

Original Article

Incidence of Invasive Aspergillosis in Acute Myeloid Leukemia Patients Receiving Intensive Chemotherapy at Sisaket Hospital

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Abstract:

Background: Invasive aspergillosis can be found among patients with acute leukemia who have prolonged neutropenia during intensive chemotherapy, resulting in poor outcome and financial loss. The incidence of invasive aspergillosis among patients with acute myeloid leukemia (AML) varies relatively from each center. This study aimed to determine the incidence of invasive aspergillosis in Sisaket Hospital and its effect on outcome of AML treatment. **Methods:** We retrospectively evaluated the incidence of invasive aspergillosis, occurring during intensive chemotherapy, as well as the effect of this infection on the achievement of complete remission (CR) and the number of deaths after induction of patients with AML. **Results:** All 16 patients with AML, undergoing 17 courses of induction chemotherapy, were evaluated. The incidence of invasive aspergillosis was 41.2%, 23.5% were classified as probable cases, and 17.7% were specified as possible cases. Invasive aspergillosis mostly occurred after the first course of chemotherapy (6 of 7 cases, 85.7%). The median time of development of invasive aspergillosis was 15 days after initiating chemotherapy. As a result of AML treatment, 58.8% of the patients could achieve complete response, 17.7% had resistant disease, and 23.5% had early death or hypoplastic death. The 2-year overall survival and 2-year relapse-free survival rates were 37% and 10%, respectively. The development of invasive aspergillosis did not show any adverse effect on the complete response rate after induction. **Conclusion:** The incidence of invasive aspergillosis in Sisaket Hospital was relatively high, but did not show any adverse effect on AML treatment outcome.

Keywords : ● Invasive aspergillosis ● Acute myeloid leukemia

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นิพนธ์ต้นฉบับ

อุบัติการณ์ของการติดเชื้อรา Invasive Aspergillosis ในผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดเฉียบพลันชนิดมัยอีลอยด์ (Acute Myeloid Leukemia) ที่ได้รับการรักษาด้วยยาเคมีบำบัด ในโรงพยาบาลศรีสะเกษ

กัญญพร เจริญประเสริฐ

แผนกโลหิตวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ โรงพยาบาลศรีสะเกษ

บทคัดย่อ

หลักการและเหตุผล การติดเชื้อรา *Aspergillus* พบได้บ่อยในผู้ป่วยมะเร็งเม็ดเลือดขาวที่ได้รับการรักษาด้วยยาเคมีบำบัด ซึ่งการติดเชื้อรานี้ นอกจากจะทำให้สิ้นเปลืองค่าใช้จ่ายมากขึ้นแล้ว ยังอาจส่งผลกระทบต่อการรักษามะเร็งเม็ดเลือดขาวอีกด้วย **วิธีการวิจัย** ผู้วิจัยเก็บข้อมูลผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดเฉียบพลันชนิดมัยอีลอยด์ (acute myeloid leukemia) ที่ได้รับการรักษาด้วยยาเคมีบำบัดในโรงพยาบาลศรีสะเกษ จำนวน 16 ราย เพื่อศึกษาอุบัติการณ์ของการติดเชื้อรา *aspergillus* และผลของการติดเชื้อรานี้ต่อผลการรักษามะเร็งเม็ดเลือดขาว **ผลการศึกษา** พบอุบัติการณ์ของการติดเชื้อราร้อยละ 41.2 โดยเป็นการวินิจฉัยระดับ probable invasive aspergillosis (IPA) ร้อยละ 23.5 และการวินิจฉัยระดับ possible IPA ร้อยละ 17.7 ส่วนผลการรักษามะเร็งเม็ดเลือดขาวพบว่า สามารถทำให้โรคสงบได้ร้อยละ 58.8 การรักษาล้มเหลวร้อยละ 17.7 และเสียชีวิตก่อนประเมินผลการรักษาร้อยละ 23.5 โดยอัตราการรอดชีวิตที่ 2 ปี คิดเป็นร้อยละ 37 และอัตราการมีชีวิตโดยปลอดโรคที่ 2 ปี คิดเป็นร้อยละ 10 โดยพบว่าการติดเชื้อรานี้ไม่ได้ส่งผลกระทบต่อรักษามะเร็งเม็ดเลือดขาว **สรุป** อุบัติการณ์ของการติดเชื้อรา *aspergillus* ค่อนข้างสูงในโรงพยาบาลศรีสะเกษ อย่างไรก็ตาม การติดเชื้อราดังกล่าวนี้นี้ไม่ได้ส่งผลกระทบต่อรักษามะเร็งเม็ดเลือดขาว

