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Original Article

Complications and outcomes of pediatric patients with hyperleukocytic acute lymphoblastic leukemia with CCLG-2008 protocol

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Abstract: A treatment protocol (CCLG-2008) has been carried out for pediatric ALL patients over 5 years in most regions of China. However, its efficiency on ALL with high WBC hasn't yet been reported. In this study, we retrospectively analyzed the data of 399 patients who were treated by protocol of CCLG-2008 between January 2009 and June 2014, especially focused on the outcome of the group with high WBC (above 50×10^9/L). 121 patients met the criteria of WBC count over 50×10^9/L at newly diagnosis, of which, 65 cases had WBC over 100×10^9/L (38 cases between 100×10^9/L and 200×10^9/L, 8 cases between 200×10^9/L and 300×10^9/L, and 19 cases over 300×10^9/L). Early complications occurred in 42 of 121 patients (34.7%). Importantly, patients with super-hyperleukocytosis (WBC over 300×10^9/L) had a significantly shorter event free survival (EFS, $P = 0.006$), higher relapse ($P = 0.022$), higher early death (ED, $P = 0.005$) and higher treatment related death (TRD, $P = 0.036$) compared to ALL with WBC below 300×10^9/L. WBC over 300×10^9/L confers a poorer outcome which should be considered as an independent prognosis factor who need more effective treatment to improve their long term survival.

Keywords: Pediatric acute lymphoblastic leukemia, hyperleukocytosis, event free survival, early death, treatment related death

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. With improved contemporary therapy, the treatment outcome of pediatric ALL has been significantly improved, leading to continuous complete remission (CCR) in about 85% of children with ALL. However, there are still factors affecting treatment outcome, such as age, initial leukocyte count, immunophenotype, cytogenetic features, early treatment response [1-3]. High WBC (Hyperleukocytosis) in a patient with ALL is associated with morbidity and mortality. Pediatric ALL with hyperleukocytosis frequently associates with leukostasis, hyperviscosity, and severe metabolic as well as electrolyte derangements [4-7]. Patients with hyperleukocytosis are at risk for early death, neurological complications including intracranial hemorrhage, pulmonary leukostasis syndrome, and tumor lysis syndrome that lead to a mortality rate as high as 20% during remission induction therapy [8, 9]. The effect of very high WBC over 100 or 200×10^9/L at initial stage on the outcome of pediatric acute lymphoblastic leukemia (ALL) was described by different clinical trials [5, 9, 10]. ALL children with hyperleukocytosis always show a high incidence of complications, higher relapse rates, shorter event free survival (EFS) and overall survival (OS) [7, 11, 12].

The treatment protocol (CCLG-2008) has been launched in China since Aug 2008 for front-line pediatric ALL patients based on risk stratification. At present time, there are few reports on Chinese pediatric ALL patients treated by CCLG-2008 protocol. Liu X et al [13] indicated in a retrospective study at the reassignment of risk group in low and median risk groups children with acute lymphoblastic leukemia by minimal

Table 1. Risk stratification (CCLG-2008 protocol)

