

Infections During Induction Therapy of Protocol CCLG-2008 in Childhood Acute Lymphoblastic Leukemia: A Single-center Experience with 256 Cases in China

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Abstract

Background: Infections remain a major cause of therapy-associated morbidity and mortality in children with acute lymphoblastic leukemia (ALL).

Methods: We retrospectively analyzed the medical charts of 256 children treated for ALL under the CCLG-2008 protocol in Beijing Children's Hospital.

Results: There were 65 infectious complications in 50 patients during vincristine, daunorubicin, L-asparaginase and dexamethasone induction therapy, including microbiologically documented infections ($n = 12$; 18.5%), clinically documented infections ($n = 23$; 35.3%) and fever of unknown origin ($n = 30$; 46.2%). Neutropenia was present in 83.1% of the infectious episodes. In all, most infections occurred around the 15th day of induction treatment ($n = 28$), and no patients died of infection-associated complications.

Conclusions: The infections in this study was independent of treatment response, minimal residual diseases at the end of induction therapy, gender, immunophenotype, infection at first visit, risk stratification at diagnosis, unfavorable karyotypes at diagnosis and morphologic type. The infection rate of CCLG-2008 induction therapy is low, and the outcome of patients is favorable.

Key words: Acute Lymphoblastic Leukemia; Childhood; Induction Therapy; Infection

INTRODUCTION

Bacterial and fungal infections are major causes of morbidity and mortality in children during chemotherapy for ALL.^[1-3] Infections increase the risk of death and may also increase the risk of relapse due to interruption of treatment and the need for a decreased dose of the chemotherapeutic agent.^[4] To further lower the risk of serious and long-lasting infections by additional supportive measures, detailed information on the frequency and characteristic features of infections is needed. Therefore, patient data from 256 children with ALL who were treated according to the CCLG-2008 protocol in Beijing Children's Hospital were analyzed for differences in the frequency and origin of febrile episodes.

METHODS

Patients

Two hundred and fifty-six acute lymphoblastic leukemia (ALL) patients treated with CCLG-2008 from April, 2008 to March, 2010 were enrolled in this single-center study. Infectious complications and hematological toxicities were analyzed. Patients were regularly followed-up in our Hematology Department or by telephone. The median follow-up for all patients was 53 months (range, 3–72 months). Table 1 summarizes the characteristics of all patients.

Classifications and treatments

The patients were stratified into standard-risk (SR), intermediate-risk (IR) and high-risk (HR) groups according to age, white blood cell count, immunophenotype,

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cytogenetic and molecular aberrations, prednisone response, morphological remission at the end of induction therapy (based on BFM risk criteria), minimal residual disease (MRD) at the end of induction therapy and the beginning of consolidation therapy.^[5-8] Induction chemotherapy of CCLG-2008 is outlined in Table 2.

Statistical analysis

Fever was defined as a single axillary temperature of $\geq 38.5^{\circ}\text{C}$ or a temperature of $\geq 38.0^{\circ}\text{C}$ for ≥ 4 h. An infectious complication was defined as fever requiring

antibiotic (and/or antimycotic and/or antiviral) treatment. Infectious episodes were categorized as microbiologically or clinically documented infections (MDI/CDI) or as fever of unknown origin (FUO). The term 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 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 FUO when there was no clinical, radiological or microbiological evidence of infection. Neutropenia was defined as a neutrophil count of $< 500/\text{L}$, or a count of $< 1000/\text{L}$ with a predicted decrease to $< 500/\text{L}$.^[9,10]

One cycle of chemotherapy was defined as the period from the start of chemotherapy to the day before the next cycle of chemotherapy. Response to treatment was assessed according to the BMF criteria.^[11] At the time of diagnosis or at the beginning of chemotherapy, all children had a central venous catheter (CVC) inserted.

If patients had infection at their first visit [Table 1], intravenous (i.v.) antibiotics (the second cephalosporin) were given for 5–7 days or until the temperature was $< 38.0^{\circ}\text{C}$ for 2–3 days. Moreover, all patients in this group were treated with prophylactic sulfamethoxazole compound tablets during the induction period routinely from the beginning of induction therapy, at a daily dose of 25 mg/kg (4 days consecutively with 3-days interval).

