Outcome of infants with acute lymphoblastic leukemia treated with the Chinese Children's Cancer Group Acute Lymphoblastic Leukemia 2015 study protocol

Infants diagnosed with acute lymphoblastic leukemia (ALL) constitute a subgroup of patients notorious for their inferior outcome, high risk of treatment failure and susceptibility to treatment-related toxicities when compared to older children with ALL. This subgroup accounts for less than 5% of all pediatric ALL cases, with overall event-free survival (EFS) reported in the range of 40-50%.[1] The presence of *KM2TA*-rearrangement (*KMT2A*-r) is a well-defined prognostic factor for infants with ALL. Despite various multi-center studies aimed at testing new treatment strategies to enhance outcomes, success has proven elusive.[2-5] The results of the Chinese Children's Cancer Group ALL-2015 (CCCG-ALL-2015) study, a multicenter collaboration in China for the treatment of pediatric ALL, are already available elsewhere.[6,7] In this report, we present the treatment outcomes of the infant patients enrolled in this study and analyze the factors influencing treatment outcomes.

Patients were enrolled between January 2015 and December 2019. Written informed consent was obtained from the patients' parents or legal guardians. All infants were categorized into an intermediate-risk (IR) or high-risk (HR) group. Infants aged <6 months and *KMT2A*-r, with a white blood cell count (WBC) ≥300x10^9/L at presentation, or those experiencing induction failure defined by the presence of ≥5% blast on morphology assessment of the day 46 bone marrow aspirate or minimal residual disease (MRD) ≥1%, were stratified to the HR group. Dose adjustments based on age were not implemented in this study.

Event-free survival was computed from diagnosis to the first adverse event, including induction failure, relapse, death from any cause, development of a second malignant neoplasm, withdrawal upon parental request, or off-protocol by the decision of the treating physician. Overall survival (OS) was defined as the duration from diagnosis to death due to any cause. Outcome data were updated on December 2022. The cumulative incidence of relapse (CIR) and treatment-related fatal infections were estimated by Kalbfleisch and Prentice, and compared with Grey's test. The Kaplan-Meier method was used to estimate EFS and OS. Cox's hazards model was used for univariate or multivariate analyses. Statistical analyses were performed using R software, version 3.6.3 and SPSS 25.0. A two-tailed P<0.05 was considered statistically significant.

Among the 134 enrolled infant ALL, median age was 254 days (range, 46-364 days) (*Online Supplementary Table S1*). Median WBC was 62.7 (1.3-777x10^9/L), with 11.2% having a WBC ≥300x10^9/L. There were 71 (53.0%) with *KMT2A*-r ALL (median age, 7.4 months) and 63 with *KMT2A*-g ALL (median age, 9.4 months). Among the 71 *KMT2A*-r, 60 had fusion partners identified, 32 (53.3%) had *KMT2A::AFF1* fusion, 10 (16.7%) had *KMT2A::MLLT1*, 15 (25%) had *KMT2A::MLLT3*, and 3 (5%) had *KMT2A::MLLT10*. In the *KMT2A*-r patients, 20 (27.8%) were aged <6 months at diagnosis and 12 (16.9%) had WBC ≥300x10^9/L at presentation, with 5 being both <6 months and WBC ≥300x10^9/L, thus classified as HR. WBC >300x10^9/L was less commonly encountered in the *KMT2A*-g patients, occurring in 3 (4.8%).

As of December 2022, with a median follow up of 4.2 years (range, 0.08-7.2 years), 45 patients had died. Eighteen subjects (13.4%) experienced discontinuation of protocol-specified treatment; 10 were withdrawn upon parental request (*Online Supplementary Figure S1*). For the entire cohort, 5-year EFS was 52.1% (95% CI: 44.2-61.4%) and 5-year OS was 66.1 (95% CI: 58.4-74.8%). The 5-year EFS and OS for *KMT2A*-g *versus* *KMT2A*-r were 69.8 (95% CI: 59.3-82.1%) *versus* 35.6% (95% CI: 25.7-49.4%) (P<0.001), and 74.6% (95% CI: 64.5-86.1%) *versus* 58.1% (95% CI: 47.2-71.5%) (P=0.02), respectively (Figure 1A, B). The complete remission (CR) rate for the entire group was 89.6% (120/134). The CR rate was 81.6% (58/71) for *KMT2A*-r ALL and 98.4% (62/63) for *KMT2A*-g ALL. On day 5 of induction therapy (i.e., after 4 days of oral dexamethasone), 86 patients had peripheral blood blast count available, with 63 showing blast count dropped to below 1x10^9/L, considered as good responders. There was no statistically significant difference in the EFS and OS between the dexamethasone good responder and poor responder.