คำสำคัญ : ● Invasive aspergillosis ● Acute myeloid leukemia

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2561;28:145-53.

Introduction

Patients with acute myeloid leukemia (AML) who have undergone intensive chemotherapy are prone to severe infection, including invasive aspergillosis, because of prolonged and severe neutropenia.¹⁻³ The incidence of invasive aspergillosis varies and depends on individual centers, ranging from 8.9% to 22.14%.⁴⁻¹⁰ This infection does not only waste finances but also presents higher morbidity and mortality, as well as compromising antileukemia therapy.^{4,6-8,10-12} The decision to use antimold prophylaxis to prevent invasive aspergillosis among patients with AML depends on the incidence of infection at individual centers. This study aimed to determine the incidence of invasive aspergillosis among patients who have received remission-induction chemotherapy in Sisaket Hospital and to evaluate the effect of invasive fungal infection on outcome of acute leukemia treatment. The primary objective of this study is to be aware of the incidence of invasive aspergillosis among patients with AML who have received induction chemotherapy. The secondary objectives focused on the outcome of treatment of patients with AML in Sisaket Hospital and any potential effects of invasive aspergillosis concerning antileukemia therapy.

Materials and Methods

This study retrospectively analyzed all patients with acute leukemia who have been treated by chemotherapy at Sisaket Hospital from 1st July 2013 to 31st August 2015. The inclusion criteria were: (1) patients with a diagnosis of AML by morphology or flow cytometry reports; (2) age older than 15 years; (3) patients receiving intensive chemotherapy.

The patients with AML were admitted in isolated rooms during remission-induction chemotherapy, without a positive-pressure, high-efficiency particulate air filtration room. Antifungal prophylactic drug was not used during the study period. Only patients who were suspected of having invasive fungal infection were screened

for serum galactomannan antigen and chest computed tomography (CT chest). None of the patients in this study underwent bronchoscopy and bronchoalveolar lavage because of the high bleeding risk from severe thrombocytopenia. All of the suspected cases (having abnormal finding on chest X-ray or CT chest) promptly started antifungal drug treatment with amphotericin-B.

Clinical data, including age at diagnosis, sex, initial complete blood count, the duration of neutropenia, nadir absolute neutrophil count, diagnosis and category of invasive aspergillosis and treatment outcome were obtained from medical records.

Definitions

The definition of invasive aspergillosis was based on the 2008 criteria of the European Organisation for Research and Treatment of Cancer/Intensive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Disease Mycoses Study Group (2008 EORTC/MSG). Invasive aspergillosis is divided in possible, probable and proven invasive fungal diseases.^{14,15} All categories were included in this study. The results of serum galactomannan antigen-detection testing were considered positive when optical density reached 0.5 or higher. The probable cases were diagnosed with positive serum galactomannan and the possible cases were documented when infiltration on CT chest was compatible with IPA and the serum galactomannan result was negative.

The treatment outcomes were defined by the complete remission rate (CR), overall survival rate (OS) and relapse-free survival rate (RFS). CR is defined when bone marrow contains less than 5% blast cells, the blood cell counts are within normal limits and no signs or symptoms of the disease are observed.¹⁶ OS was calculated from the date of diagnosis until the date of death from any cause or until the date of last follow-up. RFS was calculated from the date of diagnosis until (1) relapse (2) death from any cause or (3) the date of last follow-up.