The first-line i.v. antibiotic therapy consisted of the third cephalosporin, carbapenems, and vancomycin. In case of bacteremia, i.v. antibiotic therapy was continued for at least 7 days and 3–5 days after defervescence. In case of FUO, i.v. antibiotics were given for 5–7 days or until the temperature was $< 38.0^{\circ}\text{C}$ for 2–3 days. The antibiotic therapy was adjusted according to culture results and the clinical response of the patient. After 5–6 days of neutropenic fever, antifungal therapy was initiated either with fluconazole or with itraconazole orally at the discretion of the physicians.

Statistical evaluation was done with SSPS version 20.0 software (SPSS Inc., USA). Hematologic parameters were compared between subgroups of patients using the nonparametric Mann–Whitney test for the numeric variables and the Chi-square test for the categorical variables. Spearman

Table 1: Patient characteristics at diagnosis

Characteristics	Patients evaluated	Infection group	Noninfection group
Number of patients*	256 (100)	50 (19.6)	206 (80.4)
Gender*			
Male	158 (61.7)	26 (52.0)	132 (64.1)
Female	98 (38.3)	24 (48.0)	74 (35.9)
Age			
Age < 1-year*	5 (1.9)	4 (8.0)	1 (0.5)
1-year \leq age < 10 years*	196 (76.7)	39 (78.0)	157 (76.2)
Age \geq 10 years*	55 (21.4)	7 (14.0)	48 (23.3)
Immunophenotype			
B lineage*	226 (88.3)	36 (72.0)	190 (92.2)
T lineage*	22 (8.5)	12 (24.0)	10 (4.9)
Others*	8 (3.2)	2 (4.0)	6 (2.9)
Infection at first visit*	121 (47.3)	33 (66.0)	88 (42.7)
No infection at first visit*	135 (52.7)	17 (34.0)	118 (57.3)
Risk stratification			
SR*	136 (53.1)	27 (54.0)	109 (52.9)
IR*	107 (41.8)	21 (42.0)	86 (41.7)
HR*	13 (5.1)	2 (4.0)	11 (5.4)
Unfavorable karyotypes* [†]	46 (18.0)	8 (16.0)	38 (18.4)
WBC ($\times 10^9/\text{L}$) [‡]	36.6 \pm 8.7	34.5 \pm 6.6	38.1 \pm 8.8
Neutrophil count ($\times 10^9/\text{L}$) [‡]	2.3 \pm 0.3	1.2 \pm 0.2	2.5 \pm 0.4
Hemoglobin (g/L) [‡]	86.4 \pm 2.3	83.7 \pm 2.4	87.2 \pm 2.2
Platelet ($\times 10^9/\text{L}$) [‡]	102.6 \pm 10.1	98.6 \pm 5.7	112.3 \pm 9.9
C-reactive protein (mg/L) [‡]	35.5 \pm 5.7	31.6 \pm 4.3	37.1 \pm 5.9
Circulating blasts ($\times 10^9/\text{L}$) [‡]	26.9 \pm 8.3	23.4 \pm 6.4	28.4 \pm 8.6

*Data are the number of patients and percentage (n (%)); [†] t (9,22), t (4,11), t (1,19) and t (11,14); [‡]Data are the mean \pm SD. SR: Standard-risk; IR: Intermediate-risk; HR: High-risk; SD: Standard deviation; WBC: White blood cell.

Table 2: VDLD induction chemotherapy

Items	SR	IR and HR
Pred	60 mg·m ⁻² ·d ⁻¹ , p.o. t.i.d., d1 25% of total dose, d2 50% of total dose, d3 75% of total dose, d4 100% of dose, d1–7	60 mg·m ⁻² ·d ⁻¹ , p.o. t.i.d., d1 25% of total dose, d2 50% of total dose, d3 75% of total dose, d4 100% of total dose, d 1–7
Dexamethasone	6 mg·m ⁻² ·d ⁻¹ , p.o. t.i.d., d8–28	6 mg·m ⁻² ·d ⁻¹ , p.o. t.i.d., d8–28
L-ASP	5000 u·m ⁻² ·d ⁻¹ , i.m./i.v., d8, 11, 14, 17, 20	5000 u·m ⁻² ·d ⁻¹ , i.m./i.v., d8, 11, 14, 17, 20, 23, 26, 29
VCR	1.5 mg·m ⁻² ·d ⁻¹ , i.v., d8, 15, 22, 29	1.5 mg·m ⁻² ·d ⁻¹ , i.v., d8, 15, 22, 29
DNR	30 mg·m ⁻² ·d ⁻¹ , i.v. (1 h), d8, 15	30 mg·m ⁻² ·d ⁻¹ , i.v. (1 h), d8, 15, 22, 29
Intrathecal therapy	MTX d1, 15, 33	MTX, Pred, Ara-C d15, 33

