

Infection Features of Acute Leukemia Patients during Induction Chemotherapy: A Retrospective Analysis of 203 Cases

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Abstract

Infection is a major complication of chemotherapy for Acute Leukemia (AL). Two hundred and three patients with newly diagnosed AL were recruited in this study. By analyzing infection incidence (82.8%, 168/203), infection-related mortality (7.1%, 12/168), clinical features, and risk factors, as well as the correlation with efficacy for the patients during induction chemotherapy, we aimed to understand the significance of infection in patients with them, thereby guiding clinical treatment. All of the patients, 168 cases suffered from infection; among of them, there were clear sites of infection accounted for 94.6% (159/168), and the most infection sites were lungs, gastrointestinal tract, and oral cavity. 213 of pathogens were detected, including gram-negative bacilli (39.0%, 83/213), Gram-positive cocci (34.3%, 73/213), fungi (23.5%, 50/213), and virus (3.3%, 7/213). Diagnosis/clinical diagnosis of the patients with invasive fungal disease accounted for 24.6%, and the main pathogen was *Candida*. Multivariate analysis of the risk factor of infection showed that was neutropenia ($P < 0.001$, OR = 14.37, 95% CI 2.576 - 116.518); however, infection did not affect the rate of CR/CRi ($\chi^2 = 2.564$, $P = 0.109$).

Conclusion: During the first induction therapy for newly diagnosed AL patients, the rate of infection and fungal infection was high, Lung is the most common site of infection, Gram-negative bacteria is more common, agranulocytosis increase the chance of infection, it does not affect the complete remission rate.

Introduction

Infection is one of the most common complications in AL, especially during induction chemotherapy^[1,2]. The infection-related mortality is quite high, infection could delay chemotherapy, and increase the risk of recurrence^[3], and the mortality of febrile neutropenia reaches 10 - 20%^[4-6]. Therefore, we retrospectively analyzed the infection status of 203 cases of newly diagnosed AL patients in our hospital during induction chemotherapy, and tried to understand clinical features and risk factors of the infection, and the relationship with the efficacy during initial induction treatment for acute leukemia patients, thereby guiding clinical treatment.

Materials and Methods

Patients

From January 2015 to February 2016, 203 cases of hospitalized patients with newly diagnosed AL during induction chemotherapy at the Department of Hematology of the Second Hospital of Shanxi Medical University, among the patients, 106 cases were male and 97 were female, median age of 47 (16 - 79) years. There were 155 cases of acute myeloid leukemia (AML), in which 32 cases were Acute Promyelocytic Leukemia (APL), 46 cases were Acute Lymphoblastic Leukemia (ALL), including 15 cases of philadelphia chromosome-positive acute lymphoblastic leukemia (ph + ALL) and 2 cases of acute mixed leukemia (MAL).

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Keywords: Acute leukemia; Induction chemotherapy; Infection; Risk factor; Complete remission



Regimen for induction therapy

The “7 + 3” regimen (cytarabine × 7d and anthracycline or anthraquinone × 3d) was performed for induction therapy in patients with AML (non-APL); part of the elderly patients or hypoproliferative acute leukemia (HAL) patients received CIG regimen (cytarabine, idarubicin and recombinant human granulocyte colony - stimulating factor); APL patients were treated with retinoic acid, arsenic trioxide and/or anthracyclines; ph - ALL patients were treated with VDLP ± C regimen (vincristine, daunorubicin, L-asparaginase, and dexamethasone ± cyclophosphamide), whereas ph + ALL patients were imatinib replace L-asparaginase.

Diagnostic criteria of infection and related definition

Diagnostic criteria of infection referred to “The diagnostic criteria of nosocomial infection of Chinese Ministry of Health (trial implementation)”^[7], and diagnostic criteria of neutropenia with fever^[6,8,9] and Diagnostic criteria and treatment principles of invasive fungal disease in patient with hematonosis or malignancy^[10-12]. The axillary temperature of patients during induction chemotherapy was more than 38.0°C or over 37.7°C for one hour, detailed physical examination and microbiology, imaging and laboratory test, exclude drugs and transfusion-related fever.

