI) is a major complication during acute myeloid leukemia (AML) treatment [1]. The high morbidity and mortality associated with IFI further complicate the outcomes of acute leukemia patients [2]. Therefore, many preventive measures, including antifungal chemoprophylaxis and air treatment, have been incorporated into the treatment protocol in order to decrease the rate of IFI and IFI-related mortality [3–7]. However, in countries with limited resources, such as Thailand, novel antifungal agents and specialized air filtration systems are often unaffordable. The use of antifungal drugs as a primary prophylaxis was not covered by Thailand's healthcare schemes during the study period, and only a small percentage of those patients could

Variya Nganthavee and Woraphun Phutthasakda contributed equally to this work.

✉ Ployploen Phikulsod
ployploen.phi@mahidol.ac.th

[1] Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[2] Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand

[3] Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

afford these drugs. Moreover, most hospitals in Thailand still lack isolation rooms that are appropriate for AML patients who received chemotherapy. Furthermore, isolation rooms that exist are usually not equipped with the appropriate air treatment system. Current incidence and outcome data are therefore needed to facilitate healthcare policy review. In Southeast Asia, there are limited data of studies of IFI during AML treatment in patients who did not receive antifungal prophylaxis and most studies focused on the incidence rate during the remission-induction period, not the consolidation phase [8, 9]. Accordingly, the aim of this study was to investigate the incidence, risk factors, and outcomes of IFI during the whole course of chemotherapy in newly diagnosed AML patients in a resource-limited country which antifungal prophylaxis was not routinely prescribed.

Patients and methods

Study design

This retrospective chart review was conducted at the Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, to investigate the incidence of IFI in adult patients (aged > 15 years) with newly diagnosed AML that were treated with curative-intent chemotherapy during 1 January 2012 to 31 December 2016. To enhance the homogeneity of the study population, we included only the first and second courses of remission-induction chemotherapy and courses of consolidation chemotherapy with high-dose cytarabine. Episodes with antifungal prophylaxis or preexisting antifungal treatment were excluded. We also excluded AML M3, relapsed AML patients, and chemotherapy courses with low-intensity regimen. Baseline demographic and clinical data, type of AML, and chemotherapy course were recorded. Hospitalization data were collected from medical records, including type of chemotherapy, type of ward and room, duration of neutropenia, white blood cell count, serum albumin level before treatment, IFI incidence, sites of fungal infection, and mortality rates.

Hospital and ward settings

Our center is a 2300-bed tertiary referral hospital that is located in Bangkok. It is the biggest hematology referral center in the country. Thailand is located in Southeast Asia, with a tropical climate and an average temperature range of 17.5 to 36.2 °C. Our chemotherapy wards were not equipped with a high-efficiency particulate arrestor (HEPA) filter or positive pressurization during the study period. Patients were treated in either isolated or shared rooms, and some of both types of rooms were air-conditioned.

Definition of IFI

Diagnosis of IFI was made using the revised 2008 consensus criteria of the European Organization for Research and Treatment of Cancer/Infectious Disease Group and the National Institute of Allergy and Infectious Diseases Mycosis Study Group (EORTC/MSG), which classifies IFI into possible, probable, or proven IFI [10]. IFI risk in this study was defined as the risk of developing probable or proven IFI.

Diagnosis of IFI

The standard surveillance and diagnostic procedures for IFI in patients with febrile neutropenia included once or twice weekly screening of serum galactomannan, high-resolution chest computed tomography (CT) after 72–96 h of persistent fever, chest symptoms, and/or abnormal chest X-ray. Bronchoscopy and/or bronchoalveolar lavage were ordered based on clinical findings and the discretion of the attending pulmonologist. Clinical symptoms combined with tissue biopsy, CT scan, and/or endoscopy were used to identify IFI at suspected sites.

Treatment of IFI

Amphotericin B (1–1.5 mg/kg/day) was given to febrile neutropenia patients with normal renal function as an empirical antifungal if fever persisted more than 72–96 h, or if fungal infection was clinically suspected. Micafungin was used as an alternative empirical treatment. The patient was then switched to an appropriate antifungal agent once the fungal pathogen was identified. Patients with suspected invasive aspergillosis (IPA) received voriconazole as a preemptive treatment that was continued at least 3 months or until resolution of the infection. Voriconazole was also given as a secondary prophylaxis in subsequent chemotherapy courses if there were strong suspicion or evidence of IPA.

Statistical analysis

All data analyses were performed using SPSS Statistics version 22 (SPSS, Inc., Chicago, IL, USA). Categorical data are given as number and percentage, and continuous data are reported as either mean ± standard deviation (SD) (normal distribution) or median and range (non-normal distribution). In univariate analysis, the independent samples *t* test was used for normally distributed variables, and the Mann-Whitney *U* test was used for non-normally distributed variables. Univariate analysis of categorical variables was performed using the chi-square test or Fisher's exact test. Variables with a *p* value less than 0.1 in univariate analysis

were entered into a backward stepwise logistic regression model to calculate the odds ratio (OR) and 95% confident interval (CI). Patient survival was analyzed using the Kaplan-Meier method, and a log-rank test was used to test for differences between survival curves. A two-sided p value of less than 0.05 was considered statistically significant.