	Risk Group		
	Low-risk (Must meet the following 1-8 criteria at the same time)	Intermediate-risk (Must meet the following 1-4 criteria at the same time, and at least meet the following one of 5-10 criteria)	High-risk (At least meet the following one of 1-5 criteria)
I	Age (y): ≥1 and <10	Cytogenetic and molecular: t (9; 22) or BCR-ABL fusion gene negative, T (4; 11) with MLL/AF4 or MLL related gene negative	Cytogenetic and molecular: t (9; 22 or BCR-ABL fusion gene positive, t (4; 11) with MLL/AF4 or MLL related gene positive
II	Presenting WBC: $<50\times10^9$/L	Prednisone induced response on day 8: PB blasts <1000/ul	Prednisone induced response on day 8: PB <100 ul
III	Cytogenetic and molecular: t (9; 22) or BCR-ABL fusion gene negative, T (4; 11) with MLL/AF4 or MLL related gene negative, t (1; 19) with E2A-PBX1 fusion gene negative	BM: induction treatment of SR on day 15: M3 or the induction treatment of IR on day 15: M1/M2	induction treatment of IR on day 15: M3; induction treatment on day 33: NCR (>5%), M2/M3
IV	Immunophenotype: B-cell precursor ALL	MRD on day 33: $<10^{-2}$	MRD: on day 33$\geq10^{-2}$ or on day 84$\geq10^{-3}$
V	Prednisone induced response on day 8: PB blasts/μ <1000/ml	Age ≥10 Age <1 years and no rearranged MLL	
VI	BM: on day 15: M1; M2 on day 33: CR (<5%)	Immunophenotype: T-ALL; t (1; 19) with E2A-PBX1 fusion gene positive	
VII	CNS3: no	CNS3: yes (and no other high risk factors)	
VIII	MRD: on day 33$<10^{-4}$	Presenting WBC: $\geq50\times10^9$/L	

WBC: White blood cell count; PB: Peripheral blood; MRD: Minimal residual disease; CR: Complete remission; CNS: Central nervous system; ALL: Acute lymphoblastic leukemia; IR: Intermediate-risk; BM: Bone marrow.

residual disease (MRD) could reduce the relapse rate and mortality, and was more accurate in reflecting OS, EFS and DFS in patients. Gao C et al [14] showed that *NOTCH1* mutations are associated with favorable long-term prognosis in pediatric T-cell acute lymphoblastic leukaemia. Jing Lu et al [15] reported that mixed-phenotype acute leukemia didn't benefit from the CCLG-2008 protocol. These reports derived from CCLG-2008 focus on the clinical features, biological characteristics, early response to treatment and long-term outcomes of pediatric ALL patients with or without specific fusion transcripts. However, the efficacy of CCLG-2008 on patients with hyperleukocytosis, especially in related to other clinical features, early complications, and treatment outcomes are unclear. Therefore, we reviewed and compared clinical parameters and treatment outcome according to the degree of hyperleukocytosis at presentation. This study represents the first analysis based on hyperleukocytosis and clinical features, early complications, and outcomes in a cohort of Chinese pediatric ALL patients treated on CCLG-2008 protocol.

Materials and methods

Patients and date collection

Between January 2009 and June 2014, 399 children with newly diagnosed ALL were enrolled to this protocol at the Children's Hospital of Soochow University. The diagnosis of ALL was based on morphology, immunology, cytogenetics and more specific molecular genetic analysis (MICM tests). According to risk factors, such as age, WBC, immunophenotype, gene arrangement, the level of minimal residual disease (MRD), etc, patients were classified into three groups, namely low risk group, intermediate group, and high group (**Table 1**) and received risk-based treatments with the protocol of CCLG-2008 (**Figure 1**). With the guideline of risk factors indicated in the protocol of CCLG-2008, patients with high WBC (over 50×10^9/L) would be potentially classified into intermediate group or high group.

Of 399 cases, 121 patients had an initial leukocyte count (WBC) over 50×10^9/L. According to the literatures, the very high WBC value at initial stage was defined differently either over 100 or 200×10^9/L on the risk of their effects on the outcome of pediatric acute lymphoblastic leukemia (ALL) by different clinical trials (**Table 2**). Therefore, we classified patients with high WBC into four groups: namely, 50×10^9/L to 99×10^9/L (group 1), 100×10^9/L to 199×10^9/L (group 2), 200×10^9/L to 299×10^9/L (group 3), and over 300×10^9/L (group 4) in order to stratify the influence of high WBC on the outcome for patients treated under CCLG-2008 protocol.

The data collected for analysis are age, gender, hepatomegaly, splenomegaly, immunophenotype, chromosome abnormality, fusion gene, and complete hemogram data such as leukocyte count, hemoglobin concentration (Hb), and platelet count (Plt) at presentation. Serum electrolytes, creatinine, blood urea nitrogen, uric acid, lactate dehydrogenase (LDH) and fibrinogen (Fib) were documented. MRD was performed by either flow cytometry or RT-PCR to evaluate the treatment response.

