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Prognostic Factors Influencing Infection-related Mortality in Patients with Acute Leukemia in Korea*

We retrospectively reviewed the medical records of 284 patients with neutropenic fever following chemotherapy for acute leukemia at the Catholic Hematopoietic Stem Cell Transplantation Center from January 1998 to December 1999, to identify prognostic factors for infection-related mortality. Twenty-eight patients died of infections. There was no difference in median age, gender ratio, or underlying disease between the dying and surviving groups. Bacteria were the main pathogens following chemotherapy, and Gram positive organisms predominated in the dying group. Pneumonia and sepsis were the main causes of death. There were 72 cases of invasive fungal infection and their mortality was 27.8%. Invasive fungal infection and previous history of fungal infection were independent prognostic factors for outcome. Recovery from neutropenia was the significant protective factor for mortality. In conclusion, the prognostic factors identified in this study could be useful for deciding on more intensive treatment for those patients at greater risk of death. To our knowledge, this is the first Korean study delineating prognostic factors in acute leukemic patients with infectious complications.

Key Words : *Leukemia; Infection; Prognosis, Neutropenia; Mycoses; Fungal Infection*

Jin-Hong Yoo, Su Mi Choi, Dong-Gun Lee, Jung-Hyun Choi, Wan-Shik Shin, Woo-Sung Min, Chun-Choo Kim

The Catholic Hemopoietic Stem Cell Transplantation Center, The Catholic University of Korea, College of Medicine, Seoul, Korea

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Address for correspondence
Wan-Shik Shin, M.D.
Department of Internal Medicine, St. Mary's Hospital, The Catholic University of Korea, 62 Yoido-dong, Youngdungpo-gu, Seoul 150-010, Korea
Tel : +82.2-3779-1151, Fax : +82.2-3779-1774
E-mail : jhyoo@catholic.ac.kr

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INTRODUCTION

Infection is a major concern in the management of patients with acute leukemia after cytotoxic chemotherapy (1-4). Breeches in host defenses and immuno-compromised status are inevitable consequences of cytotoxic chemotherapy as well as of the underlying disease itself. Neutropenia is the major problem in most patients who receive chemotherapy and can predispose them to infection: at least half of the patients with febrile neutropenia have infections (2).

Successful management of acute leukemia depends upon appropriate control of the infectious complications. In order to deal with such post-chemotherapeutic infectious complications, adequate assessment and prediction of the clinical course are needed (5). In this study, we tried to identify the prognostic factors influencing infection-associated mortality in patients with acute leukemia.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of all acute leukemic patients with febrile neutropenia following chemotherapy at the Catholic Hemopoietic Stem Cell Transplantation (HSCT) Center from January 1998 through December 1999. Antimicrobial prophylaxis consisted of ciprofloxacin 500 mg, roxithromycin 300 mg, fluconazole 50 mg p.o. daily during the neutropenia.

An empirical antibiotic regimen was given to febrile patients according to the guidelines of the Infectious Diseases Society of America (IDSA) (4). If clinical, histopathological or radiological signs suggested invasive fungal infection (IFI), antifungal therapy consisting of intravenous infusion of conventional or liposomal amphotericin B was initiated. The diagnosis of IFI was made on the basis of the definitions proposed by the consensus group of the European Organization for Research and Treatment of Cancer in conjunction with the Mycoses Study Group (EORTC/MSG) (6).

Fever was defined as a single oral temperature of $\geq 38.3^{\circ}C$, or a temperature of $\geq 38.0^{\circ}C$ for ≥ 1 hr. Neutropenia was defined as a neutrophil count of less than 500/μL, or a count of less than 1,000/μL with a predicted decrease to less than 500/μL (4, 7).

The term microbiologically-defined infection (MDI) was used if a clinically significant pathogen was identified from a normally sterile specimen, or from an affected site, by culture or biopsy, whereas the term clinically-defined infection (CDI) was employed if fever was accompanied by appropriate clinical findings, for example, pulmonary infiltration or inflammation of the skin or soft tissue. Fever was designated as "unexplained fever (UF)" when there was no clinical, radiological or microbiological evidence of infection.