L-ASP: L-asparaginase; VCR: Vincristine; DNR: Daunorubicin; MTX: Methotrexate; SR: Standard-risk; IR: Intermediate-risk; HR: High-risk; i.v.: Intravenous.

and logistic regression was used to examine the degree of correlation between infection and variables. The Kaplan–Meier method was used to estimate overall survivor (OS) and event free survivor (EFS), and the intergroup comparisons were conducted using the log-rank test. $P < 0.05$ was considered as statistically significant.

RESULTS

Infections in standard-risk, intermediate-risk and high-risk groups

Fifty out of the 256 (19.6%) patients had infections based on our criteria. However, there was no differences among the three risk groups, that is, 2/13 (15.4%) in HR versus 21/107 (19.6%) in IR versus 27/136 (19.9%) in SR ($P = 0.65$). The median number of infectious episodes was 0 per patient with a range of 0–2. The total numbers of infectious episodes were 4/13, 28/107 and 33/136 for HR, IR and SR, respectively ($P = 0.50$). There was no trend for more infectious complications in HR patients.

Types and sites of infection

The most frequent episodes were FUO, followed by CDI and MDI [Table 3]. Almost 83.1% (54/65) of all episodes occurred during the period of neutropenia. The frequent clinical infections were upper respiratory tract infection, pneumonia, and infectious diarrhea.

There were 10 bacteremias. As shown in Table 3, compared to Gram-positive cocci, Gram-negative bacilli was more frequent in bacteremias. *Klebsiella pneumoniae* was the most common Gram-negative bacilli, whereas *Streptococcus intermedius* was the most common Gram-positive cocci.

Clinical course of patients

Median lowest leukocyte count and median lowest neutrophil count on infection were $1.0 \times 10^9/L$ and $0.1 \times 10^9/L$ respectively. During the induction treatment, median durations of neutropenia, fever and antibiotics administration were 10, 6 and 13 days, respectively [Table 3].

Most infection occurred around the 15th day of induction treatment (28/65; d15 vs. d8, $P < 0.01$) while only four patients had infection around the 29th day (4/65; d29 vs. d22, $P < 0.05$). Figure 1 shows the neutrophil count at different time points of induction treatment (0.9 ± 0.1 , d8; 0.8 ± 0.1 , d15; 2.6 ± 0.2 , d22; 1.1 ± 0.1 , d29; 1.9 ± 0.1 , d33). Compared to other time points of induction treatment, day 15 and day 8 showed more severe bone marrow depression.

No patient died during the vincristine, daunorubicin, L-asparaginase and dexamethasone (VDLD) induction treatment, and only one patient with appendicitis required treatment in an intensive care unit. Chemotherapy postponement was observed in 18 (7.0%) patients due to infection, and the median period of chemotherapy delay was 8 days (range, 3–19 days).

Factors related with infection during induction treatment

There were significant correlations of infection episodes

Table 3: Characteristics of infectious complications and hematological toxicities

Characteristics	Values
Type of infection	
CDI	23 (35.3%)
Upper respiratory tract infection	11
Pneumonia	7
Appendicitis	2
Infectious diarrhea	3
MDI	12 (18.5%)
Bacteremia	
<i>Escherichia coli</i>	2
<i>Klebsiella pneumoniae</i>	3
<i>Pseudomonas aeruginosa</i>	2
<i>Enterobacter cloacae</i>	1
<i>Streptococcus intermedius</i>	2
Urinary infection	
<i>Serratia marcescens</i>	1
Fungal infection	
<i>Aspergillus</i> species	1
FUO	30 (46.2%)
Accompanied with neutropenia	54 (83.1%)
Median lowest leukocyte count ($\times 10^9/L$) on onset	1.0 (0.28–5.20)
Median lowest neutrophil count ($\times 10^9/L$) on onset	0.1 (0–0.96)
Median days of fever	6 (2–24)
Median days of neutropenia duration	10 (6–24)
Median days of antibiotics administration	13 (3–24)

CDI: Clinically documented infections; MDI: Microbiologically documented infections; FUO: Fever of unknown origin.