Treatment

The newly diagnosed ALL patients were routinely given oral allopurinol to reduce uric acid level, intravenous fluid hydration (3 L/m^2/d) and alkalization to prevent tumor lysis syndrome (TLS). Steroids were administrated as soon as the diagnosis of ALL was established. Leukopheresis was carried out for those patients who were not sensitive to steroid and kept WBC at high level (over 100×10^9/L) after 3 days steroid administration combining with vincristine (VCR). Induction therapy would be given when WBC count below 50×10^9/L and followed by consolidation therapy, intensive therapy and maintenance therapy. The flow chart was illustrated in **Figure 1**. Patients with high WBC were fallen into intermediate group or high group combining with other risk factors and treated by the protocol based on risk stratification.

Definition

Hyperleukocytosis was defined as the value of WBC over 50×10^9/L and super-hyperleukocytosis as WBC over 300×10^9/L.

Early morbidity and mortality were defined as adverse events that occurred during the first 14 days after presentation [8]. Laboratory TLS was defined as: (i) >25% change from baseline values or the presence of serum levels above normal laboratory values in any two or more of the

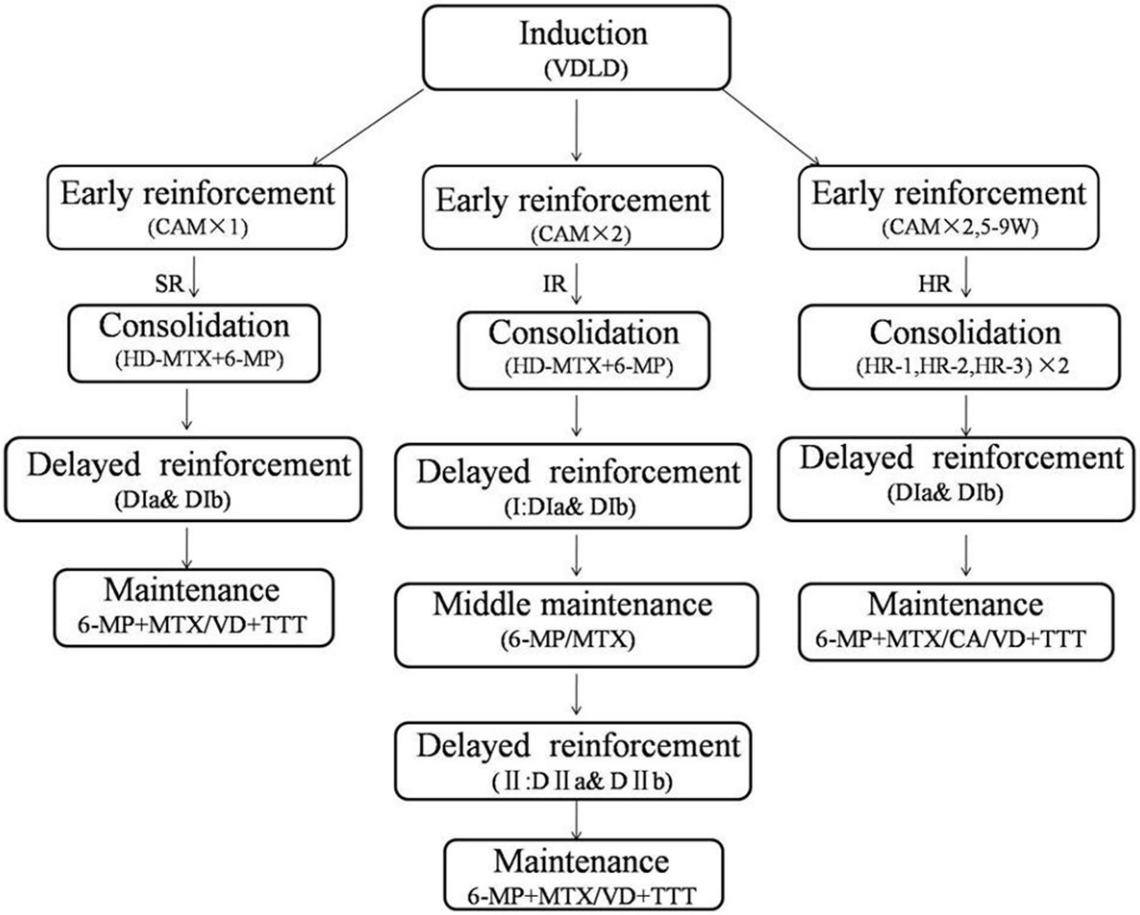

Figure 1. Outline of the treatment regimens. SR treatment regimens, which consisted of induction, early reinforcement, consolidation, delayed reinforcement I, delayed reinforcement II and maintenance therapy elements. IR treatment regimens, which consisted of induction, early reinforcement, consolidation, delayed reinforcement I, middle maintenance, delayed reinforcement II and maintenance therapy elements. HR treatment regimens, which consisted of induction, early reinforcement, consolidation, delayed reinforcement and maintenance therapy elements. IR means Intermediate-risk; HR means High-risk.