Baseline information included age, sex, and underlying diseases. Patients who died due to infection were assigned to the death group (DG) and the data of the DG were compared to those of the surviving group (SG).

Statistical analyses were carried out with SPSS 10.0 (SPSS Korea, Seoul, Korea), and prognostic factors were evaluated by univariate and multivariate logistic regression analysis. *P* values <0.05 were considered statistically significant.

RESULTS

Demographic characteristics of patients

We initially enrolled consecutively 326 patients with acute leukemia from January 1998 through December 1999. As 42 of the patients did not have febrile episodes, 284 with such episodes were eligible for the study. Their median age was 32.5 (15-68), and there were 179 males and 105 females. Acute myelogenous leukemia (AML) was the most common underlying disease (n=189, 66.5%), followed by acute lymphocytic leukemia (ALL; n=90, 31.7%). There were 4 cases of biphenotype leukemia, and one case of undifferentiated type.

One hundred and fifty-three patients (53.9%) received initial induction chemotherapy, while 131 (46.1%) received reinduction chemotherapy. Acute myelogenous leukemia (AML) was the predominant underlying diagnosis in both groups, with no significant difference between them. There was no significant difference in demographic characteristics between the groups of dead and surviving patients (Table 1).

Table 1. Comparison of the general characteristics of dead and survived patients

	DG (n=28)	SG (n=256)
Median age (range) (yr)	35 (18-61)	32 (15-68)
Gender ratio (male:female)	18:10	161:95
Underlying diagnosis		
AML	17 (60.7%)	172 (67.2%)
ALL	11 (39.3%)	79 (30.9%)
Biphenotype		4 (1.6%)
Undifferentiated		1 (0.3%)

DG, dead group; SG, survived group; AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia.

Microbiological characteristics

As shown in Table 2, the number of isolation of Gram-positive cocci (GPC) was comparable to that of Gram-negative bacilli (GNB) (76 versus 74, respectively). GPCs were more frequent in the DG and GNBs were slightly more frequent in the SG, however, which was not statistically significant (Z=1.531, p=0.629). *Escherichia coli* was the most common GNB in the SG, whereas *P. aeruginosa* was the most common organism in the DG (7% in SG vs. 19% in DG, p=0.04). Staphylococci, streptococci, and enterococci were frequently isolated GPCs in both groups.

Table 2. Microbiological profiles

Organisms	DG	SG	*p*
Bacteria			
Gram positive cocci	11 (69%)	65 (49%)	0.63
Staphylococcus aureus	4	9	0.01
Coagulase (–) staphylococci	3	15	0.18
Alpha-hemolytic streptococci		4	
viridans streptococci		16	
Streptococcus pneumoniae		5	
Enterococcus species	4	15	0.06
Corynebacterium jeikeium		1	
Gram negative bacilli	5 (31%)	69 (51%)	0.63
Escherichia coli		37	
Klebsiella pneumoniae		12	
Pseudomonas aeruginosa	3	9	0.04
Aeromonas hydrophila		6	
Enterobacter species	1	2	
Citrobacter freundii	1	1	
Acinetobacter baumannii		1	
Morganella morganii		1	
Fungus	3	4	
Candida species	1	2	
Aspergillus species	2	2	
Virus	0	7	
Herpes simplex virus	0	5	
Varicella zoster virus	0	2	

Table 3. Comparison of the clinical course of dead and survived patients

	DG	SG	*p*
Type of infection			
CDI	12	90	
MDI	16	115	
UF		51	
Episode of fever before chemotherapy	8/28 (28.6%)	48/256 (18.8%)	
Median days to fever (range)	9 (1-17)	11 (1-29)	
Median leukocyte count (/μL) on onset	200 (100-900)	300 (100-900)	
Episode of hypotension	6/28 (21.4%)	19/256 (7.4%)	0.013
Median days of antibiotics administration	16 (2-48)	14 (3-86)	
Previous fungal infection	3/28 (10.7%)	1/256 (0.4%)	0.001
Invasive fungal infection	20/28 (71.4%)	52/256 (20.3%)	0.001
Median days of antifungal administration	12.5 (1-35)	12 (3-79)	
Median dosage (mg) of amphotericin-B	520 (39-2,140)	510 (85-3,180)	
Median days of neutropenia	19 (5-54)	17 (1-57)	
Median febrile days	10 (2-27)	5 (1-61)	0.001
Recovery from neutropenia	7/28 (25.0%)	247/256 (96.5%)	0.001

CDI, clinically defined infection; MDI, microbiologically defined infection; UF, unexplained fever.