Statistical analysis

SPSS 17.0 software was used for statistical analysis. Mann-Whitney test was used for comparison in groups of continuous variables. Chi-square test was used for the comparison of categorical variables between groups with risk factors for infection screened by univariate analysis, then Logistic regression was performed. All comparisons were two-tailed test, and $P < 0.05$ was considered statistically significant difference.

Results

Incidence and mortality of infection

The infection rate was 82.8% (168/203) during induction chemotherapy; 88 cases were male, 80 were female; 14 cases were dead, and 12 cases was due to infection (7.1%, 12/168), 5 males and 7 females, 5 elderly and 7 younger patients; 9 cases were AML (non-APL), 3 were ALL; one case was low-risk, eight were intermediate risk, and three were high risk.

Infection features

The site of infection

Among 168 patients with infection, patients with clear site of infection accounted for 94.6% (159/168), totally 328 cases times. The infected site was as follows: lung (26.1%, 93/328), gastrointestinal tract (17.1%, 61/328), oral cavity (12.4%, 44/328), upper respiratory tract (12.1%, 43/328), blood stream (10.4%, 37/328), cutaneous soft tissue (5.1%, 18/328), sinuses, perianal (3.7% each, 13/328), and urinary tract (1.4%, 6/328). The site of infection of 9 patients was not clear. single-site infection was accounted for 51/168, two-site was 85/168, and more than 3-site was 32/168.

Etiology information

213 pathogens were detected. Among these, 83 patho-

gens were gram-negative bacilli, including *Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *onion primary Haw de coli*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Malt bacillus subtilis*, *Aeromonas bacteria*, *Corynebacterium diphtheria* class, *Citrobacter*, *Serratia marcescens*, *Pseudomonas yellow perch*, and *Citrobacter freundii*; 11 strains of *Acinetobacter baumannii* were detected, which was accounted for 13.3% in Gram-negative bacilli, including seven strains of multi-drug resistance, two strains of extensively drug resistance, two strains of sensitivity; the drug-resistance rate of cefoperazone sulbactam, minocycline, and amikacin was 20%, following by 27.3% of imipenem, 30% of levofloxacin, and 36.4% of meropenem; mixed infection was accounted for 90.1% (10/11). 73 pathogens were gram-positive cocci, including *Enterococcus* (containing vancomycin-resistant enterococci), coagulase-negative staphylococci (containing *Staphylococcus haemolyticus*), *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus angina*, *Staphylococcus epidermidis*, and *Streptococcus songs*. 50 pathogens were fungi, including *Candida albicans*, *Candida krusei*, *C. parapsilosis*, *Aspergillus fumigatus*, lung mold, *Aspergillus flavus*, and *Candida tropicalis*. 7 pathogens were virus, accounting for 3.3 %, including EB virus, respiratory syncytial virus, and adenovirus (Table 1).

Table 1: Distribution and composition ratio of 10 pathogens.

Pathogens	Number(n)	Composition ratio(%)
Gram-negative bacilli	83	39.0
<i>Escherichia coli</i>	23	10.8
<i>Acinetobacter baumannii</i>	11	5.2
<i>Klebsiella pneumoniae</i>	9	4.2
<i>Pseudomonas aeruginosa</i>	8	3.8
<i>Stenotrophomonas maltophilia</i>	8	3.8
Others	24	11.3
Gram-positive cocci	73	34.3
<i>Enterococcus</i>	43	20.2
Coagulase-negative staphylococci	13	6.1
<i>Staphylococcus aureus</i>	7	3.3
<i>Streptococcus</i>	4	1.9
Others	6	2.8
Fungus	50	23.5
<i>Candida albicans</i>	32	15.0
Others	18	8.5
Virus	7	3.3
<i>Epstein-Barr virus</i>	5	2.3
Others	2	1.0