following parameters: potassium, uric acid, phosphate and calcium; or (ii) serum levels above normal laboratory values (potassium >5 mEq/L, uric acid >7.5 mg/dL, phosphate >5 mg/dL and calcium <8 mg/dL) in at least one of the previously described parameters and creatinine serum levels above 1.4 mg/dL. These criteria had to be met within 3 days before and 7 days after the initiation of chemotherapy in the absence of any other recognizable causes [16].

EFS was defined as the length of time after diagnosis that a person remains free of certain negative events, including the therapy-related morbidity and mortality and relapse or death due to the disease itself [17]. Treatment related death (TRD) included the following: (i) pre-treatment death (death before any anti-leukemic therapy), (ii) induction death (death after start of treatment, but before achieved remission), and (iii) death in CR1 (referring the deaths happening up to 6 months after end of treatment) [18].

Relapse was classified into very early relapse (within 18 months of first diagnosis), early relapse (18 months of first diagnosis but within 6 months after end of therapy), and late relapse (more than 6 months after end of therapy) [19].

Statistical methods

SPSS 18.0 was employed to analyze the clinical and laboratory features and complications of the four groups. Stepwise logistic regression

Table 2. Hyperleukocytic ALL in published series

Studies	No.of Patients (H/T)	Group	EFS (%, P)	RFS (N, %)	TRD (%, *P*)
Eguiguren et, al [9]	64/358	<100 ≥100	4-year EFS: 1) WBC<100×10^9/L versus ≥100×10^9/L (79% ± 4% vs 52% ± 8%; P = .0001) 2) WBC 100-200×10^9/L versus WBC>200×10^9/L (64% ± 10% vs 34% ± 14%; P = .04)	Total: (24, unclear) 100-200: (11, 30) >200: (13, 48)	Unclear
Kulkarni et, al [12]	111/762	100-199 200-299 300-399 >400	Unclear	Total: (21, 18.9) 100-199: (12, 16.4) 200-299: (7, 30.4) 300-399: (0, 0.0) >400: (2, 28.6)	Unclear
Bendik Lund et, al [18]	27/35	<200 >200	Unclear	Unclear	WBC <200×10^9/L () versus WBC ≥200×10^9/L (2.5 ± 0.3% vs 13.0 ± 3.6%; P<0.001)
Gim Kong et, al [24]	20/104	<100 100-200 >200	3-year EFS: WBC over 200×10^9/L versus 100-200×10^9/L (63.6% vs 100%; P = 0.046)	Total: (7, 15.6) <100: (6, 21.4) 100-200: (0, 0.0) >200: (1, 12.5)	Unclear

H: Hyperleukocytic; T: Total.