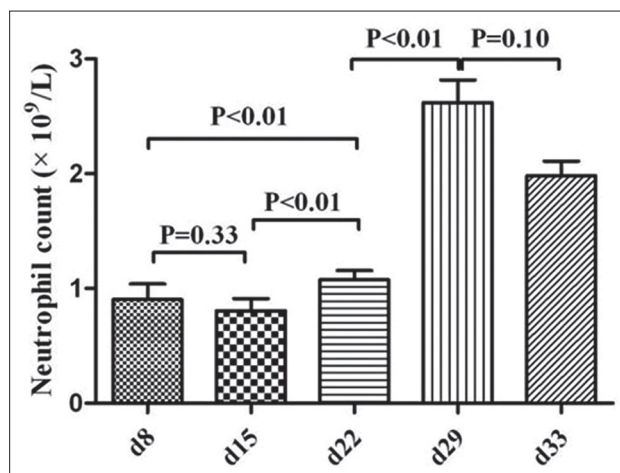


Figure 1: Neutrophil count in the different time points of induction treatment (data are the mean \pm SD).

with the neutrophil count at diagnosis ($r = -0.19$, $P = 0.03$), platelet at diagnosis ($r = -0.28$, $P < 0.01$), age ($r = -0.15$, $P = 0.05$), neutrophil count on d8 ($r = -0.28$, $P < 0.01$), d15 ($r = -0.22$, $P = 0.01$), d22 ($r = -0.20$, $P = 0.02$), d29 ($r = -0.25$, $P = 0.02$) and d33 ($r = -0.28$, $P < 0.01$), as well as with the neutropenia duration ($r = 0.26$, $P = 0.03$).

In logistic regression analysis, no correlation was found between infection and any of the following variables: Gender,

immunophenotype, infection at first visit, risk stratification at diagnosis, unfavorable karyotypes at diagnosis, morphologic type or treatment response.

Correlations of infection episodes with survival and disease progression

The remission rate of VDLD induction therapy was 93.8% (240/256). The median OS and median EFS were 55 months (range, 3–72 months) and 54 months (range, 2–72 months) respectively. Twenty-seven patients relapsed, and 35 patients died by the time of completion of this study.

The median OS and EFS of patients with infection in induction treatment were 55 and 53 months respectively, while the median OS and EFS of patients without infection during induction treatment were 55 and 54 months respectively. The OS and EFS did not show a trend of decrease ($P = 0.78$ and 0.67) with infection during induction chemotherapy. Examination of the survival curves demonstrated that infections during VDLD induction treatment were relatively slight, that is, infections did not influence the prognosis [Figures 2 and 3].

DISCUSSION

Infectious complications have been the most frequent manifestations of chemotherapy toxicity in children with acute leukemia.^[12,13] Detailed data on infectious morbidity rates in pediatric ALL are limited and focus on relatively small series of patients.^[14–16] Moreover, there are few reports in China. The purpose of this study was to evaluate the extent, the spectrum of infectious complications, and the severity of bone marrow depression in ALL children under induction chemotherapy.

Other studies showed that despite protocol guidelines for supportive care, there was still very high rate of infections in ALL treatment, especially during the induction therapy.^[2,14,16–18] Asim *et al.* reported that infection alone or in combination with other factors was responsible for deaths in 63 of 74 (85%) cases.^[2] The analysis by Nakamura showed a very high rate

of 737 infections in 72 patients.^[16] Tang *et al.* found that during induction therapy, 27.2% developed infection and among them 1.3% suffered serious infection, and 0.6% died of complication.^[17] Moreover, Liang *et al.* reported that infection was the most common cause of death during the induction therapy.^[18] However, according to our data, only 19.6% of all patients had infection during the induction therapy, and no patient died during the VDLD induction treatment; no statistical difference in infection rate was detected among SR, IR and HR groups. This large variation in infectious complications might be explained by factors including the severity and duration of neutropenia, the nature and intensity of antineoplastic therapy, the use of empiric antibiotic therapy, other host-related factors like age, use of CVCs and other external medical devices, environmental and geographical factors and length of hospital stay.