In addition, the spectrum of pathogens was different for different site; the pathogens with the three largest number of strains were analyzed (Figure 1). 82 pathogens were detected in respiratory: 44 strains were bacillus, including 10 strains of *Acinetobacter baumannii*, 9 strains of *maltophilia Aeromonas*, 6 strains of *Escherichia coli*, 6 strains of *Burkholderia* each; 14 strains were bacteria, including 9 strains of enterococci; 24 strains were fungal, including 15 strains of *albicans*. 54 pathogens were detected in gastrointestinal: 40 strains were cocci, all

being Enterococcus; 6 strains of bacillus, 4 strains of Klebsiella pneumonia, and 2 strains of Proteus; 8 pathogens were fungal, all being Candida, including 6 strains of Candida albicans. 67 pathogens were found from blood culture: 16 strains were gram-positive cocci, including 11 strains of coagulase-negative staphylococci (all were methicillin-resistance) 4 strains of Staphylococcus aureus; 25 strains of bacillus, including 10 strains of E. coli and 4 strains of Pseudomonas aeruginosa. 19 pathogens were fungi, including 10 strains of Candida albicans. 7 pathogens were virus.

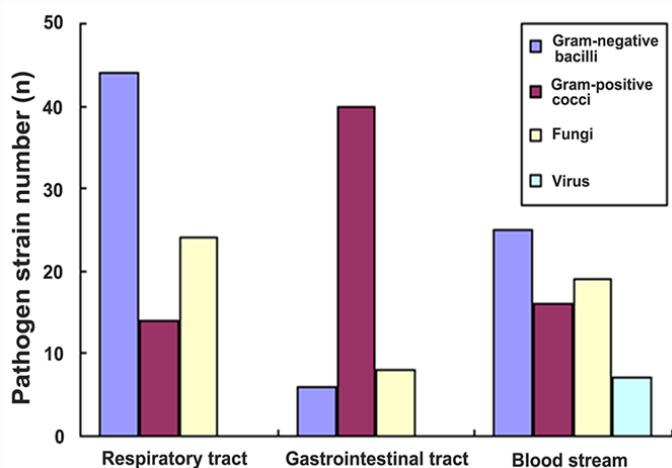


Figure 1: The spectrum of pathogens of the three largest number of strains.

By analyzing of infection with different age, it was found that the common infection site of elderly patients was lung

(65.2%, 30/46), gastrointestinal tract (30.4%, 14/46), blood flow (26.1%, 12/46), whereas the common infection sites of non-elderly patients was slightly different, including lung (40.1%, 63/157), gastrointestinal tract (29.9%, 47/157), and oral cavity (22.9%, 36/157); both groups there was no significant difference in terms of detection rate of bacillus and fungal and mortality, and detection rate of cocci in non-elderly group was significantly higher than that in older group (Table 2).

Table 2: Analysis of infection for 46 cases of elderly patients and 157 cases of non-elderly patients.

Group	Elderly (%)	Non-Elderly (%)	χ^2	P value
Pathogens				
Gram-negative bacilli	47.1%(33/70)	35.0%(50/143)	2.930	0.087
Gram-positive bacilli	21.4%(15/70)	40.6%(58/143)	7.635	0.006
Fungus	27.1%(19/70)	21.7%(33/143)	0.421	0.516
Mortality	10.9%(5/46)	4.5%(7/157)	1.647	0.199

Analysis of risk factor

By univariate analysis of infection factors in AL patients during induction chemotherapy, it was showed that neutropenia, neutropenia time > 7 days, AML, and co-infection before chemotherapy were risk factors of infection for AL patients (Table 3). Multivariate analysis found that neutropenia was independent risk factor of infection.

Table 3: Infection risk factors for the AL patients during induction chemotherapy.

Factor	Uni-variate analysis				Multivariate analysis		
	Cases(n)	infection(n)(%)	χ^2	P value	OR	95% CI	P value
Sex			0.100	0.752			
Male	106	88(83.0)					
Female	97	80(82.5)					
Age 1(years old)			8.601	0.197			
16 - 20	20	14(70.0)					
21 - 30	37	29(78.4)					
31 - 40	31	26(86.7)					
41 - 50	31	26(86.7)					
51 - 60	39	34(87.2)					
61 - 70	38	33(86.8)					
71 - 79	7	6(85.7)					
Age 2(years old)			0.307	0.579			
< 60	157	129(82.2)					
≥ 60	46	39(85.7)					
Type of leukemia			26.528	0.000	1.972	0.252 - 15.444	0.518
AML(non-APL)	123	110(89.4)					
ALL	46						
Ph -	31	16(51.6)					
Ph + ALL	15	12(80.0)					
MAL	2	2(100.0)					
APL	32	26(81.3)					
Stratification of risk			0.641	0.866			
Low risk	21	16(76.2)					