Table 3. Clinical characteristics and Laboratory findings of ALL children with hyperleukocytosis

	Initial WBC count (×10^9/L)										*p*-value
	50-99		100-199		200-299		≥300		Total		
	N = 56	%	N = 38	%	N = 8	%	N = 19	%	N = 121	%	
Gender											0.253
Female	22	(39.3)	17	(44.7)	1	(12.5)	5	(26.3)	45	(37.2)	
Male	34	(60.7)	21	(55.3)	7	(87.5)	14	(73.7)	76	(62.8)	
Age (years)											
<1	0	(0.0)	3	(7.9)	0	(0.0)	3	(15.8)	6	(5.0)	0.017
1-10	52	(92.9)	29	(76.3)	6	(75.0)	12	(63.2)	99	(81.8)	0.018
>10	4	(7.1)	6	(15.8)	2	(25.0)	4	(21.1)	16	(13.2)	0.261
Hepatomegay											0.021
<5 cm	50	(89.3)	34	(89.5)	7	(87.5)	12	(63.2)	103	(85.8)	
≥5 cm	6	(10.7)	3	(7.9)	1	(12.5)	7	(36.8)	17	(14.0)	
Splenomegay											0.102
<5 cm	40	(71.4)	26	(68.4)	6	(75.0)	8	(42.1)	80	(66.1)	
≥5 cm	16	(28.6)	11	(28.9)	2	(25.0)	11	(57.9)	40	(33.1)	
Immunophenotype											
T	6	(10.7)	7	(18.4)	4	(50.0)	11	(57.9)	28	(23.1)	<0.001
B	48	(85.7)	31	(86.1)	4	(50.0)	8	(42.1)	91	(75.2)	<0.001
T+B	2	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.7)	0.707
Ploidy groups											
Normal diploid	28	(50.0)	12	(31.6)	4	(50.0)	9	(47.4)	53	(43.8)	0.248
Unfavorable	4	(7.1)	9	(23.7)	1	(12.5)	1	(5.3)	15	(12.4)	0.099
Hyperdiploid	5	(8.9)	3	(7.9)	0	(0.0)	0	(0.0)	8	(6.6)	0.660
Fusion gene											
BCR/ABL	3	(5.4)	3	(7.9)	2	(25.0)	1	(5.3)	9	(7.4)	0.254
SIL/TAL1	0	(0.0)	4	(10.5)	0	(0.0)	5	(26.3)	9	(7.4)	0.001
MLL related	5	(8.9)	5	(13.2)	1	(12.5)	4	(21.1)	15	(12.4)	0.454
WBC (×10^9/L)											<0.001

Median	70.1	144.2	250.3	474.52	107.515	
Range	50.74-96.9	101-192.5	214.1-285	318.64-932	50.74-932	
LDH (U/L)						<0.001
Median	784.3	1108.5	1530.8	2236	1107.95	
Range	136.6-8920.5	282.3-8102.8	371.8-6092.6	676.7-16486	136.6-16486	
α-HBDH (U/L)						0.011
Median	708.5	803.4	1333.8	1672.4	817.1	
Range	34.2-88445	179.3-88445	395.3-4666.	34.2-10473	129.9-7334.5	
Fib (g/L)						<0.001
Median	2.80	2.32	2.59	1.71	2.475	
Range	1.33-5.15	0.5-5	1.05-3.73	0.43-3.30	0.43-5.15	

WBC: White blood cell count; LDH: Lactic dehydrogenase; α-HBDH: α-Hydroxybutyrate; Fib: Fibrinogen.