Results

Characteristics of the study population

Two hundred ninety-two chemotherapy courses from 112 newly diagnosed AML patients without antifungal prophylaxis or treatment were included in our analysis. Course types comprised 145 remission-induction and 147 consolidation chemotherapy courses. Thirty-three of the included courses were second inductions. The mean age of patients was 44 ± 13 years (range 15–73), and 52% were female. Eleven patients had diabetes, and one patient had alcoholic cirrhosis. Six patients had central intravenous insertions due to hemodynamic instability, and no patient received parenteral nutrition during neutropenia. Demographic characteristics, underlying diseases, and type of AML compared between total patients and total courses of chemotherapy are given in Table 1. The vast majority of patients (96.5%) underwent remission-induction with 3 + 7 regimen (cytosine arabinoside (100–200 mg/m^2/day × 7 days) and idarubicin (12 mg/m^2/day × 3 days)). Over 50% (51.8%) of patients achieved complete remission after one cycle, 21.4% achieved complete remission after two cycles, and 26.8% of patients failed to achieve remission. The median number of consolidation cycles with high-dose cytarabine (HDAC) (6000 mg/m^2/day on days 1, 3, and 5) was 3. Sixty-three percent of consolidation courses (n = 93) were first or second cycles. The median duration of neutropenia in this cohort was 13 days. The highest duration of neutropenia was 24 days (range 8–63) during the first induction, followed by 21 days (range 0–54) for the second induction, and 8 days (range 0–22) for consolidation (p < 0.001). The average duration of neutropenia during the consolidation phase was significantly longer in the third cycle and fourth cycle than in the first and second cycles of HDAC (10 ± 4 days vs. 8 ± 3 days; p = 0.006).

Table 1 Demographic characteristics, underlying diseases, and type of AML compared between total patients and total courses of chemotherapy

Characteristics	Patients (N = 112)	Courses (N = 292)
Age (years), mean ± SD	44 ± 13	42 ± 13
Female gender, n (%)	59 (52.2%)	166 (56.8%)
Underlying diseases, n (%)		
Diabetes mellitus	10 (8.9%)	21 (7.1%)
Cirrhosis	1 (0.9%)	9 (0.3%)
Type of AML, n (%)		
M0	13 (11.6%)	13 (4.5%)
M1	8 (7.1%)	24 (8.2%)
M2	24 (21.4%)	67 (22.9%)
M4	35 (31.3%)	84 (28.8%)
M5	14 (12.5%)	39 (13.4%)
M6	2 (1.8%)	2 (0.7%)
M7	2 (1.8%)	7 (2.4%)
MDS, RAEB II	7 (6.3%)	19 (6.5%)
blastic phase CML	4 (3.6%)	5 (1.7%)
biphenotypic AML	1 (0.9%)	4 (1.4%)
No data	2 (1.8%)	6 (2.1%)

AML acute myeloid leukemia, *SD* standard deviation, *MDS* myelodysplastic syndromes, *RAEB II* refractory anemia with excess blasts, *CML* chronic myeloid leukemia

Incidence of IFI

Of the 292 course admissions, neutropenia occurred in 97.9% and 98.6% of induction and consolidation courses, respectively. The overall IFI rate was 22.3%. The incidence of all-category and probable/proven IFI during induction chemotherapy was 42.1% and 18.8%, respectively. The incidence of probable/proven IFI was highest in the first cycle of induction chemotherapy (20.5%), followed by the second cycle of induction (6.1%) and the consolidation phase (2.7%) (Table 2). Focusing on the patients receiving consolidation therapy, most IFI (4 probable/proven IFI cases) occurred during the first or second cycle of HDAC, with only one possible IFI case during the fourth cycle. The cumulative incidence of all-category and probable/proven IFI at day 100 after chemotherapy was 49.1% and 25.0%, respectively. There were 10 cases (3.4%) of proven IFI, 19 cases (6.5%) of probable IFI, and 36 cases (12.3%) of possible IFI. Mold infections were identified as the etiology of IFI in 27 of 29 cases (93.1%). The most often observed site of IFI was the lungs (93.8%). Six proven cases (5 aspergillosis and 1 penicilliosis) had involvement at more than one site, including the sinus, lung, and tonsil or skin and soft tissue. Two *Fusarium* infections were identified in this cohort, one involving the sinuses and the other involving the lungs. *Candida albicans candidemia* and soft tissue infection by *Candida tropicalis* were the only two identified yeast infections.

Clinical characteristics of and factors related to IFI

We further investigated for factors associated with probable or proven IFI. That analysis revealed a significantly higher rate of IFI in patients with older age (p < 0.001), underlying disease (p = 0.002), longer duration of neutropenia (p < 0.001), and receiving induction chemotherapy

Table 2 IFI rates, types of IFI, and sources of infection compared among chemotherapy phases

	Overall	1st induction	2nd induction	Consolidation
IFI rate, *n* (%)	65 (22.3%)	51 (46.4%)	9 (27.3%)	5 (3.4%)
IFI excluding possible IFI, *n* (%)	29 (9.9%)	23 (20.5%)	2 (6.1%)	4 (2.7%)
Type of IFI, *n*				
Proven				
Aspergillus flavus	4	3	0	1
Aspergillus fumigatus	1	1	0	0
Candida tropicalis	1	1	0	0
Candida albicans	1	1	0	0
Fusarium spp.	2	0	1	1
Penicillium spp.	1	0	1	0
Probable	19	17	0	2
Possible	36	28	7	1
Source of infection, *n*				
Disseminated (bloodstream or more than one site of infection)	7	5	1	1
Lung	56	45	7	4
Sinus	2	1	1	0

IFI invasive fungal infection

($p < 0.001$). The first cycle of induction chemotherapy and non-remission status were factors associated with IFI risk ($p = 0.036$ and $p = 0.005$, respectively). No significant association was observed between IFI and gender, ward type, serum albumin level at AML diagnosis, central venous catheter insertion, or number of lowest leukocyte count (Table 3). In multivariate analysis, neutropenia lasting longer than 10 days (OR 27, 95% CI 3.5–207.5; $p = 0.002$), age older than 45 years (OR 4.3, 95% CI 1.5–12.6; $p = 0.009$), and serum albumin level less than 3 g/dl at AML diagnosis (OR 4.6, 95% CI 1.3–15.6; $p = 0.016$) were identified as factors significantly correlated with higher risk of IFI.