Table 4. Causes of death

Infection-related	
Pneumonia	13
Sepsis and/or multiorgan failure	12
Skin and soft tissue infection	1
Typhlitis	1
Disseminated fungal infection*	1
Non-infection related	
Pulmonary hemorrhage	2
Ventricular arrhythmia	1

*Disseminated invasive aspergillosis (*Aspergillus flavus*).

Clinical course of patients

There were 102 cases of clinically-defined infection (CDI) (35.9%), 131 of microbiologically-defined infection (MDI) (46.1%), and 51 of unexplained fever (UF). Seventy-two patients (25.4%) were diagnosed with invasive fungal infection on the basis of EORTC/MSG criteria. Median days from neutropenia to the onset of fever, initial leukocyte count, duration of antibiotic treatment, duration of antifungal treatment, total dosage of amphotericin-B, and duration of neutropenia were not significantly different between DG and SG (Table 3). More patients in the DG experienced episodes of hypotension during their clinical course than those in SG (6/28, 21.4% vs. 19/256, 7.4%; χ^2=6.168, p=0.013). The incidence of invasive fungal infection in the DG was higher than in the SG (71.4% vs. 20.3%; χ^2=34.8; p=0.001). Median febrile period was greater in the DG than in the SG (10 vs. 5 days, p=0.001). While 247 patients (96.5%) in the SG recovered from neutropenia, only 25% of patients in the DG (n=7) did so (χ^2=136.5, p=0.001). Four patients had prior fungal infections. Three of them developed invasive fungal infections after the cytotoxic chemotherapy and all of them died. Overall, thirty-one patients died in hospital (mortality 11.0%). Of these, 90.3% (28/31) were infection-related deaths. As Table 4 indicates, pneumonia and sepsis were the most common causes of death.

Evaluation of prognostic factors

We performed univariate and multivariate analysis to identify significant prognostic factor(s) using in-hospital infection-related death as a dependent variable. A number of potential variables were evaluated. As Table 5 shows, episodes of hypotension, previous fungal infection, invasive fungal infection, recovery from neutropenia, median days to fever, pneumonia, and total febrile days were selected as significant variables by univariate analysis. Multivariate analysis of these variables finally selected three significant prognostic factors: previous history of fungal infection, episodes of invasive fungal infection, and recovery from neutropenia.

Table 5. Uni- and multivariate analysis of prognostic factors

	Univariate analysis O.R. (95% C.I.)	Multivariate analysis O.R. (95% C.I.)
Episode of fever before chemotherapy	1.70 (0.70-4.20)	
Episode of hypotension	3.40 (1.20-9.40)	1.59 (0.31-8.25)
Bacteremia	0.34 (0.08-1.49)	
Pneumonia	8.09 (3.46-18.90)	1.30 (0.27-6.29)
Pseudomonas aeruginosa infection	3.30 (0.84-12.96)	
Staphylococcal infection	2.04 (0.81-5.14)	
Previous fungal infection	30.6 (3.1-305.2)	82.5 (3.0-243.8)
Invasive fungal infection	9.8 (4.1-23.5)	15.7 (2.8-86.7)
Recovery from neutropenia	0.04 (0.01-0.36)	0.01 (0.001-0.031)
Days to fever	1.15 (1.04-1.30)	1.03 (0.88-1.20)
Duration of antibiotics	1.03 (0.99-1.06)	
Duration of antifungals	1.01 (0.97-1.05)	
Total dosage of amphotericin-B	1.00 (0.99-1.01)	
Days of neutropenia	1.03 (0.99-1.07)	
Total febrile days	1.10 (1.04-1.15)	1.03 (0.95-1.11)

O.R., odd ratio; 95% C.I., 95% confidence interval.

