INVASIVE FUNGAL INFECTION AMONG FEBRILE PATIENTS WITH CHEMOTHERAPY-INDUCED NEUTROPENIA IN THAILAND

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Abstract. Invasive fungal infections (IFI) can cause serious morbidity and mortality among febrile patients with chemotherapy-induced neutropenia (CIN). In order to evaluate the incidence, treatment outcome and factors associated with IFI in this patient population in Thailand, we retrospectively reviewed the medical record of patients admitted to Siriraj Hospital from January 2008 to June 2010. Criteria used to diagnosed IFI were those of 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 2008 criteria. Three hundred ten episodes of chemotherapy-induced neutropenia occurred in 233 patients. IFI were found in 37 episodes (12%) and occurred only in patients who received chemotherapy for hematological malignancies. The incidence of IFI among patients with hematologic malignancies was 14%. Most commonly occurred in AML patients (17%). Patients who received aggressive induction chemotherapy regimens for AML had the highest incidence of IFI (20.5%). Of the 37 episodes, 12 were candidiasis, 5 were aspergillosis, 1 was zygomycosis, 1 was fusariosis, 10 were probable and 9 were possible IFI. The IFI-related mortality was 35%. The clinical factor associated with IFI was a temperature > 39 °C during febrile neutropenia. A higher mortality rate was seen in patients aged > 40 years and those with a serum albumin level < 3 g/dl.

Keywords: febrile neutropenia, invasive fungal infection, risk factor, incidence, chemotherapy

INTRODUCTION

Chemotherapy-induced neutropenia (CIN) is a complication of chemotherapy. This increases the risk of morbidity and mortality. Use of aggressive chemotherapy and broad-spectrum antibiotics has increased the incidence of IFI in this group of patients (Cornely *et al*, 2011). The overall mortality rate of IFI ranges from 10-59% (Pagano *et al*, 2010; Cornely *et al*, 2011). Because of high mortality, prophylactic antifungal therapy has been used to prevent IFI. The epidemiology of IFI has changed in western countries, with an increasing incidence of non-*Candida* species causing IFI due to the use of prophylactic antifungal therapy (Martino and Subira, 2002; Pagano *et al*, 2006; Lass-Florl, 2009; Cornely *et al*,

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2011; Ananda-Rajah *et al*, 2012).

However, the incidence of IFI varies by geographical factors, host factors, ward facilities and preventive measures. Local epidemiological data are required to guide management. However, data regarding the incidence of IFI in Southeast Asia are limited. This study aimed to determine the incidence, etiology of and factors associated with IFI at a tertiary care hospital in Bangkok, Thailand. This data can inform IFI prevention and treatment strategies in this study population.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of febrile patients with CIN admitted to Siriraj Hospital, a tertiary care teaching hospital in Bangkok, Thailand from January 2008 to June 2010. In our institution, there are two oncology wards with 22 beds each and no hepa-filters or isolation rooms. Patients receiving chemotherapy regimens at high risk for causing CIN are admitted to the oncology ward until the neutropenia resolves. Chemotherapy regimens at lower risk for causing CIN are administered on an out-patient or short stay inpatient basis. No institutional chemoprophylaxis policies for fungal infection were implemented during this study. Prophylactic antifungal drugs were given based on the physician's and patients' decisions. A serum galactomannan level (Marr *et al*, 2004) was measured twice a week in each patient. Patients who had serum galactomannan index higher than 0.5 or an abnormal chest radiograph, had a chest CT scan. Antifungal therapy, if indicated, was based on the suspected organism: deoxycholate amphotericin B for initial empirical treatment and voriconazole for suspected aspergillosis cases.

Factors associated with IFI and worse outcomes were studied. Data recorded consist of patient age, sex, body weight, height, body mass index, underlying diseases, comorbid diseases, chemotherapy regimen, laboratory results (*ie*, complete blood count, serum albumin level, liver function test, serum creatinine level), duration of neutropenia, peak temperature, clinical signs and symptoms at time of fungal infection diagnosis, radiographic data, serum galactomannan level, histological, microbiological and clinical criteria for IFI, treatment and outcome. This study was approved by Siriraj Hospital ethics committee. Written informed consent from patients were exempted for a retrospective study by the ethics committee.