Table 4. Early complications in children with ALL and hyperleukocytosis

	Initial WBC count ($\times 10^9$/L)										*p*-value
	50-99		100-199		200-299		≥300		Total		
	N	%	N	%	N	%	N	%	N	%	
Neurologic events	0	(0.0)	0	(0.0)	0	(0.0)	4	(21.1)	4	(3.3)	0.001
Respiratory events	9	(16.1)	5	(13.2)	1	(12.5)	2	(10.5)	17	(14.0)	0.929
TLS	0	(0.0)	2	(5.3)	1	(12.5)	8	(42.1)	11	(9.1)	<0.001
DIC	0	(0.0)	0	(0.0)	1	(12.5)	4	(21.1)	5	(4.1)	0.001
Early death	1	(1.8)	0	(0.0)	0	(0.0)	4	(21.1)	5	(4.1)	0.005

TIS: Tumor lysis syndrome; DIC: Disseminated intravascular coagulation; CR: Complete remission; BM: Bone marrow; CNS: Central nervous system.

analysis was used to determine the features were most strongly associated with hyperleukocytosis. Relapse rates, TRD, ED, and EFS, ere estimated by using the Kaplan-Meier method. The log-rank test was used to compare survival curves within the four groups. Cox regression analysis was performed to evaluate predictors of adverse events. *P*-value <0.05 was considered statistically significant.

Results

Patients clinical and laboratory characteristics

A total of one hundred and twenty-one patients with ALL were eligible for this analysis. The clinical characteristics and laboratory findings of patients with hyperleukocytosis are shown in **Table 3**. The median age of patients was 4.1 years (range, 3 months to 15.4 years), and among these four groups, the forth group which had super-hyper-leukocytosis was significantly associated with age younger than 1 year (P = 0.017), massive hepatomegaly (P = 0.021), T-cell immune phenotype (P<0.001), positive SIL/TAL1 fusion gene (P = 0.001). The median initial leukocyte count was 107.5×10^9/L (range, $50.74\text{-}932\times10^9$/L). Hemoglobin, platelet, uric acid, creatinine and urea were not significantly different among the four groups. However, serum levels of lactic dehydrogenase (LDH), α-Hydroxybutyrate (α-HBDH), and fibrinogen were siginificantly higher in patient with super-hyperleuko-cytosis than the other groups (P<0.001, 0.011, and <0.001, respectively).

Early complications

Among 121 patients, early complications occurred in 42 patients (34.7%) (**Table 4**), In addition to respiratory events, incidence of other early complications was significantly higher in the forth group than other groups. Early death occurred in 5 children, of which, 4 cases were in the forth group (4/19, 21.1%) with WBC count at 413×10^9/L, 480×10^9/L, 771×10^9/L, and 932×10^9/L, respectively. These patients died within 24-48 hours after hospitalization, and experienced DIC, intracranial hemorrhage and TLS. On the contrary, only one case with WBC at 56×10^9/L died of severe pneumonia and acute pulmonary edema associated with

Table 5. Therapeutic responses in children with ALL and hyperleukocytosis

	Initial WBC count (×10^9/L)										
	50-99		100-199		200-299		≥300		Total		*P*-value
	N	%	N	%	N	%	N	%	N	%	
CR on day 33	42	(84.0)	29	(87.9)	6	(85.7)	10	(90.9)	87	(86.1)	0.964
Relapses (total)	8	(19.0)	11	(37.9)	0	(0.0)	5	(50.0)	24	(27.6)	0.049
BM	7	(87.5)	9	(81.8)	0	(0.0)	4	(80.0)	20	(83.3)	1.000
CNS	0	(0.0)	1	(9.1)	0	(0.0)	0	(0.0)	1	(4.2)	1.000
Testis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	—
Combined	1	(12.5)	1	(9.1)	0	(0.0)	1	(20.0)	3	(12.5)	1.000
Early period	5	(62.5)	4	(36.4)	0	(0.0)	4	(80.0)	13	(54.2)	0.328
Mid period	1	(12.5)	5	(45.5)	0	(0.0)	0	(0.0)	6	(25.0)	0.130
Later period	2	(25.0)	2	(18.2)	0	(0.0)	1	(20.0)	5	(20.8)	1.000
Death (total)	21	(37.5)	14	(36.8)	2	(25.0)	12	(66.7)	49	(40.8)	0.097

CR: Complete remission; BM: Bone marrow; CNS: Central nervous system.