DISCUSSION

The inevitable deficit of host defense following chemotherapy places most patients in danger of infectious complications (1-4). As the clinical manifestations of infection in immunocompromised patients are in many respects different from those in immunocompetent ones, detection and management are almost always troublesome. For the successful treatment of infection, knowledge of significant prognostic predictors is important. There have been many reports of prognostic indicators of infection (5, 8-12). However, as far as we know, this is the first study of the prognostic factors of infectious complications in febrile neutropenic patients with acute leukemia in Korea.

Of the 284 patients in this study, 31 (10.9%) died. Most of these (90.3%, 28/31) died as a result of infection. Pneumonia and sepsis were the most common causes of death. Pneumonia itself seemed to be a predictor of death in univariate analysis, but multivariate analysis failed to confirm this. Though pneumonia is known to be an important infectious complication after chemotherapy (1, 13, 14), other factors could contribute to a serious clinical outcome.

The unique feature of the microbiological profile of the DG was the predominance of Gram positive cocci (69%) compared with SG. Over the last decade, there has been a shift towards Gram positive cocci (GPC) from Gram negative bacilli (GNB) as causative pathogens in immunocompromised hosts (1, 15). In our data, numbers of GPC and GNB were nearly equal, but there is a trend of steady increase in the frequency of GPC in our institution, especially following HSCT (16, 17). With regard to Gram negative organisms, *P. aeruginosa* was the major pathogen in the DG. As reported elsewhere (1), patients with GNB infections usually had a poor prog-

nosis. Among the GNBs, *P. aeruginosa* infection was particularly strongly associated with high mortality (18-20). In our study, however, univariate analysis showed that Gram positive cocci and *P. aeruginosa* infection did not influence the prognosis significantly, as indicated in Table 5.

Viral infection was relatively rare, and all cases involved herpes viruses. As the main defect in host immunity after chemotherapy is in innate rather than adaptive immunity, viral infection post-chemotherapy does not seem to be common or fatal.

Invasive fungal infection is probably the most fatal infectious complication in febrile neutropenic patients (21, 22). Among our patients, there were only 7 cases of microbiologically defined fungal infections. As the condition of febrile neutropenic patients seldom permits invasive diagnostic procedures, it is hard to confirm fungal infections in suspicious cases. Hence we used the EORTC/MSG criteria for invasive fungal infections (IFIs) to identify 72 cases (proven 7, probable 36, possible 29). The mortality of patients with IFI was 27.8% (20/52) and the incidence of IFI was much higher in the DG than in the SG (71.4% vs. 20.3%; p=0.001). Four patients had previous histories of IFI, and three of these suffered a recurrence (1 proven rhinocerebral aspergillosis, 1 probable, and 1 possible invasive aspergillosis) and all of them died. These findings strongly suggest that invasive as well as previous fungal infections are important factors affecting outcome. As both univariate and multivariate analysis showed, these two variables were independent influences on the final prognosis. However, dosage and duration of antifungal treatment did not affect survival.

Episodes of cardiovascular instability (hypotension) were more frequent in the DG than the SG, but multivariate analysis failed to show that this variable was an independent prognostic factor.

Neutropenia is the main defect in host defense after chemotherapy. As the neutrophil count and the duration of neutropenia are closely related to susceptibility to infection (2, 23, 24), variables associated with neutropenia seemed likely to affect the prognosis. In our study, although duration of neutropenia did not differ significantly between the DG and the SG, the neutrophil count was restored in fewer patients in the DG than in the SG (25.0% vs. 96.5%; p=0.001). As shown by the uni- and multivariate analysis, recovery from neutropenia was the significant protective factor for survival.

In summary, fungal infection (previous as well as invasive) and recovery from neutropenia were the main independently influential prognostic factors in acute leukemic patients with infectious complications after chemotherapy. The prognostic factors revealed in this study could help to identify patients with an increased risk of dying, and more intensive treatment focused on these factors could improve the outcome of infectious complications.

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