Definition

Neutropenia was defined as an absolute neutrophil count < 500 cells/mm^3. Febrile neutropenia (FN) was defined as (a) a single oral fever spike of >38.3°C or an oral temperature of ≥ 38°C for at least 1 hour, with (b) an absolute neutrophils count < 500 cells/mm^3; or (c) < 1,000 cells/mm^3 with a predicted decline to < 500 cells/mm^3 over the next 48 hours (Freifeld *et al*, 2011). We classified IFI as a proven, probable or possible, using the criteria revised 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 2008 (De Pauw *et al*, 2008). Patient who died prematurely with a clinical suspicion of invasive pulmonary aspergillosis (IPA) without a chest CT scan was considered to be a putative case if there were pulmonary nodules, cavities or air crescents on chest X-ray.

Statistical analysis

Subject characteristics were described using means, standard deviations, medi-

Table 1
Baseline characteristics of febrile patients with chemotherapy-induced neutropenia.

	Solid tumor (*n*=45)	Hematological malignancies (*n*=188)	*p*-value
Mean age (range) in years	56 (15-78)	44.4 (15-77)	<0.001
Number of males/females	11/34	93/95	0.002
Mean body weight (kg)	52.7 ± 9.8	57.5 ± 11.3	0.007
Mean BSA in m^2	1.51 ± 0.16	1.60 ± 0.18	0.003
Hemoglobin at presentation of FN in g/dl	9.5 ± 2.1	8.3 ± 1.5	<0.001
Neutrophil count at presentation with FN in cells/μl	195 (0-1,000)	50 (0-1,390)	<0.001
Lowest ANC in cells/μl	80 (0-610)	0 (0-950)	<0.001
Percentage of subjects with neutropenia for > 7 days	4.2	74.8	<0.001
Serum albumin level at presentation with FN in g/dl	3.3 ± 0.9	3.5 ± 0.7	0.19
Proportion of subjects with IFI	0/48	47/262	0.001

BSA, body surface area; FN, febrile neutropenia; ANC, absolute neutrophils count; IFI, invasive fungal infection.

ans, minima and maxima, frequencies and percentages. Univariate analysis used the Student's *t*-test and the Mann-Whitney *U* test for continuous variables, and the chi-square test for categorical variables. Variables associated with IFI and deaths attributable to fungal infections on univariate analysis ($p \leq 0.1$) were included in a logistic regression model in which goodness of fit was assessed with the Hosmer-Lemeshow test. For all tests, a two-tailed $p < 0.05$ was considered to be significant. The statistical software SPSS, version 13.0 was used to conduct the analyses.

RESULTS

Demographic data

During January 2008-June 2010, 233 patients developed 310 episodes of fever during CIN: 130 (54.9%) were female. Of the 233 febrile patients with CIN, 188 patients (80.7%) had a diagnosis of hematological malignancies [84 (36%) with acute myeloid leukemia (AML), 22 (9.4%) with acute lymphoblastic leukemia (ALL), 72 (30.9%) with lymphoma, 7 (3.7%) with blast-phase chronic myeloid leukemia (CML), 2 (0.9%) with myelodysplastic syndrome (MDS) and 1 (0.9%) with multiple myeloma]. The patient characteristics are shown in Table 1. The underlying comorbidities among the 233 patients included 17 (7.3%) with cardiac disease, 10 (4.3%) with diabetes mellitus, 6 (2.6%) with HIV infection, 4 (1.7%) with chronic liver disease, and 1 (0.4%) with chronic obstructive lung disease.