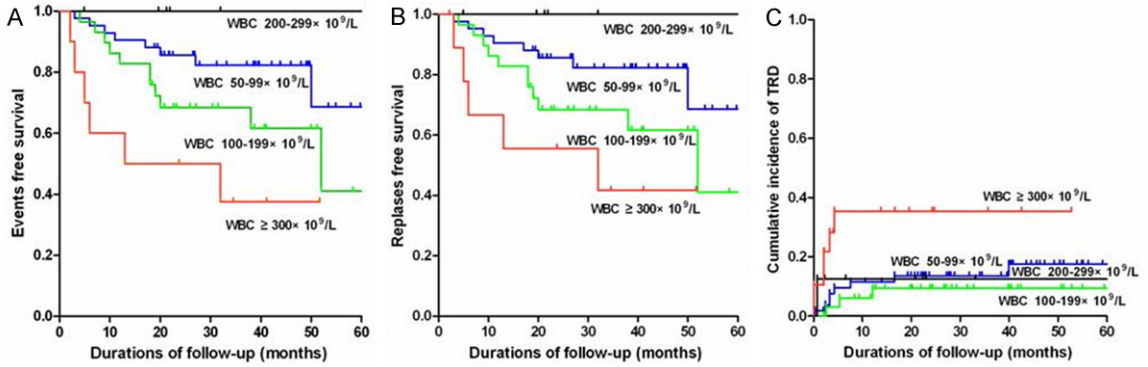

Figure 2. EFS, RFS and TRD in different groups classified by white blood cell count at diagnosis. Patients with WBC classified into four groups, namely the first group as WBC at 50-99×10^9/L, the second group as WBC at 100-199×10^9/L, the third group as WBC at 200-299×10^9/L, and the forth group as WBC at WBC ≥300×10^9/L, respectively. A. Kaplan-Meier estimate of event free survival of children with ALL and hyperleukocytosis (P = 0.006); B. Kaplan-Meier estimate of relapse rates of children with ALL and hyperleukocytosis (P = 0.022); C. Kaplan-Meier estimate of TRD of children with ALL and hyperleukocytosis (P = 0.036).

heart failure on the 6th day. Univariate analysis indicated that the initial higher WBC count (>300×10^9/L) (OR (odds ration): 12.83, 95% CI(confidence interval): 1.43-115.03, P = 0.023), TLS (OR: 6.63, (95% CI): 1.11-39.73, P = 0.038) and DIC (OR: 44.62, (95% CI): 7.23-275.20, P<0.01) were the most significant prognostic factors for developing early death.

Outcomes

Of 121 patients, 20 cases (16.5%) abandoned induction chemotherapy due to early complications, early death and financial constraint. Only 101 patients (83.5%) received the risked-adapted treatment of CCLG-2008 protocol and were included in the outcome analysis. CR was achieved in 86.1% (87/101) with the median day of 33th after induction therapy while the relapse rate was 27.6% (24/87) (**Table 5**). The relapse rate was significantly associated with WBC value (**Table 5**, P = 0.049) and highest in the forth group (5/10). Bone marrow relapse ranked top relapse rate at 83.8% (20/24) and 13 cases were belonged to very early period relapse. As the outcomes of these four groups of ALL illustrated in **Figure 2**, the forth group demonstrated a shortest EFS, highest relapse rate, and highest TRD among all groups. (**Figure 2A-C**, P = 0.006, P = 0.022 and P = 0.036, respectively). Interestingly, the third group had the highest EFS and lowest relapse rate (**Figure 2A-C**) with unknown reason.

Univariate analysis was employed to evaluate the association among EFS, RFS, TRD and WBC, age, sex, immunophenotype, gene rearrangement, chromosomal abnormality, and prednisone pretreatment on 8th day, MRD on 15th, 33th day, and 84th day. We found that WBC over 300×10^9/L, positive BCR/ABL fusion gene rearrangement, lack of prednisone response, MRD on day 33th and 84th day were significantly associated with shorter EFS, high relapse rates and TRD, which were further confirmed with a stepwise Cox regression model. In this analysis system, WBC over 300×10^9/L and MRD on day 84th were the independent predictors for shorter EFS and high relapse rates (OR (95% CI): 14.23 (2.52-80.52), $P<0.01$ and 10.09 (3.05-33.44), $P<0.01$, respectively), and MRD on day 84th were the independent predictors for high TRD (OR (95% CI): 32.3 (3.61-289.23), $P<0.01$).