Outcomes of AML patients with IFI

IFI was previously reported to be associated with poor survival [2, 11]. In the present study, we found a significantly higher in-hospital mortality rate among episodes with probable/proven IFI than among episodes without IFI (20.7% vs. 3.1%; $p = 0.001$). In contrast, no significant difference in mortality was observed between the possible infection and non-infection groups (2.8% vs. 3.1%; $p = 1.00$). Furthermore, patients with probable/proven IFI stayed in the hospital longer than patients without IFI (37 days vs. 25 days; $p < 0.001$) (Table 3). The survival probability at 100 days in patients with possible IFI, probable IFI, and proven IFI was 0.76 ($p = 0.673$), 0.74 ($p = 0.609$), and 0.54 ($p = 0.06$), respectively, in comparison with 0.89 in patients with no evidence of IFI (Fig. 1). Patients with probable/proven IFI had higher 100-day and 1-year mortality rates than patients with no IFI, but the difference was statistically significant only for the 1-year mortality rate compared between proven IFI and non-IFI patients (Figs. 1 and 2).

Discussion

IFI especially mold infections have impacts on AML treatment around the globe [12–16]. Several studies reported that novel antifungal therapies effectively reduce the rate of IFI during hematologic malignancy treatment [7] and primary prophylaxis with posaconazole was reported to reduce mortality in patients with febrile neutropenia [3]. Antifungal prophylaxis is recommended for patients undergoing aggressive chemotherapy. However, for the developing world, the economic burden of this method is high. In sub-Saharan Africa, antifungal agents active against invasive molds were inaccessible (as of 2012) [17]. The benefit of antifungal therapy needs to be evaluated according to the local epidemiology of IFI and cost-effectiveness. As a result, health policies not only in Thailand but also in many countries including Taiwan and China did not cover the use of primary prophylactic therapy [8, 9, 18–21]. The treatment facilities were also scarce of isolation rooms and air treatment systems. The new-generation drugs which proved to be more effective towards mold are not reimbursable and unaffordable to many patients, which therefore have been selectively given only to some patients [18].

To evaluate the baseline IFI rate in AML patients in our setting, we set forth to investigate the incidence of IFI

Table 3 Univariate analysis of patient characteristics compared between patients with probable or proven IFI and patients without IFI

Characteristics	Probable/ proven IFI	No IFI	*p* value
Age (years), mean ± SD	51 ± 10	41 ± 13	*< 0.001*
Age > 45 years, *n* (%)	24 (18.5%)	106 (81.5%)	*< 0.001*
Age < 45 years, *n* (%)	5 (4.0%)	121 (96.0%)	
Female gender, *n* (%)	15 (9.9%)	136 (90.1%)	0.4
Male gender, *n* (%)	14 (13.3%)	91 (86.7%)	
No underlying disease, *n* (%)	22 (9.3%)	215 (90.7%)	*0.002*
Underlying disease, *n* (%)	7 (36.8%)	12 (63.2%)	
Induction, *n* (%)	25 (22.7%)	85 (77.3%)	*< 0.001*
Consolidation, *n* (%)	4 (2.7%)	142 (97.3%)	
1st induction, *n* (%)	23 (27.4%)	61 (72.6%)	*0.036*
2nd induction, *n* (%)	2 (7.7%)	24 (92.3%)	
Remission, *n* (%)	8 (12.9%)	54 (87.1%)	*0.005*
No remission, *n* (%)	17 (35.4%)	31 (64.6%)	
Air-conditioned ward, *n* (%)	16 (10.8%)	132 (89.2%)	0.76
Non-air-conditioned ward, *n* (%)	13 (12.0%)	95 (88.0%)	
One-bed unit, *n* (%)	2 (14.3%)	12 (85.7%)	0.871
Four-bed unit, *n* (%)	3 (13.6%)	19 (86.4%)	
22-bed unit, *n* (%)	24 (10.9%)	196 (89.1%)	
Central venous catheter insertion, *n* (%)			0.139
Yes	2 (33.3%)	4 (66.7%)	
No	27 (10.8%)	223 (89.2%)	
Duration of neutropenia (days), median (range)	28 (6–54)	9 (0–50)	*< 0.001*
Neutropenia > 10 days, *n* (%)	25 (20.0%)	100 (80.0%)	*< 0.001*
Neutropenia ≤ 10 days, *n* (%)	1 (0.8%)	120 (99.2%)	
Lowest ANC (cells/μl), median (range)	0 (0–50)	0 (0–350)	0.094
Albumin level at AML diagnosis (mg/dl), mean ± SD	3.6 ± 0.6	3.8 ± 0.8	0.129
Serum albumin ≤3 mg/dl, *n* (%)	6 (26.1%)	14 (73.9%)	*0.035*
Serum albumin >3 mg/dl, *n* (%)	23 (10.1%)	205 (89.9%)	
Hospital length of stay (days), mean ± SD	37 ± 10	25 ± 10	*< 0.001*
In-hospital mortality, *n* (%)	6 (20.7%)	7 (3.1%)	*0.001*