Intermediate risk	115	97(84.3)					
High risk	67	55(82.1)					
ANC			117.00	0.000	14.37	2.576 - 116.518	0.000
0 - 0.09	138	138(100.0)					
0.10 - 0.19	17	11(64.7)					
0.20 - 0.29	18	7(38.9)					
0.30 - 0.39	5	2(40.0)					
0.40 - 0.49	2	1(50.0)					
≥ 0.5	23	10(43.5)					
Time of neutropenia			14.240	0.000	0.926	0.143 - 6.019	0.936
> 7 days	152	140(92.1)					
≤ 7 days	51	28(54.9)					
Chemotherapy prior to infection			82.817	0.000	1.026	0.162 - 6.518	0.978
Yes	134	116(86.6)					
No	69	16(23.2)					
Glucocorticoids			23.781	0.000	0.029	0.001 - 0.841	0.039
Yes	46	28(60.9)					
No	157	140(89.2)					
Diabetes			0.001	0.979			
Yes	20	16(80.0)					
No	183	152(83.1)					

Note: b: regression coefficient, OR: odds ratio, 95% CI: 95% confidence interval.

Table 4: Risk factors of fungal infection for AL patients during induction therapy.

Factor	Uni-variate analysis				Multivariate analysis		
	Cases(n)	Infection(n)(%)	χ^2	P value	OR	95% CI	P value
Age			7.287	0.007	2.604	1.160 - 5.842	0.020
≥ 60 years old	46	17(37.0)					
< 60 years old	157	33(21.0)					
Sex			2.951	0.086	0.611	0.301 - 1.239	0.072
Male	106	26(24.5)					
Female	97	24(24.7)					
Type of leukemia			3.234	0.357			
AML	125	35(27.3)					
Non-AML	78	15(19.2)					
Stratification of risk			5.302	0.151			
Low and intermediate risk	136	32(23.5)					
High risk	67	18(26.9)					
ANC			23.373	0.000	15.961	2.036 - 125.091	0.006
< 0.5	153	50(32.7)					
≥ 0.5	50	0					
Time of neutropenia			10.627	0.001	1.960	0.888 - 4.327	0.096
> 14 days	66	30(45.5)					
≤ 14 days	137	20(14.6)					
Chemotherapy prior to infection			1.070	0.301			
Yes	134	36(26.9)					
No	69	14(20.3)					
Diabetes			5.647	0.172			
Yes	20	6(30.0)					
No	183	44(24.0)					

Glucocorticoids			2.143	0.367		
Yes	46	18(39.1)				
No	157	32(20.4)				

50 cases of patients with diagnosis/clinical diagnosis invasive fungal disease, composed of 26 males and 24 females. Univariate analysis showed that age ≥ 60 years old, neutropenia, and neutropenia time > 14 days were risk factors. Multivariate analysis showed that age ≥ 60 years old and neutropenia were risk factors of fungal infection (Table 4).

Correlation of infection with efficacy

Comparison of 168 cases of infection with 35 patients with non-infection in sex, age, risk stratification of leukemia, and chemotherapy, resulted in comparable balance. CR /CRi rate of the two groups of patients was not significant difference (Table 5).

Table 5: Correlation analysis of infection and efficacy for AL patients.