Discussion

It is reported that the incidence of hyperleukocytosis in adult ALL varied from 10% to 30% [20-22]. In pediatric ALL, the incidence was 6.1-18% for WBC >100×10^9/L and 5-8.4% for WBC >200×10^9/L [5, 11, 10, 23]. Our result revealed a similar incidence of 17.6%, 7.3%, and 5.1% when WBC was higher than 100×10^9/L, 200×10^9/L and 300×10^9/L, respectively.

A number of adverse factors, such as age <1 year, male, T-ALL, mediastinal mass, massive hepatosplenomegaly, massive splenomegaly, 11q23 rearrangement, presence of the Philadelphia chromosome, loss of p16 expression, <50 chromosomes, CNS leukemia at diagnosis, and high LDH level (>1,000 mg/dL) were reported to have a positive relationship with hyperleukocytosis in ALL [9, 15, 21, 24]. In the present study, we found that ALL patients with WBC over 300×10^9/L frequently demonstrated a younger age (<1 year), massive hepatosplenomegaly, T-cell immunophenotype, SIL-TAL1 fusion gene, high LDH and α-HBDH, as well as low Fibrinogen. The most frequent occurrence of early complications was TLS (42.1%), others were central nervous system hemorrhage, DIC and early death, especially in patients with WBC over 300×10^9/L. Hyperleukocytosis is a significant risk factor for early morbidity and mortality in adult and pediatric patients with ALL. In acute hyperleukocytic leukemia, the early mortality rate is reported to vary from 20% to 40% which was similar to ours [8, 9, 23].

Eguiguren et al reported that the 4-year EFS of ALL patients with WBC >100×10^9/L was 52%, while those with lower WBC (<100×10^9/L) was 79% ($P<0.001$) [9]. They also found that patients with a leukocyte count of 100 to 200×10^9/L had a significantly better EFS than those with counts >200×10^9/L (64% vs 34%, $P = 0.04$). Maurer et al reported that the 3-year EFS of ALL patients with an initial leukocyte count over 200×10^9/L was 55% [25]. They also identified high leukocyte count at diagnosis and massive splenomegaly as adverse prognostic factors for EFS in multivariate analysis. In our data, the estimated 5-year EFS was below 50.0% in the group with super-hyperleukocytosis which was much lower than other groups.

Eguiguren et al further reported that the recurrence rate in ALL patients with hyperleukocytosis was as high as 37.5%. For patients with a leukocyte count of 100-200×10^9/L, the recurrence rate was 30%, and for those with a leukocyte count >200×10^9/L, the recurrence rate was even higher (48%) [9]. They have also found a high incidence of relapse in both bone marrow and CNS, especially in patients whose leukocyte counts were >200×10^9/L. On the contrary, Kong SG et al reported that relapse rate was 15.6% (7/45) and they didn't find the difference in relapse between the patients with and without hyperleukocytosis [24]. In our study, the relapse rates was 19.0%, 37.9%, 50% corresponding to WBC at 50-99×10^9/L, 100-199×10^9/L, and >300×10^9/L respectively. With our limited size of patients, it is indicated that high WBC has potential impact on relapse. The site for relapse was mainly at bone marrow, only one case of T-ALL with super-hyperleukocytosis showed a combined relapse of bone marrow and CNS.

Conclusions

In conclusion, our study revealed that ALL patients with WBC over 300×10^9/L had a worst outcome due to early complications, high rate of relapse. These patients might potentially benefit from more supportive care and better protocol such as upfront bone marrow transplantation in first CR and in combination with

target therapy to improve their poorer outcome.

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Disclosure of conflict of interest

None.

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