For the entire group, MRD negativity on day 19 and day 46, IR group, and *KMT2A*-g had superior EFS on univariate analysis, and the MRD negativity on day 19, IR group and *KMT2A*-g remained significant on multivariate analysis (Table 1). Among *KMT2A*-r patients, factors associated with an inferior EFS were <3 months and day 19 and day 49 MRD positive (Table 2). *KMT2A*-r subtypes had no prognostic value for EFS and OS (Figure 1C, D). For the *KMT2A*-r subgroup, multivariate analysis of EFS only showed day 19 with MRD >0.01% as a significant factor (P=0.008). WBC >100x10^9/L at presentation was of prognostic significance in the *KMT2A*-g group, along with inferior OS (55% *vs*. 83.7%; P=0.01) and EFS (50% *vs*. 79%; P=0.01). Dexamethasone poor response was associated with a poorer EFS among the *KMT2A*-g subgroup (P=0.009) (*Online Supplementary Table S2*).

The infection rates for sepsis, severe pneumonia, and invasive fungal infection were 44.8% (60/134), 17.9% (24/134), and 9.0% (12/134). There were 18 deaths in remission, including 8 severe pneumonia (44.4%), 7 septic shock (38.9%), 2 invasive

fungal infections (11.1%) and one third-degree atrioventricular block (5.6%). The cumulative incidence of fatal infection during the entire treatment was 13.5% (95%CI: 7.7-19.3%). Twenty-nine recurrences (21.6%) occurred at a median of 15.7 months (range 1.6 month to 39.2 months); five patients relapsed more than 2 years post diagnosis. Among these, 23 (17.2%) relapses manifested in the bone marrow, two (3% in male patients) were isolated testicular relapse, three (2.2%) were isolated CNS recurrences and one (0.7%) involved combined bone marrow and CNS relapse. The 5-year CIR for the entire group was 23.0% (15.7-30.3%). The 5-year CIR was 30.2% (95% CI: 18.8-41.6%) in the *KMT2A*-r subgroup and 15.9% (95% CI: 6.8-25.0%) in the *KMT2A*-g subgroup (P=0.05).

Seven subjects underwent hematopoietic stem cell transplantation (HSCT) without chimeric antigen receptor T-cell therapy (CAR-T therapy), all of whom had *KMT2A*-r. HSCT timing ranged from 4.2 to 33.8 months post diagnosis. Among transplant recipients, 3 subjects died of progressive and refractory disease, one succumbed to an accident, and the remaining 3 subjects were alive with a duration follow-up of from 37.5 to 51.1 months. Six patients received CAR-T therapy: 2 received CD19 and 4 received CD19/CD22. Five patients received HSCT after CAR-T therapy at a mean interval of 71 days post CAR-T; these 5 remained in remission. Notably, the subject with *KMT2A*-g who did not receive HSCT post CAR-T experienced a second relapse six months post CAR-T therapy, and succumbed to progressive disease ten months later. This cohort of infants with ALL is part of the CCCG-ALL-2015 study which had enrolled 7,640 subjects. The infant cohort, constituting approximately 1.7% of the entire CCCG-ALL-2015