Patient characteristics differed between those with solid tumors and those with hematological malignancies. Patients with hematological malignancies were on average younger, had a higher mean body weight (BW) and a greater body surface area (BSA). Patients with hematological malignancies had a longer duration of neutropenia, and lower hemoglobin and neutrophils counts (Table 1). The chemotherapy regimens for this cohort are summarized in Table 2.

Table 2
Chemotherapy regimens of patients who developed invasive fungal infections.

Regimen	IFI cases/total cases
Lymphoid protocol	
Low intensity	
CVP	0/3
CP	0/1
VAD	0/1
Moderate	
CHOP	2/31
High dose MTX	0/2
GDP	0/1
ESHAP	0/13
ICE	2/7
Very aggressive	
HyperCVAD	8/26
CODOX-M	0/8
IVAC	0/1
ALL protocol	2/16
High dose MTX+AraC	3/3
Acute myeloid leukemia protocol	
Low intensity	
Imatinib	0/1
Hydroxyurea	0/1
Decitabine	0/1
Conventional regimen	
3+7	17/70
ATRA-Ida	0/3
Salvage regimen	
FLAG	1/7
FLAG-Ida	1/2
MEC	0/1
Consolidation	
HiDAC	4/50
Others	
1+5	1/1
2+5	1/1

CVP, cyclophosphamide, vincristine, prednisolone; CP, cyclophosphamide, prednisolone; VAD, vincristine, doxorubicin, dexamethasone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; MTX, methotrexate; GDP, gemcitabine, cisplatin, prednisolone; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; ICE, ifosfamide, carboplatin, etoposide; HyperCVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine; CODOX-M, cyclophosphamide, vincristine, doxorubicin, methotrexate; IVAC, ifosfamide, etoposide, cytarabine; ALL protocol, standard Berlin-Framkfurt-Muenster acute lymphoblastic protocol; AraC, cytarabine; HiDAC, high dose cytarabine; 1+5, 1 day of idarubicin and 5 days of standard-dose cytarabine, 2+5, 2 days of idarubicin and 5 days of standard dose cytarabine; 3+7, 3 days of idarubicin and 7 days of standard dose cytarabine; ATRA, all-trans retinoic acid; Ida, idarubicin; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; FLAG-Ida, fludarabine, cytarabine, granulocyte colony stimulating factor with idarubicin; MEC, mitoxantrone, etoposide, intermediate dose cytarabine.

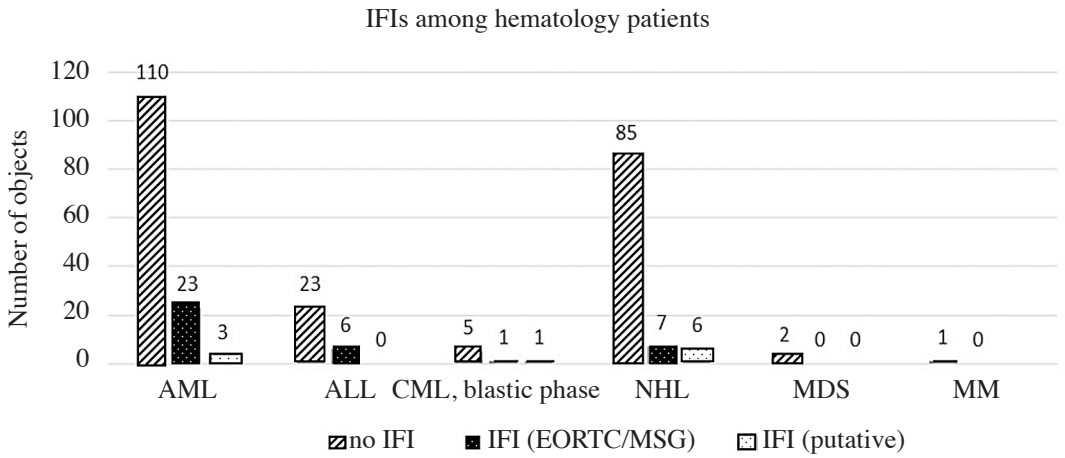

Fig 1–Number of invasive fungal infections (IFI) among patients with febrile neutropenia by their underlying hematological malignancy type. IFI incidence rate was different according to underlying disease of chemotherapy-induced febrile neutropenia. The incidence of IFI was highest in febrile neutropenia following acute leukemia treatment. Patients who had clinical suspicion of IFI but died before making definite diagnosis were defined as putative cases. AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; NHL, non-Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; IFI, invasive fungal infection; 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.