Statistics

Baseline characteristics of patients with AML were described in descriptive analysis. Categorical variables are expressed as frequencies and percentages, and nonnormally distributed continuous variables are expressed as medians with interquartile ranges (IQR). Baseline characteristics of each subgroup were compared using the chi-square or Fisher's exact test for categorical variables and the t-test or nonparametric test for continuous variables. We used the Kaplan-Meier method to analyze survival and used the log-rank test to assess differences between survival curves. The factors influencing the survival were checked initially using univariate analysis and the variables that were statistically significant ($p\text{-value} \leq 0.05$) using univariate analysis were used for multivariate analysis. Independent prognostic factors were determined by multivariate regression analysis using the forward stepwise cox proportional hazard model. All reported p-values were two-sided. All analyses were performed with the use of SPSS Software, Version 23.

Results

Patient characteristics

The 16 patients with AML including 17 courses of remission-induction chemotherapy, comprised 8 males

(50%) and 8 females (50%). The median age of the patients at diagnosis was 48 years (range, 17-58 years). The diagnosis could be classified as AML, non-M3 (11 patients), acute biphenotypic leukemia (1 patient), chronic myeloid leukemia, blastic phase (1 patient) and acute promyelocytic leukemia (APL or AML-M3) (3 patients). The total white blood cell counts at diagnosis ranged from $2 \times 10^9/\text{L}$ to $348.1 \times 10^9/\text{L}$. All AML, non-M3 patients received induction chemotherapy with 7+3 regimen (7-day cytarabine and 3-day idarubicin) whereas the patients with APL received idarubicin and all-trans-retinoic-acid (ATRA) for remission-induction chemotherapy. All patients, who achieved complete response after induction course, received consolidation chemotherapy (high-dose cytarabine for AML, non-M3, and APL consolidation protocol for patients with APL). Only one patient underwent allogeneic stem cell transplantation. The baseline characteristics of the patients in this study are shown in Table 1.

Invasive aspergillosis among patients with AML

After remission-induction chemotherapy, 15 of 17 courses of chemotherapy (88.2%) led to febrile neutropenia. Invasive aspergillosis was diagnosed among 7 patients (41.2%), classified as probable in 4 and possible in 3 patients. Invasive pulmonary aspergillosis (IPA) was identified in all patients. In 6 (85.7%) of these 7

Table 1 Clinical characteristics of patients

Characteristics	Patient with invasive aspergillosis	Patient without invasive aspergillosis	p-value
No. of patients	7	9	-
Age, year, median (range)	48 (28-55)	42 (17-58)	0.416
Sex, male, no. (%)	4/7 (57.14%)	4/9 (44.44%)	0.614
Acute leukemia subtype, (n)			
- AML, non M3	6	7	0.640
- APL	1	2	
Initial WBC at diagnosis ($\times 10^9$ cell/L)	45.442 ± 49.528	86.340 ± 131.287	0.386
Time of neutropenia, ANC $< 0.2 \times 10^9$ cell/L (mean, days)	20.29 ± 5.219	13.90 ± 13.254	0.192
Nadir ANC (cell/mm ³)	53.00 ± 50.78	93.20 ± 64.58	0.172
Cost of induction chemotherapy (mean)	231,401.6	172,358.7	0.031

Table 2 Characteristics of patients with possible and probable invasive aspergillosis

No.	Sex	Age (year)	Diagnosis [#]	Interval to diagnosis*	Nadir WBC, x 10 ³ /mm ³	CT chest	SGM** (index value)	Outcome (CR ⁺⁺)
Probable IPA								
1	M	28	Biphenotypic leukemia	14	0.1	positive ⁺	0.49	not CR
2	F	52	AML	20	0.2	positive	2.12	CR
3	M	49	AML	13	0.2	positive	0.75	CR
4	M	48	AML	- ⁺⁺⁺	0.4	positive	0.65	CR
Possible IPA								
5	F	52	CML, blastic phase	20	0.2	positive	0.25	CR
6	F	45	AML	17	0.7	positive	0.15	CR
7	M	55	APL	30	0.3	positive	0.46	CR

*Number of days from initiation of chemotherapy until diagnosis of invasive aspergillosis