A *p* value<0.05 indicates statistical significance

IFI invasive fungal infection, *SD* standard deviation, *ANC* absolute neutrophil count, *AML* acute myeloid leukemia

following chemotherapy courses that were administered to our patients without primary antifungal prophylaxis or protective environment. In our previous study of patients with chemotherapy-induced febrile neutropenia (CIN), we found that patients with AML had the highest incidence of IFI during CIN episodes [22]. In the present study, we confirmed a high incidence of IFI in AML patients, with molds being the overwhelmingly most often observed causative pathogens. The highest infection rate occurred during the first cycle of AML induction. The overall IFI rate during the remission-induction phase was 42.1%, which is comparable with previous reports from studies conducted in Western countries among AML patients that did not receive primary prophylaxis [23, 24]. A recent study from the USA found that a high rate of IFI as a result of clinical practices that did not comply with primary prophylaxis can be reduced to 0% after implementing an antifungal program [25]. A literature review for studies that investigated IFI in AML is shown in Table 4. These findings indicate that a high rate of IFI was found in AML patients who did not receive adequate prevention regardless of the geographic location or climate and that prevention methods should be emphasized. Itraconazole is an attractive option to prevent mold infection in low- and middle-income countries for its acceptable toxicity and price [28]. Inconsistent efficacy due to drug bioavailability may be solved by trough level guidance [29]. Nevertheless, the previous report showed that only itraconazole oral suspension, not capsule, exhibited effectiveness in fungal prophylaxis in neutropenic patients [30]. In several developing countries, including Thailand, itraconazole oral suspension is costly and not included in all medical reimbursement scheme. Moreover, studies from middle-income countries (Thailand, Brazil, and Mexico) using a cost-estimation model show that posaconazole is cost-effective for fungal prevention [31–33]. More studies should be done to verify the real cost-benefit of the drug in each country and we hope the data will convince policy makers to improve the healthcare policy.

In our review, we found data of IFI according to the EORTC diagnostic criteria from low-income countries are underrepresented, possibly due to the diagnostic challenge both technically and financially. The current guideline for pulmonary fungal infection diagnosis requires accessibility to serum galactomannan test, CT scan, and/or bronchoscopy. In our previous study and Gheith et al.'s from Tunisia, CT scan was not always readily available. Some critical patients with suspected IPA died before getting it done and this might have resulted in an underestimation incidence [15, 22]. In this study, the situation was better. The suspected IPA case has been prioritized as an urgent need for CT scan. The prioritization protocol, the establishment of an antifungal stewardship program, and an expansion of CT machine number led to a shorter wait time for CT scan and regular serum galactomannan test. However, in some patients whose symptoms had resolved and been defined non-suspected IPA by ID specialist, the scheduled CT scan would be canceled. In this retrospective study, not all the patients had CT scan result, but there were no suspect IPA cases who did not get a CT scan. A bronchoscopy with lung biopsy is very risky in leukemia patients with pancytopenia especially those who are critically ill. This procedure should be done in ICU or

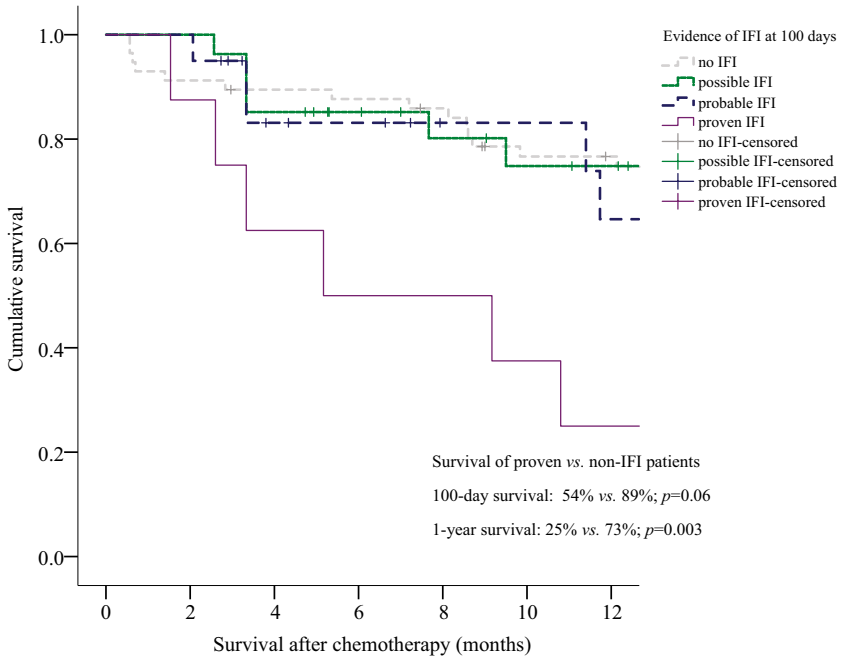

Fig. 1 Survival of patients with different categories of invasive fungal infection (IFI)

operating room with adequate monitoring and blood component replacement. Hence, it added up the cost and risk for patients. In our study, only a few cases are deemed suitable or worth the risk of the procedure to get a definite diagnosis. Tests that are less invasive and less expensive with high sensitivity are ideal. Molecular testing, such as PCR assays, has emerged as an alternative method for the diagnosis and identification of causative pathogen of IFI [34–36]. In addition, real-time qualitative PCR allows quantification of a specific pathogen and pan-fungal PCR using the melting curve analysis or probe detection allows multiple pathogen identification. These new molecular techniques with high sensitivity and specificity have been reported as rapid, reliable, and cost-effective methods to identify fungal infection [37–40]. If the methods are able to be established in-house and replace the current cumbersome diagnostic strategy, it may reduce the cost and improve accessibility to IFI diagnosis in resource-limited countries. Therefore, with the help