Invasive fungal infection

Of the 310 febrile episodes with CIN in this study, 37 (12%) were due to IFI diagnosed using EORTC/MSG criteria. All the episodes occurred in patients with hematological malignancies. The incidence of IFI among patients with hematological malignancies was 14%. AML was the most common underlying disease among these with IFI; 17% of AML patients had IFI. Patients who received aggressive induction chemotherapy for AML had the highest incidence of IFI (20.5%). In total, there were 12 proven and 2 probable cases of candidiasis, 5 proven, 8 probable and 9 possible cases of aspergillosis, 1 proven case of zygomycosis and 1 proven case of fusariosis. The lungs were the most common site of infection for invasive aspergillosis (81.8%). All *Candida* infections were disseminated (candidemia in 85.7%; hepatosplenic abscess in 14.3%). Aspergillosis occurred in 14 patients with AML, 4 with ALL, 2 with non-Hodgkin lymphoma (NHL) and 2 with CML. *Candida* infections occurred in 7 patients with AML, 2 with ALL and 5 with NHL. Two unusual fungal pathogens were also identified in AML patients: zygomycosis occurred in a relapsed AML patient treated with FLAG-Ida (fludarabine, cytarabine, granulocyte colony stimulating factor with idarubicin) salvage regimen; this was proven with a sinus biopsy along with an abnormal chest and abdominal CT scan. The other unusual fungal pathogen was *Fusarium* spp found on hemoculture with no specific organ involvement. In our study, 10

Table 3
Clinical characteristics of patients with infectious fungal diseases.

Fungal disease	Clinical characteristics	Outcomes
Candidiasis (*n*=14)	Candidemia 12 cases	9 deaths
	C. tropicalis 6 episodes	
	C. albicans 4 episodes	
	C. glablata 2 episodes	
	Probable chronic candidiasis: 2 cases	1 death
	Typical hepatosplenic microabscess	
Aspergillosis (*n*=32)	5 proven cases (confirmed by pathology)	1 death
	Pulmonary tract infection 1 case	
	Sinusitis 4 cases	
	8 probable cases	1 death
	A. fumigatus were cultured in 2 BAL specimen	
	Aspergillus spp were cultured in 1 sputum specimen	
	9 possible cases	2 deaths
	10 putative cases without chest CT	10 deaths
	3: abnormal CXR, serum galactomannan positive	
	7: abnormal CXR, serum galactomannan negative	
Zygomycosis (*n*=1)	Sinusitis proven by pathology with pulmonary nodules and halo sign in chest CT	Survived
Fusariosis (*n*=1)	*Fusarium* spp were cultured in blood	Survived
EORTC/MSG criteria (*n*=37)	1 co-infection: candidemia + invasive sinus aspergillosis	13 deaths (35%)

CT, computed tomography; CXR, chest X-ray; 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; BAL, bronchoalveolar lavage.

patients died without having a chest CT scan. These patients were suspected to be IPA cases due to prolonged neutropenia and the specific abnormalities seen on chest X-ray. If these 10 cases are included. The overall incidence of IFI would be 15% and among hematology cases would be 18%. To investigate incidences by different cancer regimens, we categorized them by the type of lymphoid malignancy and AML protocols. Interestingly, the incidence of IFI was the same for both groups of patients undergoing aggressive lymphoid therapy and induction therapy of AML (Table 2). The clinical characteristics and isolated pathogens of IFI cases are shown in Fig 1 and Table 3.