**Serum galactomannan

⁺CT chest positive; found infiltration compatible with invasive pulmonary aspergillosis

⁺⁺CR, complete remission

⁺⁺⁺IPA was documented before starting induction chemotherapy

[#]AML: acute myeloid leukemia, CML: chronic myeloid leukemia, APL: acute promyelocytic leukemia

patients, invasive aspergillosis occurred during the first course of chemotherapy, and one patient had IPA before initiation of chemotherapy. The characteristics of patients with possible and probable invasive aspergillosis are shown in Table 2. The median time of IPA diagnosis was 15 days (range, 13 to 20 days) after induction chemotherapy (excluding one patient with documented IPA before initiation of chemotherapy). All factors including age at diagnosis, AML subtype, initial white blood cell counts at diagnosis, duration of neutropenia, or nadir ANC did not show increased risk of invasive aspergillosis (Table 1).

The costs of induction chemotherapy for AML ranged from THB 100,098 to THB 305,449.3. The mean costs of AML induction were THB 231,401.6 and THB 172,358.7 in AML with IPA and without IPA subgroups, respectively. This study found that the development of IPA during the induction course significantly wasted more finances ($p = 0.031$).

Outcome of treatment

Response to induction therapy

Regarding the result of acute leukemia treatment, 58.8% of patients could achieve complete response, 17.7% had resistant disease, and 23.5% had early death or hypoplastic death. Patients with acute leukemia with invasive aspergillosis had a higher CR rate but without statistical significance. The CR rates were 85.7% and 40% among patients with and without IPA subgroup, respectively ($p = 0.136$). After follow-up, 10 (62.5%) of 16 patients died for which the causes of death included acute leukemia (60%), and treatment-related mortality (40%). The rate of early/hypoplastic death after the first induction chemotherapy was 23.5% (4 patients from 17 courses of chemotherapy). Invasive aspergillosis was documented and seemed to be the cause of death in only 1 of these 4 patients with early/hypoplastic death. The others died from severe bacterial infection including severe bacterial pneumonia (2 patients) and deep neck infection (1 patient).

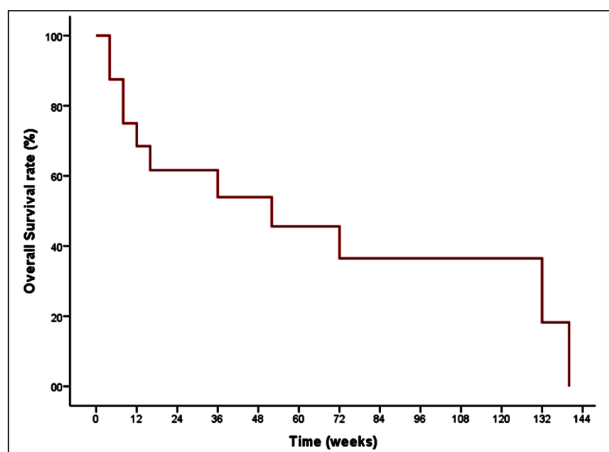


Figure 1 The overall survival (OS) of acute myeloid leukemia patients (shows the 1-year-OS rate of 46% and 2-year-OS rate of 37%)

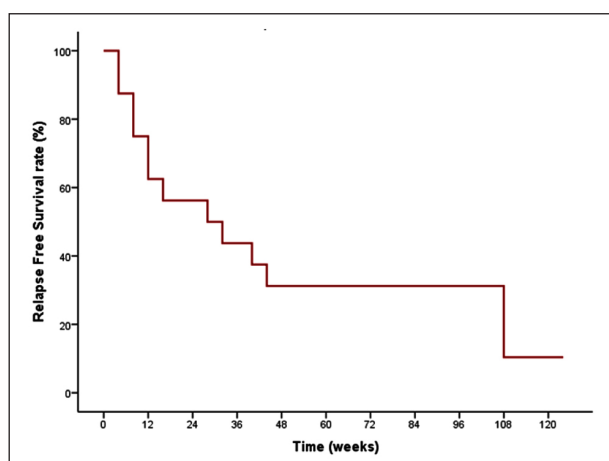


Figure 2 The relapse free survival (RFS) of acute myeloid leukemia patients (shows the 1-year-RFS rate of 31% and 2-year-RFS rate of 10%)