The most frequent infectious episodes in our series were FUO, followed by CDI and MDI. In contrast to our analysis, Lex *et al.* and Rahiala *et al.*, found FUO at 36–54% and clinically or microbiologically documented episodes at 60–46%.^[14,19] Since all authors used the same definitions, reasons for these differences remain unclear. In the group of clinically documented episodes, the most frequent infections in our patients were pneumonia, which is similar to the data of Rahiala *et al.* and Graubner *et al.*^[4,14] Although previous studies showed that Gram-positive organisms represented the majority of bloodstream isolates, we did not find an increasing incidence of Gram-positive isolates throughout the study period.^[4,12,14] In our analysis, Gram-negative bacilli was more frequent in bacteremias. This large variation in etiology detection indicates possible difference in inherited factors for susceptibility toward infections and difference in environmental factors.

Infectious complications differed considerably during the VDLD induction treatment phases. While only four patients had infection around the 29th day, the majority of infectious episodes was found at day 8 and day 15, suggesting that doctors should pay more attention on the neutrophil count, CRP and temperature at day 8 and day 15. Laminar air flow ward may

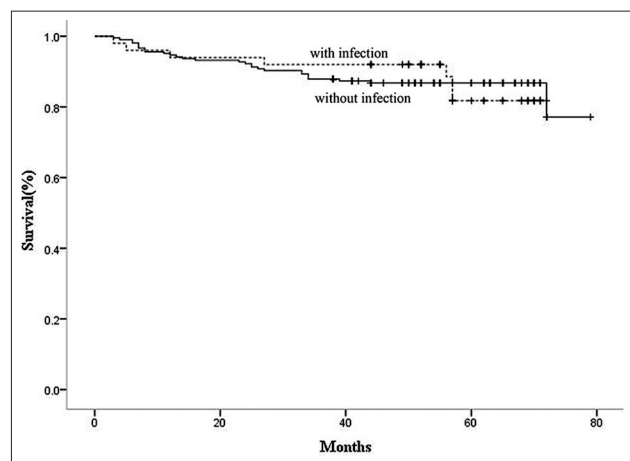


Figure 2: Overall survival of patients according to the presence or absence of infections.

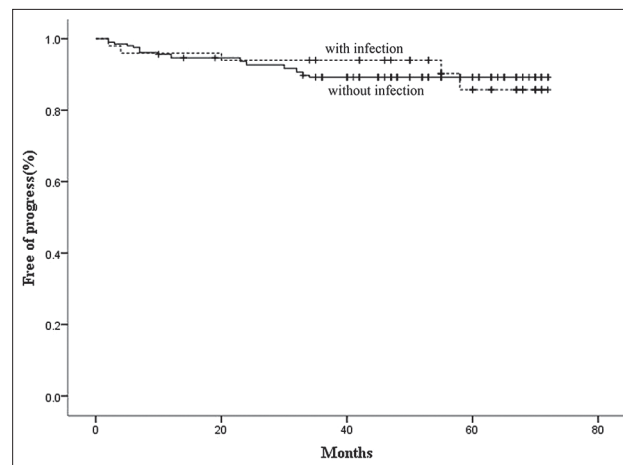


Figure 3: Event free survival of patients according to the presence or absence of infections.

be a better choice for patients in the susceptible periods.

Neutropenia is the main defect in host defense after chemotherapy. In our study, almost 83.1% of the infections occurred during the period of neutropenia. Compared to other time points of induction treatment, patients on day 8 to day 15 showed more susceptibility to infection and lower neutrophil count, suggesting a close relationship between neutropenia and infection. Mono-therapy with a broad spectrum anti-pseudomonal beta-lact (a carbapenem) or piperacillin-tazobactam is recommended for uncomplicated episodes of fever in neutropenic patients. Vancomycin should be reserved for children with clear indications for Gram-positive coverage.^[20,21] Empiric antifungal therapy may be warranted for patients who have persistent fever after 4–7 days of broad-spectrum antibiotics and no identified source of fever.^[22]

The infections in this study were independent of treatment response, MRD at the end of induction therapy, gender, immunophenotype, infection at first visit, risk stratification at diagnosis, unfavorable karyotypes at diagnosis or morphologic type and the Kaplan–Meier analysis of our data showed that infection during induction therapy had no significant influence on the prognosis of ALL patients in this study.

Infection is a life-threatening complication of chemotherapy in children with leukemia. In the present retrospective study, the infection rate was only 19.6%, with no deaths occurring in the induction therapy. These results indicate that the risk of infection and therapy-related death during induction with protocol CCLG-2008 are lower while the remission rate and quality of the induction are better. However, longer follow-up is still needed to estimate the long-term result.

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