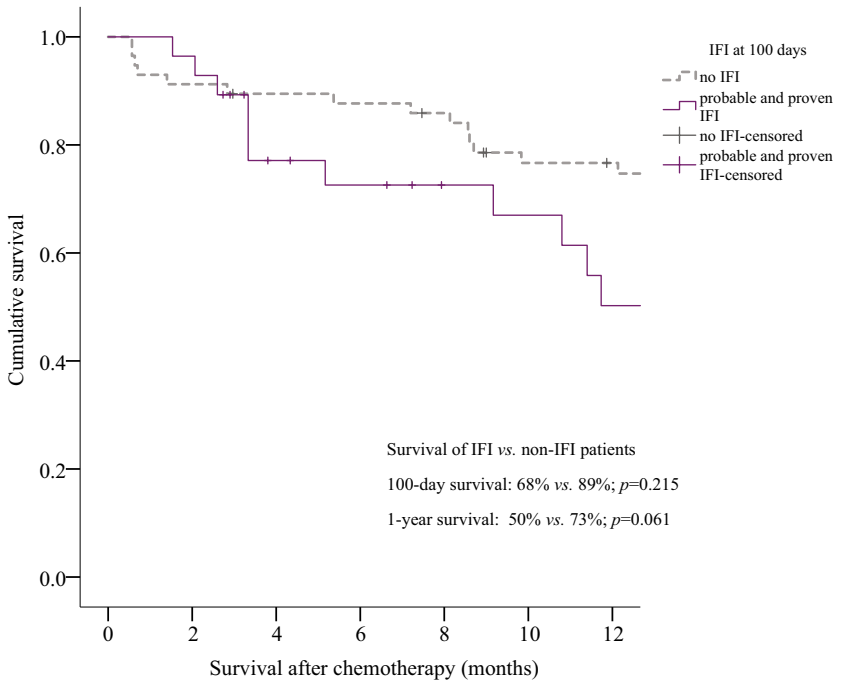

Fig. 2 Survival of invasive fungal infection (IFI) patients vs. non-IFI patients

Table 4 Literature review of studies that investigated the incidence IFI among patients with AML [8, 9, 13, 15, 18–21, 23–27]

Researcher (country)	Total, *n*	Year	Type of treatment	HEPA filter	Antifungal prophylaxis	All-cat. IFI	Probable/proven IFI
Neofytos D et al. (USA)	254	2005–2010	Induction	NA	7.9% (flcz/vrcz/casp)	48.4%	7.9%
Lien MY et al. (Taiwan)	105	2008–2015	Induction	32%	None	33.0%	20%
Tang JL et al. (Taiwan)	298	2004–2009	Induction	None	None	34.6%	10.7%
Korula A et al. (India)	222	2008–2013	Induction	None	98.2% (vrcz/pscz/amB)	38.8%	3.2% (proven only)
Gheith S et al. (Tunisia)	55	2009–2011	AML with FN	None	None	14.5%	16.4%
Morris A et al. (USA)	79	2011–2014	Induction	NA	None	NA	19.7%
Xu XH et al. (China)	166	2012–2016	Induction	None	70.6% (flcz/itcz/vrcz/pscz)	5.9% vs 22.9%	NA
Our cohort	133	2012–2016	Induction	None	None	42.1%	18.8%
Hammond SP et al. (USA)	175	2004–2006	First 100 days	NA	None	NA	12.0%
Nucci M et al. (Brazil)	230	2007–2009	1 year	None	56.1% (flcz/itcz/vrcz)	NA	20.1%
Chen C et al. (Taiwan)	643	2008–2013	1 year	NA	None (mcfg during SCT)	22.4%	9.3%
Kumar J et al. (India)	20	2013–2014	Induction/consolidation	NA	None	20%	NA
Our cohort	112	2012–2016	First 100 days	None	None	49.1%	25.0%
Lewis G et al. (USA)	76	2000–2008	Consolidation	None	58% (flcz)	NA	2.6%
Wang L et al. (China)	130	NA	Consolidation	NA	11.5% (NA)	6.2%	3.1%
Our cohort	147	2012–2016	Consolidation	None	None	3.5%	2.7%

IFI invasive fungal infection, *AML* acute myeloid leukemia, *HEPA* high-efficiency particulate arrestor, *All-cat.* all-category, *NA* not available, *FN* febrile neutropenia, *flcz* fluconazole, *itcz* itraconazole, *vrcz* voriconazole, *pscz* posaconazole, *ampB* amphotericin B, *mcfg* micafungin

of new technology, the proposed criteria that depend more on clinical characteristics and allow chest X-ray to be used instead of CT scan would be of benefit for patients in low-income countries and those who are critically ill [41].

The incidence of IFI during the consolidation phase of AML treatment has been less well studied; however, the inclusion of data from this phase of treatment is essential for a cost-risk-benefit evaluation of prophylaxis therapy. Similar to previous reports, our study found a low rate of IFI among consolidation patients, and that rate was significantly lower than the infection rate among induction patients [26, 27]. The variations among reported IFI incidence rates are likely due to differences in the study population and type of treatment. Predictive factors for IFI in this study included the duration of neutropenia greater than 10 days, age greater than 45 years, and serum albumin level less than 3 mg/dl at AML diagnosis. Age and neutropenic period were identified as risk factors for IFI in several studies [42–44]. Our data showed that the highest duration of neutropenia occurred during remission-induction chemotherapy courses, especially the first cycle. This may explain the high IFI rate during the induction period. Hypoalbuminemia could reflect disease severity and a poor nutritional state. Serum albumin and nutrition status were reported as factors that increase the risk of infection and that worsen AML treatment outcome [9, 45]. Similarly, we found the low albumin level (< 3 mg/dl) to be a significant risk factor for IFI in this study. This knowledge may alert clinicians to closely monitor and give antifungal chemoprophylaxis to this high-risk group. IFI caused high mortality (19–50%) and worsened long-term survival in AML patients [1, 2, 23]. In the present study, we found an in-hospital mortality rate in the probable/proven IFI group of 20.7%. This rate is lower than the 49% IFI mortality rate reported in our previous study [22]. This correlates with the reported observation that treatment outcomes of invasive fungal infections have improved over time, and this improvement may be associated with the use of new antifungal drugs [12]. We also found significantly worse short-term outcomes in patients with IFI compared with those without IFI, including longer hospital length of stay, higher in-hospital mortality, and higher proportion of patients that failed to achieve remission after induction chemotherapy. However, there was no significant difference in longer term survival at 100 days and 1 year between patients with and without IFI. The main limitation of our study is its retrospective nature.