Risk factors for IFI

Patients with hematological diseases had a higher risk for developing an IFI. IFI occurred only in patients with hematological malignancies in our study. Therefore, we analyzed factors associated with IFI diagnoses among these patients. The clinical factors significantly associated with IFI (including putative cases) among hematological malignancy cases were: peak temperature >39°C during an episode of CIN (OR=6.2; 95% CI: 1.9-20.8), an aggressive AML induction chemotherapy regimen (OR=1.79; 95% CI: 0.93-3.42) and the lowest number of absolute neutrophils count (ANC) that patients had during neutropenia episode

Table 4
Risk factors for developing IFI among FN patients with hematological malignancies.

Factors	IFI cases (*n*=47)	Non-IFI cases (*n*=215)	Univariate analysis	
			OR (95% CI)	*p*-value
Mean age (range) in years	44.2 (15-75)	41.8 (14-77)	1.01 (0.99-1.03)	0.34
Male sex % (*n*)	55.3 (26)	43.7 (94)	1.6 (0.85-3.0)	0.15
Median BSA (m^2)	1.61	1.6	1.4 (0.2-8.9)	0.72
Percent (*n*) with first chemotherapy	42.6 (20)	40.9 (88)	0.94 (0.49-1.77)	0.84
Percent (*n*) with acute leukemia	72.3 (34)	65.1 (140)	1.4 (0.69-2.81)	0.34
Percent (*n*) with AML	68.1 (32)	62.8 (135)	1.3 (0.7-2.5)	0.5
Percent (*n*) with an AML induction regimen	42.6 (20)	29.3 (63)	1.79 (0.93-3.42)	0.08
ANC (range) at diagnosis of FN in cells/μl	30 (0-770)	54 (0-1,390)	0.99 (0.99-1)	0.15
Serum albumin at diagnosis of FN in g/dl	3.5±0.6	3.5±0.7	1.03 (0.63-1.67)	0.92
Percent (*n*) with duration of neutropenia >7 days	93.9 (31/33)	75.3 (125/166)	5 (1.2-22.2)	0.03
Lowest ANC (range) in cells/μl	0 (0-40)	1 (0-950)	1.03 (1.01-1.06)	0.034
Percent (*n*) with temperature >39°C	93.6 (44)	70.2 (151)	6.2 (1.9-20.8)	0.003

AML, acute myeloid leukemia; ANC, absolute neutrophils count; BSA, body surface area; CI, confidence interval; FN, febrile neutropenia; IFI, invasive fungal infection; OR, odds ratio.

(OR=1.03; 95% CI: 1.01-1.06) on univariate analysis (Table 4). On the multivariate model, a peak temperature > 39°C was the only factor significantly associated with IFI (OR=5.9; 95% CI: 1.3-26, *p*=0.019). We found no association between IFI and age, sex, body mass index, type of underlying hematological malignancy, hemoglobin, ANC, serum albumin level, serum creatinine level or liver function test results. The relationship between central venous catheterization, prophylactic antifungal therapy (AFT), comorbidities and IFI could not be evaluated due to the small number of patients. In our study only 3 patients had antifungal chemoprophylaxis: 1 of the 2 cases who received fluconazole prophylaxis and 1 case who received itraconazole prophylaxis developed aspergillosis. Interestingly none of the 6 patients with HIV infection, 10 patients with diabetes mellitus, 4 patients with chronic liver disease cases or 1 patient with COPD in this study developed IFI.

Treatment outcomes

The overall IFI-attributable mortality rate was 35% among EORTC cases, 51% if the putative cases are included. Twelve of the 14 patients who developed candidiasis died from it and 14 of the 30 patients who developed aspergillosis died from it. The patients with zygomycosis and fusariosis survived their infections and were treated with high dose amphotericin B deoxycholate (1.5 mg/kg/day); the zygomycosis patient was also treated with multiple sinus surgical debridements. There were no significant association between causative organisms and patient outcomes on univariate or multivariate analysis. Factors associated with a poor outcome on univariate analysis were: older age (OR=1.1; 95% CI: 1-1.2), age > 40 years (OR=9.3; 95% CI: 2.2-40.2), a low serum albumin level at presentation during CIN (OR=5; 95% CI: 1.3-25), a serum albumin level

Table 5
Factors associated with fungal-attributable mortality.