Group	Cases(n)	CR/CRi(n)(%)	χ^2	P value
Infected group	168	125 (75.6%)	2.564	0.109
Non-infected group	35	28(88.6%)		

Discussion

In this study, our data showed incidence of infection was 82.8% in 203 patients with newly diagnosed AL during induction chemotherapy, and the infection-related mortality was 7.1%, which was the main cause of death, in line with the study by Masmoudi., *et al*^[13,14]. Moreover, sex, age, type of leukemia, risk stratification, and multi-site infection factor were not the factors for death. Clear site of infection were accounted for 94.6% (159/168), the most common site of infection was lung, which was consistent with the study by Cannas., *et al*^[1,2,15,16]. 213 pathogens were isolated, gram-negative bacilli still predominantly^[1,2,6,13,16], where *E. coli* was the most common pathogen, followed by *Acinetobacter baumannii*, which was in line with the studies of Chinese CHINET monitoring network of drug-resistance bacteria in 2012^[17,18]. Similarly, the high rate of detection, high rate of multi-drug resistance and extensively drug-resistance^[19], often accompanying by a mixed infection, and the common site of infection in lung should be paid attention. Gram-positive cocci is followed by pathogen, unlike other epidemiological investigation^[1,2,6,13], predominantly *Enterococcus*, illustrating that empirical antibiotic therapy should consider local epidemiological investigation. Although *Staphylococcus aureus* and coagulase-negative staphylococci were reduced, coagulase-negative staphylococci was still the most common pathogen for infection in blood stream^[15,17], but the methicillin-resistant rate was increased (100%), which was significantly higher than that in other studies^[20], probably relating to less strains of coagulase-negative staphylococcus in our study. The study also found that the infection spectrum of pathogen in different infected site was significantly different: respiratory was mainly gram-negative bacilli, predominantly drug-resistant strains; *Enterococcus* was mainly in the gastrointestinal tract, followed by bacillus of blood culture, coccus, fungi, and virus, suggesting that the initial

empirical anti-infective therapy should consider different infection pathogen^[1].

In this study, incidence of invasive fungal disease (24.6%) was significantly higher than that in CAESAR research^[21] (4.94%), and the infection was mainly caused by *Candida*^[1,12,21-23], predominantly in lung^[1,21,22]. Univariate and multivariate analysis of factor affecting fungal infection, found that age ≥ 60 years and neutropenia were the risk factors for fungal infection^[24]. The virus infection rate was low, mainly with EB virus.

Occurrence and severity of infection are related to the degree of neutropenia and duration^[5,25]. In this study, infection of 70% patients started with neutropenia, and the vast majority of patients were with severe neutropenia or the neutropenia time was more than 7 days. Univariate analysis of factors of infection found that neutropenia, especially severe neutropenia, neutropenia > 7 days, AML, co-infection before chemotherapy were the risk factors for infection, which was in line with the study by Chindaprasirt., *et al*^[26,27]. Multivariate analysis showed that neutropenia was the independent risk factor for infection. Unlike Li., *et al*^[22] study, the present study found that diabetes and the use of hormones did not increase infection. In addition, although age was not the risk factor, the feature of infection was different, the fungal infection rate of blood stream in elderly patients was higher than that in younger patients (but with a higher detection rate of coccus).

Unlike other studies^[27] that infection increases hospital stay, this study found no increase in hospital stay with infection. 168 cases of infection with a median length of hospital stay was 29 days (18 - 56 days); for non-infected patients, median hospital stay was 28 days (21 - 42 days). The difference was not significant (P = 0.59). However, it has been demonstrated that^[28-30], no matter AL patient achieves CR after chemotherapy, or the patient was without clinical contraindications, and even with severe neutropenia, it could not affect the discharge. But we need more clinical validation to confirm this conclusion.

It has been found that fungal infection is a prognostic factor^[31]. The analysis of correlation between infection and efficacy for AL patients during induction chemotherapy showed that the CR/CRi rate of 203 cases of AL patients was 76.8% (155/203), and infection was not the factor affecting efficacy, which was not consistent with the above conclusion.

During the first induction therapy for AL patients, the rate of hospital infection and fungal infection was high, the main cause of death during induction therapy was infection. The dead patient mostly were co-infected in pulmonary, gastrointestinal tract, and blood stream with high detection rate of drug-resistant strains of pathogens. Neutropenia was an independent risk factor for infection, but the occurrence of infection did not affect the rate of CR/CRi. Therefore, during chemotherapy with neutropenia and neutropenia > 14 days, whether patients can receive a preventive anti-infective therapy, early prevention and treatment have to be performed to reduce the infection incidence and mortality during chemotherapy, which may give more opportunity for the subsequent treatment.

Conflict of Interest: None.

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