Conclusion

The high incidence of IFI during AML treatment without adequate fungal prevention was demonstrated in our study. The highest incidence occurred during remission-induction chemotherapy courses, with the lowest incidence occurring during consolidation therapy. Low serum albumin level, age older than 45 years, and neutropenic period longer than

10 days were identified as predictive factors for IFI. The incidence rates revealed by this study are similar to those reported from other countries in non-protective setting, regardless of regions, and climatic conditions. IFI was also found to worsen the short-term outcomes of AML patients. Taken together, these results suggest the adoption and implementation of infection prevention protocols to prevent IFI and to improve outcomes for patients with AML.

Funding information This research was supported by Siriraj Cancer Foundation (Grant number 088/2558). None of the authors has financial relationship with the foundation.

Compliance with ethical standards

All authors declare no personal or professional conflicts of interest and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. 212/2016). The requirement for written informed consent was waived for this study due to its anonymous retrospective design.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Pagano L, Caira M, Picardi M, Candoni A, Melillo L, Fianchi L, Offidani M, Nosari A (2007) Invasive aspergillosis in patients with acute leukemia: update on morbidity and mortality--SEIFEM-C report. Clin Infect Dis 44(11):1524–1525. https://doi.org/10.1086/517849
2. Even C, Bastuji-Garin S, Hicheri Y, Pautas C, Botterel F, Maury S, Cabanne L, Bretagne S, Cordonnier C (2011) Impact of invasive fungal disease on the chemotherapy schedule and event-free survival in acute leukemia patients who survived fungal disease: a case-control study. Haematologica 96(2):337–341. https://doi.org/10.3324/haematol.2010.030825
3. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D (2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 356(4):348–359. https://doi.org/10.1056/NEJMoa061094
4. Ananda-Rajah MR, Grigg A, Downey MT, Bajel A, Spelman T, Cheng A, Thursky KT, Vincent J, Slavin MA (2012) Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. Haematologica. 97(3):459–463. https://doi.org/10.3324/haematol.2011.051995
5. Hahn T, Cummings KM, Michalek AM, Lipman BJ, Segal BH, McCarthy PL Jr (2002) Efficacy of high-efficiency particulate air filtration in preventing aspergillosis in immunocompromised patients with hematologic malignancies. Infect Control Hosp Epidemiol 23(9):525–531. https://doi.org/10.1086/502101
6. Eckmanns T, Ruden H, Gastmeier P (2006) The influence of high-efficiency particulate air filtration on mortality and fungal infection among highly immunosuppressed patients: a systematic review. J Infect Dis 193(10):1408–1418. https://doi.org/10.1086/503435
7. Halpern AB, Lyman GH, Walsh TJ, Kontoyiannis DP, Walter RB (2015) Primary antifungal prophylaxis during curative-intent therapy for acute myeloid leukemia. Blood. 126(26):2790–2797. https://doi.org/10.1182/blood-2015-07-627323
8. Tang JL, Kung HC, Lei WC, Yao M, Wu UI, Hsu SC, Lin CT, Li CC, Wu SJ, Hou HA, Chou WC, Huang SY, Tsay W, Chen YC, Chen YC, Chang SC, Ko BS, Tien HF (2015) High incidences of invasive fungal infections in acute myeloid leukemia patients receiving induction chemotherapy without systemic antifungal prophylaxis: a prospective observational study in Taiwan. PLoS One 10(6):e0128410. https://doi.org/10.1371/journal.pone.0128410
9. Lien MY, Chou CH, Lin CC, Bai LY, Chiu CF, Yeh SP, Ho MW (2018) Epidemiology and risk factors for invasive fungal infections during induction chemotherapy for newly diagnosed acute myeloid leukemia: a retrospective cohort study. PLoS One 13(6):e0197851. https://doi.org/10.1371/journal.pone.0197851
10. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T et al (2008) Revised definitions of invasive fungal disease from 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 (EORTC/MSG) Consensus Group. Clin Infect Dis 46(12):1813–1821. https://doi.org/10.1086/588660
11. Girmenia C, Micozzi A, Piciocchi A, Gentile G, Di Caprio L, Nasso D et al (2014) Invasive fungal diseases during first induction chemotherapy affect complete remission achievement and long-term survival of patients with acute myeloid leukemia. Leuk Res 38(4):469–474. https://doi.org/10.1016/j.leukres.2014.01.007
12. Dragonetti G, Criscuolo M, Fianchi L, Pagano L (2017) Invasive aspergillosis in acute myeloid leukemia: are we making progress in reducing mortality? Med Mycol 55(1):82–86. https://doi.org/10.1093/mmy/myw114
13. Korula A, Abraham A, Abubacker FN, Viswabandya A, Lakshmi KM, Abraham OC, Rupali P, Varghese GM, Michael JS, Srivastava A, Mathews V, George B (2017) Invasive fungal infection following chemotherapy for acute myeloid leukaemia-experience from a developing country. Mycoses. 60(10):686–691. https://doi.org/10.1111/myc.12646
14. Pagano L, Caira M, Candoni A, Offidani M, Fianchi L, Martino B, Pastore D, Picardi M, Bonini A, Chierichini A, Fanci R, Caramatti C, Invernizzi R, Mattei D, Mitra ME, Melillo L, Aversa F, van Lint M, Falcucci P, Valentini CG, Girmenia C, Nosari A (2006) The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica. 91(8):1068–1075
15. Gheith S, Saghrouni F, Bannour W, Ben Youssef Y, Khelif A, Normand AC, Ben Said M, Piarroux R, Njah M, Ranque S (2014) Characteristics of invasive aspergillosis in neutropenic haematology patients (Sousse, Tunisia). Mycopathologia. 177(5–6):281–289. https://doi.org/10.1007/s11046-014-9742-8
16. Hsu LY, Lee DG, Yeh SP, Bhurani D, Khanh BQ, Low CY et al (2015) Epidemiology of invasive fungal diseases among patients with haematological disorders in the Asia-Pacific: a prospective observational study. Clin Microbiol Infect 21(6):594 e7–594 11. https://doi.org/10.1016/j.cmi.2015.02.019
17. Gopal S, Wood WA, Lee SJ, Shea TC, Naresh KN, Kazembe PN, Casper C, Hesseling PB, Mitsuyasu RT (2012) Meeting the challenge of hematologic malignancies in sub-Saharan Africa. Blood. 119(22):5078–5087. https://doi.org/10.1182/blood-2012-02-387092
18. Xu XH, Zhang L, Cao XX, Li J, Zhang W, Zhu TN, Cai HC, Chen M, Han X, Yang C, Han B, Zhang Y, Zhuang JL, Zhou DB, Duan MH (2017) Evaluation of the implementation rate of primary