Survival analysis

The median follow-up time of this study was 8 months (range, 0.5 to 34 months). The median overall survival (OS) and relapse-free survival (RFS) of patients with AML in Sisaket Hospital were 12.3 and 6.8 months, respectively. Our patients with AML still presented poor prognosis with the 1-year OS and 1-year RFS rates of 46% and 31%, respectively. In addition, they also presented very poor long-term outcome with the 2-year OS of 37% and the 2-year RFS of 10% (Figures 1 and 2). Only 1 of 16 patients could achieve allogeneic stem cell transplantation; however, he early relapsed 6 months later after transplantation. Complete response after induction was the only factor showing significant improvement on overall survival ($p < 0.001$). Other factors including initial WBC, subtype of acute leukemia and the age at diagnosis did not have any impact on survival of patients with AML (Figures 3 and 4).

Discussion

The incidence of IPA during AML induction chemotherapy in Sisaket Hospital was 41.17% comprising 23.53% probable IPA and 17.64% possible IPA. In comparison, this incidence was higher than that reported in other studies. In this regard, other studies showed the incidence of invasive aspergillosis ranging from

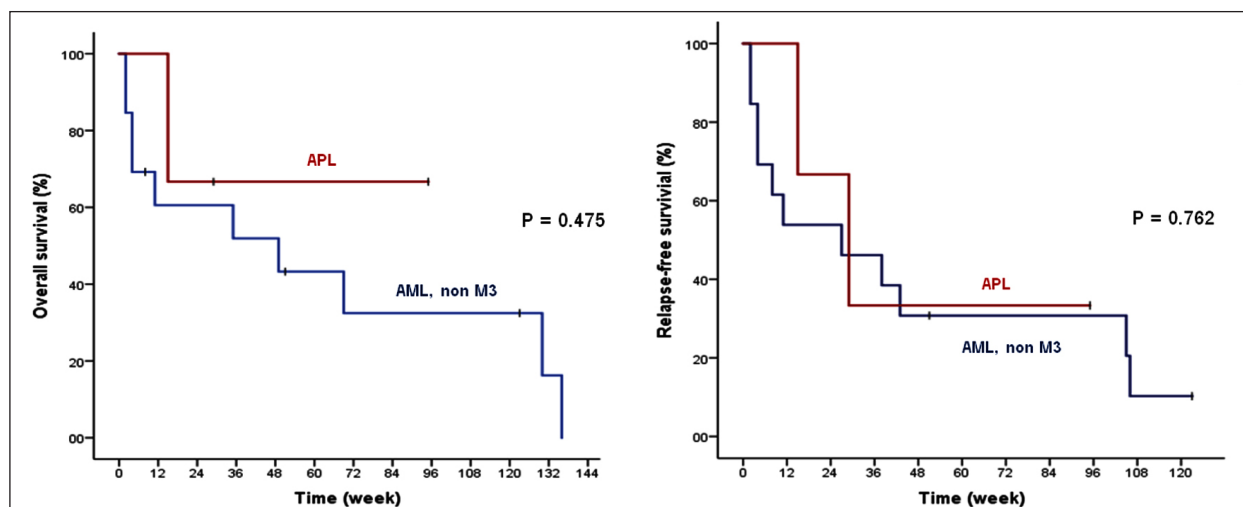


Figure 3 The overall survival (OS) and relapse free survival (RFS) of patients with AML classified as AML, non-M3 and acute promyelocytic leukemia (APL)

