Epidemiological Studies About The Invasive Fungal Infection In Leukemia Patients Receiving Induction Chemotherapy In Taiwan — Higher Incidences And Adverse Survival Impact Were Noted

Bor-Sheng Ko[1], Hsiang-Chi Kung[2], Wen-Chi Li[1], Hwei-Fang Tien[1], Yee-Chun Chen[2]
Division of hematology[1] and Infection[2], Department of Internal medicine, National Taiwan University Hospital, Taiwan.
Address: *No. 7, Chung-Shan South Rd, Taipei City 10002, Taiwan, R.O.C.*

Introduction and Purpose:

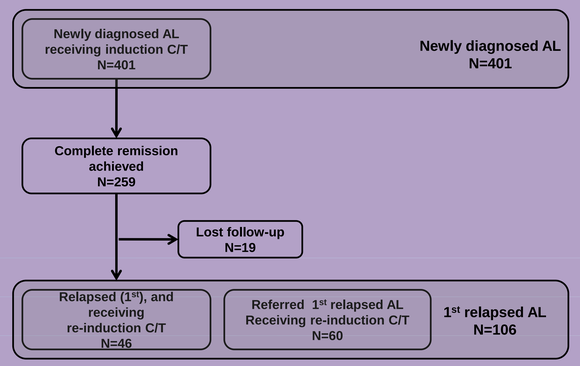
The incidence of invasive fungal infection (IFI) in patients with hematologic malignancies increased dramatically in the past years, and the epidemiological characteristics of IFI continued to evolve in leukemia patients. The epidemiology of IFI in patients with hematological malignancies in subtropic or tropic areas should be different, but to date, there is no convincing data available for patients in these regions. Furthermore, other factors such as genetic background of patients, chemotherapeutic regimens or environmental setting will also contribute to geographic variation in the epidemiology of IFIs.

This report, therefore, is aimed to illustrate the incidences of IFIs in acute leukemia patients receiving induction chemotherapy in Taiwan, a subtropic country; also we hope to identify what are the potential risk factors of IFIs for these patients, and if IFIs have negative prognostic impacts on them.

Patients and Methods:

Patients

This is a retrospective cohort study. From Jan 2004 to Dec 2009, 461 adult (>15 y/o) patients with 507 courses of induction or re-induction chemotherapy in National Taiwan University Hospital was included in the analysis. The flow of patients was illustrated:



Anti-leukemia Treatment

For patients with newly diagnosed non-M3 acute myeloid leukemia (AML), standard induction with the “3+7” regimen is used. For acute lymphoblastic leukemia (ALL), standard induction chemotherapy included the chemotherapy in the protocol of CALGB 8811, GRAALL 2003, GMALL NHL 86, or hyperCVAD, according to disease type and physicians’ decisions. All-trans retinoic acid (ATRA) followed by anthracyclines was the standard induction regimen for AML-M3 patient.

There was no routine anti-bacterial or anti-fungal prophylaxis used except for oral nystatin or sulfamethoxazole 400mg/trimethoprim 80mg once or twice daily.

Diagnosis and management of IFIs

A diagnostic and treatment algorithm based on diagnosis-driven strategy for IFIs in these patients were applied. When patients remained febrile >72hrs after broad-spectrum anti-bacterial agents and throughout workups in neutropenia stage, high-resolution computed tomography (HRCT) would be performed, and Aspergillus galactomannan tests on serum would be checked twice a week. Broncho-alveolar lavarge (BAL) was not routinely performed. The 2008 EORTC/MSG consensus criteria was used to define IFIs.

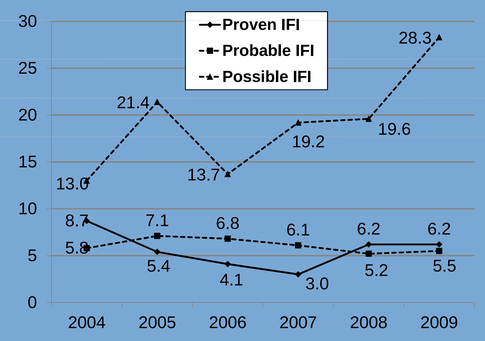
Pre-emptive anti-fungal agents, such as echinocandins, fluconazole or voriconazole, can be given if IFIs were suspected with positive evidences from workups. Anyway, empirical antifungal agents such as amphotericin-B or caspofungin were still allowed if IFIs were still suspected.

Results:

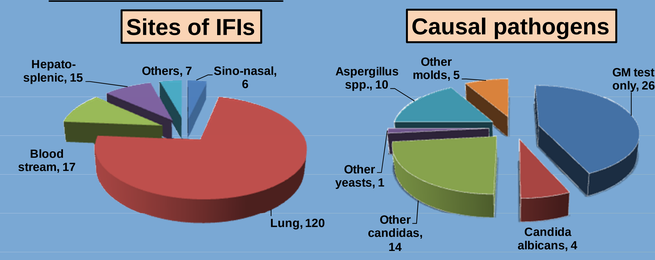
Patient Characters: Listed as the table:

Characteristic	Number (%)
Age (year)	
Median [range]	47 [15-87]
Gender	
Male/Female [ratio]	264/243 [1.08:1]
Fresh/First relapse	
Fresh	401 (79.1%)
First relapse	106 (20.9%)
Type of disease	
Non-M3 AML	374 (73.8%)
APL	31 (6.1%)
ALL	102 (20.1%)
Antecedent hematologic malignancy	
MDS	38 (7.5%)
MPN	23 (4.5%)
Others	6 (1.2%)
None	440 (86.8%)
Induction regimen	
Standard	444 (87.6%)
Low-intensity	63 (12.4%)
Induction result with 1 cycle C/T	
CR	257 (50.7 %)
PR	65 (12.8%)
Refractory	118 (23.3%)
Unknown	67 (13.2%)

Incidences of IFIs: The incidences of IFIs were illustrated in the figure. The incidences of probable and proven IFIs were around 12% throughout the period.



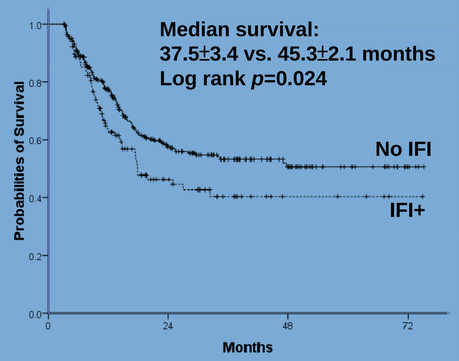
Distribution of IFIs:



Predictors for IFIs: With logistic regression, non-M3 AML, standard induction and failure to CR predicted proven or probable IFIs in these patients:

	With proven or probable IFIs	
	Estimated hazard ratio (95% CI)	p value
≧60 vs ＜60 y/o	1.591(0.827-3.061)	0.164
Antecedent hematological diseases, Yes vs No	1.606 (0.739-3.487)	0.232
Non-M3 AML vs ALL	**1.814 (0.946-3.480)**	**0.073**
Low-intensity vs Standard Chemotherapy	**0.151 (0.034-0.664)**	**0.012**
CR vs non-CR	**1.757 (0.983-3.138)**	**0.057**

Survival: Those with proven/probable/possible IFIs had worse survival than those without (median survival 40.6±2.0 vs. 25.9±3.2 months, p<0.001). Even in those who survived >3m, the impact persisted (as the figure).



Conclusions:

The incidences of IFIs are high in leukemia patients undergoing induction chemotherapy in Taiwan, and the long-term survival is significantly impacted by IFIs. Aggressive management, such as anti-fungal prophylaxis should be seriously considered in these patients.