antifungal prophylaxis and the prognosis of invasive fungal disease in acute leukemia patients in China. J Infect Chemother 23(6):360–367. https://doi.org/10.1016/j.jiac.2017.02.011
19. Chen CY, Sheng WH, Tien FM, Lee PC, Huang SY, Tang JL, Tsay W, Tien HF, Hsueh PR (2018) Clinical characteristics and treatment outcomes of pulmonary invasive fungal infection among adult patients with hematological malignancy in a medical centre in Taiwan, 2008–2013. J Microbiol Immunol Infect. https://doi.org/10.1016/j.jmii.2018.01.002
20. Nucci M, Garnica M, Gloria AB, Lehugeur DS, Dias VC, Palma LC et al (2013) Invasive fungal diseases in haematopoietic cell transplant recipients and in patients with acute myeloid leukaemia or myelodysplasia in Brazil. Clin Microbiol Infect 19(8):745–751. https://doi.org/10.1111/1469-0691.12002
21. Kumar J, Singh A, Seth R, Xess I, Jana M, Kabra SK (2018) Prevalence and predictors of invasive fungal infections in children with persistent febrile neutropenia treated for acute leukemia - a prospective study. Indian J Pediatr 85(12):1090–1095. https://doi.org/10.1007/s12098-018-2722-0
22. Phikulsod P, Suwannawiboon B, Chayakulkeeree M (2017) Invasive fungal infection among febrile patients with chemotherapy-induced neutropenia in Thailand. Southeast Asian J Trop Med Public Health 48(1):159–169
23. Neofytos D, Lu K, Hatfield-Seung A, Blackford A, Marr KA, Treadway S, Ostrander D, Nussenblatt V, Karp J (2013) Epidemiology, outcomes, and risk factors of invasive fungal infections in adult patients with acute myelogenous leukemia after induction chemotherapy. Diagn Microbiol Infect Dis 75(2):144–149. https://doi.org/10.1016/j.diagmicrobio.2012.10.001
24. Hammond SP, Marty FM, Bryar JM, DeAngelo DJ, Baden LR (2010) Invasive fungal disease in patients treated for newly diagnosed acute leukemia. Am J Hematol 85(9):695–699. https://doi.org/10.1002/ajh.21776
25. Morris AL, Naeem M, Murray T, Sen J, Thomas T, Daniels E et al. (2018) Establishing an antifungal program to reduce invasive fungal infections in patients with acute myeloid leukemia receiving induction and reinduction chemotherapy. J Oncol Pract :JOP1800307. https://doi.org/10.1200/JOP.18.00307
26. Lewis G, Hall P, Eisa N, Deremer D, Dobbins R, El-Geneidy M et al (2010) Acute myelogenous leukemia patients are at low risk for invasive fungal infections after high-dose cytarabine consolidations and thus do not require prophylaxis. Acta Haematol 124(4):206–213. https://doi.org/10.1159/000321504
27. Wang L, Hu J, Sun Y, Huang H, Chen J, Li J, Ma J, Li J, Liang Y, Wang J, Li Y, Yu K, Hu J, Jin J, Wang C, Wu D, Xiao Y, Huang X Does high-dose cytarabine cause more fungal infection in patients with acute myeloid leukemia undergoing consolidation therapy: a multicenter, prospective, observational study in China. Medicine (Baltimore) 2016;95(4):e2560. doi:https://doi.org/10.1097/MD.0000000000002560
28. Keighley CL, Manii P, Larsen SR, van Hal S (2017) Clinical effectiveness of itraconazole as antifungal prophylaxis in AML patients undergoing intensive chemotherapy in the modern era. Eur J Clin Microbiol Infect Dis 36(2):213–217. https://doi.org/10.1007/s10096-016-2780-z
29. Zhang J, Liu Y, Nie X, Yu Y, Gu J, Zhao L (2018) Trough concentration of itraconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. Infect Drug Resist 11:1283–1297. https://doi.org/10.2147/IDR.S170706
30. Glasmacher A, Prentice A, Gorschluter M, Engelhart S, Hahn C, Djulbegovic B et al (2003) Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients. J Clin Oncol 21(24):4615–4626. https://doi.org/10.1200/JCO.2003.04.052
31. Rely K, Alexandre PK, Escudero GS (2011) Cost effectiveness of posaconazole versus fluconazole/itraconazole in the prophylactic treatment of invasive fungal infections in Mexico. Value Health 14(5 Suppl 1):S39–S42. https://doi.org/10.1016/j.jval.2011.05.032
32. Tuon FFB, Lino Florencio K, da Cunha CA, Lopes Rocha JL (2018) Cost-effectiveness of posaconazole in private and public Brazilian hospitals. Rev Iberoam Micol 35(2):63–67. https://doi.org/10.1016/j.riam.2017.09.006