Factors	Dead (*n*= 23)	Not dead (*n*=24)	Univariate analysis	
			OR (95% CI)	*p*-value
Mean age in years ± SD	51±10.6	37.7±13.5	1.1 (1-1.2)	0.003
Percent (*n*) age >40 years	87 (20)	41.7 (10)	9.3 (2.2-40.2)	0.003
Percent (*n*) male	60.9 (14)	50 (12)	1.6 (0.5-5.0)	0.45
Median BSA (m^2)	1.6	1.61	0.8 (0.3-18.7)	0.89
Percent (*n*) with lymphoma	56.5 (13)	0		<0.001
Percent (*n*) with lymphoma salvage regimen	8.7 (2)	0		0.14
ANC (range) at the diagnosis of FN in cells/µl	40 (0-770)	15 (0-630)	1.0 (0.99-1.00)	0.28
ANC (range) before starting AFT in cell/µl	20 (0-6,750)	20 (0-752)	1.001 (1-1.002)	0.27
Serum albumin ± SD at the diagnosis of FN in g/dl	3.3±0.6	3.7±0.5	5 (1.3-25)	0.019
Serum albumin ± SD at the start of AFT in g/dl	2.8±0.5	3.4±0.6	1.3 (0-2)	0.007
Percent (*n*) serum albumin at start of AFT < 3 g/dl	54.5 (12)	15 (3)	6.8 (1.5-30)	0.008
Percent (*n*) total duration of neutropenia > 7 days	34.8 (8)	95.8 (23)	0.02 (0-0.20)	0.001
Lowest neutrophils count (range) in cells/µl	0 (0-40)	0 (0-20)	1.01 (0.95-1.08)	0.68

AFT, antifungal therapy; CI, confidence interval; FN, febrile neutropenia; OR, odds ratio; SD, standard deviation; BSA, body surface area, ANC, absolute neutrophils count.

< 3 g/dl at the start of antifungal treatment (OR=6.8; 95% CI: 1.5-30) and having a diagnosis of NHL ($p = 0.005$; Table 5). A total duration of neutropenia < 7 days was also significantly associated with death. Since this factor might be confounded by its association with premature death, we did not include it on multivariate analysis. On multivariate analysis, age > 40 years (OR=6.6; 95 % CI: 1-42.4; $p = 0.048$) and a serum albumin < 3 g/dl at the start of AFT (OR=6.95; 95% CI: 1.1-43.4; $p = 0.037$) were both associated with poor outcome. We found no significant association between outcome and sex, BSA, body weight, use of granulocyte-colony stimulating factor (G-CSF), mean ANC, hemoglobin level, creatinine level, bilirubin level or serum galactomannan level or neutropenia duration before AFT initiation. Ninety four percent of subjects with IFI were initially treated with amphotericin B deoxycholate. Thirty-four percent of subjects, the treatment was subsequently combined with voriconazole (16%) or itraconazole (18%).

DISCUSSION

In our study there was a high incidence of IFI among febrile patients with CIN; higher than reported previously from Thailand (Chayakulkeeree and Thamlikitkul, 2003; Phungtaharn, 2006; Roongpoovapatr and Suankratay, 2010). The incidence of IFI in our study was about two times higher among AML patients. Compared to previous studies above we found a higher incidence of aspergillosis and a lower incidence of candida. There were also two cases of emerging fungal pathogens: *Fusarium* and *Mucor*. In our study, IFI was found only among patients with hematological malignancies, especially AML, similar to several previous studies (John *et al*, 2014; Nesher and Rolston, 2014). Using EORTC/