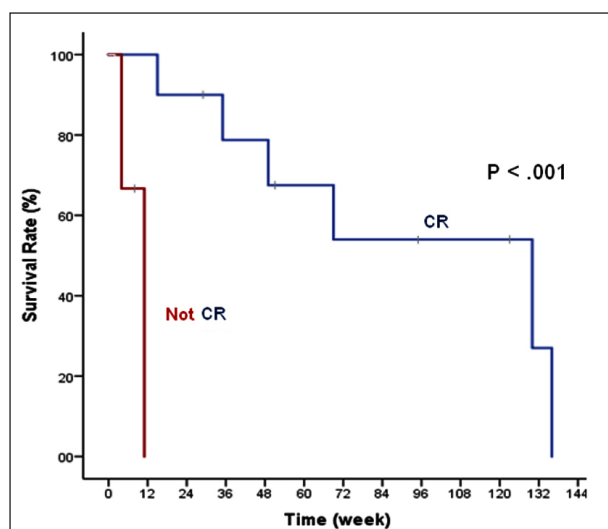


Figure 4 The survival of patients with AML who could and could not achieve CR after chemotherapy induction

8.9% to 22.14%.⁴⁻¹⁰ The high incidence rate of infection of this study may be caused by the patients not being admitted in a positive-pressure, high-efficiency particulate air filtration room during induction chemotherapy and not being given antifungal prophylaxis during the intensive treatment. This study demonstrated that the invasive fungal infection did not render onerous effect concerning treatment outcome. The development of IPA decreased in death rate and increased in CR rate after induction regimens. In this regard, the outcome of this study was contrary to related reports^{6,8,10,17}. This finding may be due to severe bacterial infection leading to early death before developing invasive aspergillosis. In addition, the patients with IPA could be given rapid and early empirical antifungal treatment¹⁸.

The patients in this study did not receive any pre-emptive strategy for IPA treatment because the turn-around time of serum galactomannan was 10 to 14 days¹⁹. All suspected cases, who were found abnormal CXR or abnormal CT chest, would receive amphotericin-B for an empirical antifungal drug. The antifungal drug was changed to the first-line drug, voriconazole when serum galactomannan showed positive result (probable case)¹⁷. As a consequence, this strategy did not cause an increase in the death rate. Therefore, it could imply that empirical antifungal treatment with amphotericin-

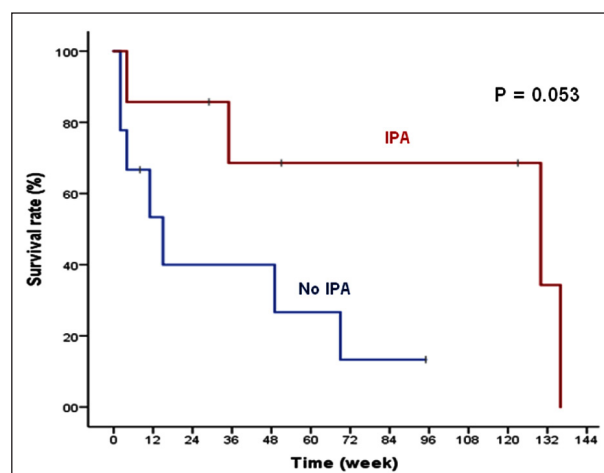


Figure 5 The survival of patients with AML who did and did not have invasive pulmonary aspergillosis (IPA) during the induction therapy

B in resource-limited institutes remains an efficient strategy³.

It could be considered that IPA prophylaxis should be used in Sisaket Hospital because of the high incidence rate^{4,20}. Even though, posaconazole is now a drug of choice for primary fungal prophylaxis for AML induction, remains unavailable for all patients and is costly⁵. A cost-effectiveness evaluation is required before replacing first-line drugs in resource-limited hospitals. At Sisaket Hospital, the outcome of patients with AML showed inferior results compared with related studies²¹⁻²⁴. The poor outcome was primarily caused by high rate of early/hypoplastic death. Preventive strategies and proper treatments for febrile neutropenic patients should decrease the mortality rate of patients with AML.

In relation to the consolidation therapy, only one patient could access allogeneic stem cell transplantation (ASCT). However, the patient developed early relapse after ASCT.

Summary

The incidence of invasive aspergillosis of patients with AML at Sisaket Hospital was high. This infection significantly causes greater expenses in induction courses of chemotherapy. However, it did not show any adverse effect on treatment outcome.

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