33. Junjarunee S, Numuang K, Lerdlitruangsin S, Itzler R (2014) Cost-effectiveness of posaconazole versus fluconazole or itraconazole in the prophylaxis of invasive fungal infections among neutropenic patients in Thailand. Value Health 17(7):A806. https://doi.org/10.1016/j.jval.2014.08.522
34. White PL, Wingard JR, Bretagne S, Loffler J, Patterson TF, Slavin MA et al (2015) Aspergillus polymerase chain reaction: systematic review of evidence for clinical use in comparison with antigen testing. Clin Infect Dis 61(8):1293–1303. https://doi.org/10.1093/cid/civ507
35. Jordanides NE, Allan EK, McLintock LA, Copland M, Devaney M, Stewart K et al (2005) A prospective study of real-time panfungal PCR for the early diagnosis of invasive fungal infection in haemato-oncology patients. Bone Marrow Transplant 35(4):389–395. https://doi.org/10.1038/sj.bmt.1704768
36. Kourkoumpetis TK, Fuchs BB, Coleman JJ, Desalermos A, Mylonakis E (2012) Polymerase chain reaction-based assays for the diagnosis of invasive fungal infections. Clin Infect Dis 54(9):1322–1331. https://doi.org/10.1093/cid/cis132
37. Valero C, de la Cruz-Villar L, Zaragoza O, Buitrago MJ (2016) New panfungal real-time PCR assay for diagnosis of invasive fungal infections. J Clin Microbiol 54(12):2910–2918. https://doi.org/10.1128/JCM.01580-16
38. Alonso M, Escribano P, Guinea J, Recio S, Simon A, Pelaez T, Bouza E, Garcia de Viedma D (2012) Rapid detection and identification of Aspergillus from lower respiratory tract specimens by use of a combined probe-high-resolution melting analysis. J Clin Microbiol 50(10):3238–3243. https://doi.org/10.1128/JCM.00176-12
39. Didehdar M, Khansarinejad B, Amirrajab N, Shokohi T (2016) Development of a high-resolution melting analysis assay for rapid and high-throughput identification of clinically important dermatophyte species. Mycoses. 59(7):442–449. https://doi.org/10.1111/myc.12492
40. Arancia S, Sandini S, De Bernardis F, Fortini D (2011) Rapid, simple, and low-cost identification of Candida species using high-resolution melting analysis. Diagn Microbiol Infect Dis 69(3):283–285. https://doi.org/10.1016/j.diagmicrobio.2010.10.003
41. Blot SI, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselaers N et al (2012) A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 186(1):56–64. https://doi.org/10.1164/rccm.201111-1978OC
42. Nucci M, Anaissie E (2014) How we treat invasive fungal diseases in patients with acute leukemia: the importance of an individualized approach. Blood. 124(26):3858–3869. https://doi.org/10.1182/blood-2014-04-516211
43. Caira M, Candoni A, Verga L, Busca A, Delia M, Nosari A, Caramatti C, Castagnola C, Cattaneo C, Fanci R, Chierichini A, Melillo L, Mitra ME, Picardi M, Potenza L, Salutari P, Vianelli N, Facchini L, Cesarini M, de Paolis MR, di Blasi R, Farina F, Venditti A, Ferrari A, Garzia M, Gasbarrino C, Invernizzi R, Lessi F, Manna A, Martino B, Nadali G, Offidani M, Paris L, Pavone V, Rossi G, Spadea A, Specchia G, Trecarichi EM, Vacca A, Cesaro S, Perriello V, Aversa F, Tumbarello M, Pagano L, on behalf of the SEIFEM Group (Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne) (2015) Pre-chemotherapy risk factors for invasive fungal diseases: prospective analysis of 1,192 patients with newly diagnosed

acute myeloid leukemia (SEIFEM 2010-a multicenter study). Haematologica. 100(2):284–292. https://doi.org/10.3324/haematol.2014.113399

44. Hoenigl M, Strenger V, Buzina W, Valentin T, Koidl C, Wolfler A, Seeber K, Valentin A, Strohmeier AT, Zollner-Schwetz I, Raggam RB, Urban C, Lass-Florl C, Linkesch W, Krause R (2012) European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) host factors and invasive fungal infections in patients with haematological malignancies. J Antimicrob Chemother 67(8):2029–2033. https://doi.org/10.1093/jac/dks155
45. Eriksson KM, Cederholm T, Palmblad JE (1998) Nutrition and acute leukemia in adults: relation between nutritional status and infectious complications during remission induction. Cancer. 82(6):1071–1077