MSG 2008 criteria (De Pauw *et al*, 2008), the incidences of IFI among CIN patients were 12%, 14%, 17% and 20.5% among the overall febrile CIN cases, among those with hematological malignancies, among AML patients and among AML patients undergoing the induction phase of chemotherapy, respectively. Previous data from Thailand reported the incidence of IFI to be 3-5% among febrile patients with CIN; all had candidiasis (Chayakulkeeree and Thamlikitkul, 2003; Phungtaharn, 2006). A more recent study found the incidence of IFI to be 9%; 8 of 9 cases were aspergillosis (Roongpoovapatr and Suankratay, 2010). The higher incidence of IFI and aspergillosis in our study could be due to an increase in the incidence of IFI or an improvement in testing to diagnose IFI. The incidence of IFI from other countries who also do not use antifungal prophylaxis varies: 12.1% in Tunisia (Gheith *et al*, 2014), 19.6% in Turkey (Gedik *et al*, 2012), 20% in Malaysia (pediatric center) (Latiff *et al*, 2002) and 34.1% in Taiwan (Tang *et al*, 2015). These cohorts had differences in underlying hematological malignancies. Since the incidence of IFI in our study was for fever among patients with CIN, it cannot be compared to those studies. However, since febrile neutropenia commonly occurs during AML treatment, we believe the incidences of AML in our study and in their studies are comparable. The IFI incidence in our study was complicated by the fact that high resolution chest CT scanning was not promptly done. Since IPA is highly aggressive, some patients were not diagnosed by CT scan before they died or by autopsy. This is a challenge of using the EORTC/MSG 2008 diagnostic guideline (De Pauw *et al*, 2008) in countries with limited resources; some diagnoses may be underreported. To detect patients with IPA, we used different criteria to meet our limitations by including abnormal chest X-ray findings. We included 10 patients with clinically suspected IPA who died before having a CT scan. Using these modified criteria we estimate the actual incidence of IFI might be 2-6% higher. This higher incidence of IFI among AML patients is still lower than reported from Taiwan at a center with a ward similar to our facility (Tang *et al*, 2015). However the incidence of IFI among AML patients in our study is still higher than centers where antifungal prophylaxis is given in Asia and other countries (Pagano *et al*, 2006; Hammond *et al*, 2010; Lee *et al*, 2011; Kurosawa *et al*, 2012). Prospective studies of disease-base population cohorts are needed to confirm this theory.

In our study, hematology patients with CIN had several factors that increased the risk of IFI, such as a lower ANC level and a longer period of neutropenia than with solid tumor treatment. This may explain why IFI were found only in our hematology patients. A peak temperature on admission of >39°C with CIN was associated with a greater risk for an IFI among hematological malignancy patients. An association between ANC and neutropenia duration with IFI was seen only on the univariate model in our study. The IFI mortality rate in our study was high (35-51%). This poor outcome may reflect the efficacy of conventional amphotericin B used for empiric treatment. Factors associated with poor outcome were age >40 years and a serum albumin level <3 g/dl at the initiation of antifungal therapy. Whether this reflects poor nutritional status or a high catabolic state has yet to be established. We did not find a significant correlation between degree or duration of neutropenia or other chemistry findings and IFI. Having a diagnosis of non-Hodgkin's lymphoma was found

to be a poor prognostic factor among IFI patients on univariate analysis but not on multivariate analysis. The explanation for this is unknown.

The limitations of this study were lack of availability of CT scans during the study period and the retrospective nature of this study. A prospective study incorporating scheduled CT scan surveillance should be conducted to confirm the incidence of IFI found in this study. However this study reflects real practice in a developing country with limited resources. There was a high incidence of IFI in our study. Effective prophylaxis of IFI should be used in the study population.

In this study, we found a high incidence of IFI among febrile patients with CIN and a high mortality rate, especially among patients with AML. Patients aged >40 years and a low albumin level had significantly higher mortality rates. We hope the results of this study will guide clinicians and policymakers in making decision to improve care in the study population.

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