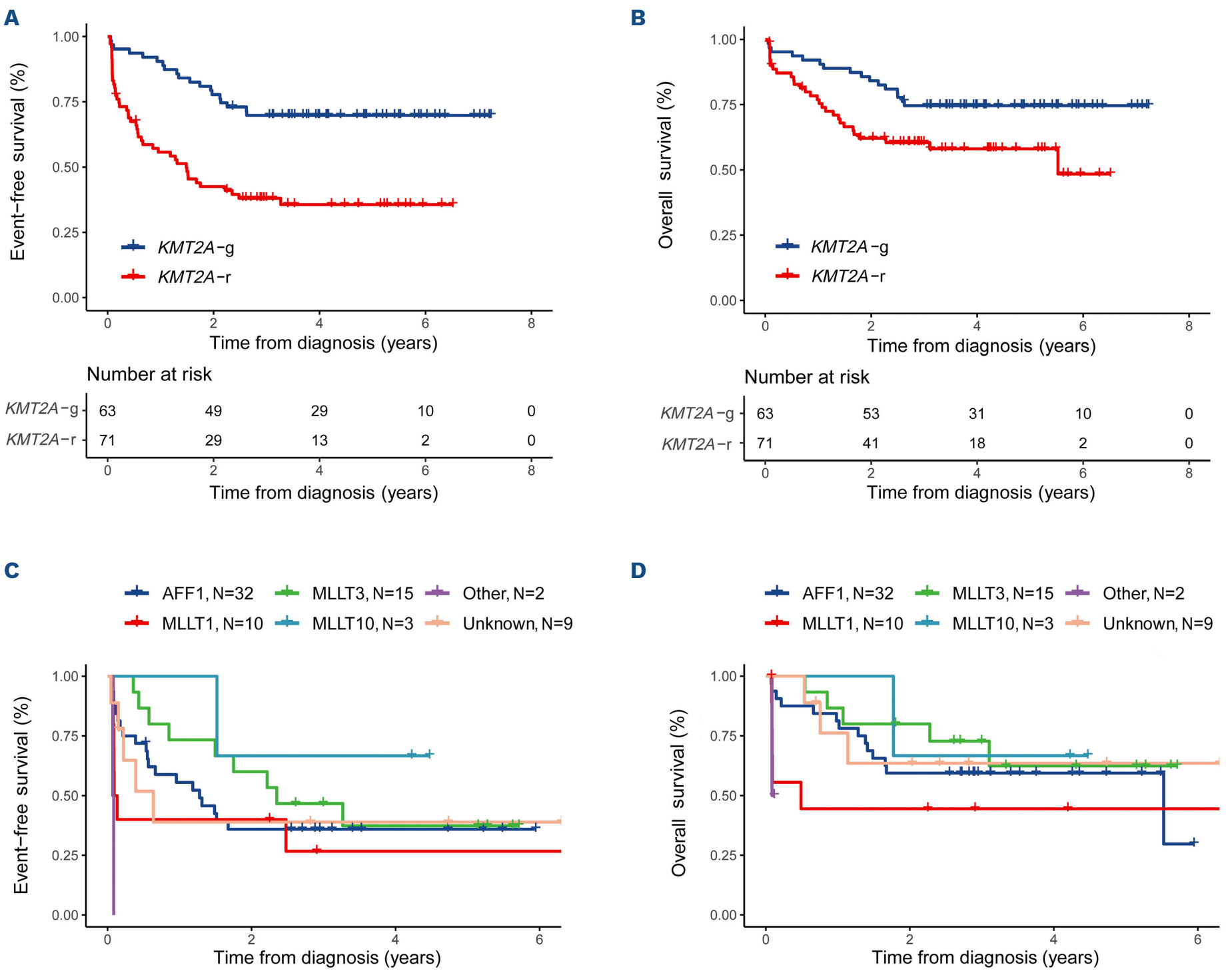

Figure 1. 5-year event-free survival and overall survival of infant acute lymphoblastic leukemia according to genetic subtypes. (A) 5-year event-free survival (EFS) of the *KMT2A*-r group compared with the *KMT2A*-g group: 69.8 (95% CI: 59.3-82.1%) *versus* 35.6% (95% CI: 25.7-49.4%), respectively (P<0.001). (B) 5-year overall survival (OS) of the *KMT2A*-r group compared with the *KMT2A*-g group: 74.6% (95% CI: 64.5-86.1%) *versus* 58.1% (95% CI: 47.2-71.5%), respectively (P=0.02). (C) The EFS of the various *KMT2A*-r subtypes. (D) The OS of the various *KMT2A*-r subtypes.

protocol, was notably lower than the anticipated 3-4% based on comparisons with other studies. Within our cohort, the percentage of infants under six months of age at diagnosis was 18.4%, significantly lower than the 50-68% reported in previous studies.[3,8] Moreover, *KMT2A*-r was observed in 53.0% of the enrolled subjects, a figure also below the 74-83% reported in other studies.[3,8] It is noteworthy that high-risk subjects appeared to be under-represented in our enrolled patients. Additionally, only 11% of our subjects had WBC >300x10^9/L, significantly lower than that in the Interfant 06 and JPLSG MLL10 studies, which reported 29% and 30%, respectively[3,8] (*Online Supplementary Table S3*).

In our study, first lumbar puncture (LP) and central nervous system (CNS) assessment was deferred to day 5 of induction and demonstrated a lower CNS involvement after 4 days of dexamethasone prophase. The isolated CNS relapse rate was 2.2% and combined BM and CNS relapse was 0.7%, contrasting with the isolated CNS relapse rate of 11.9% in the Interfant 06 study.[3] Performing LP when the blast count in peripheral blood was reduced after the pre-phase treatment might be a safer approach. Notably, CNS relapse rate remained low despite a relatively high rate of traumatic LP (approx. 10%) in our cohort.

The early treatment-related mortality (TRM) was high in

Table 1. Risk analysis of event-free survival in infants with acute lymphoblastic leukemia.

	N (%)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
KMT2A status					
KMT2A-g	63 (47.0)	1	-	1	-
KMT2A-r	71 (53.0)	3.1 (1.8-5.3)	<0.001	2.8 (1.4-5.8)	0.005
Age					
≥3 mth	131 (97.8)	1		-	-
<3 mth	3 (2.2)	2.2 (0.5-9.0)	0.27	-	-
≥6 mth	109 (81.3)	1		-	-
<6 mth	25 (18.7)	1.3 (0.7-2.4)	0.39	-	-
≥9 mth	55 (41.0)	1		-	-
<9 mth	79 (59.0)	1.5 (0.9-2.4)	0.15	-	-
Final risk group					
IR	126 (94.7)	1	-	1	-
HR	7 (5.3)	3.8 (1.6-9.0)	0.002	3.5 (1.1-11.4)	0.04
Sex					
Female	69 (51.5)	1	-	-	-
Male	65 (48.5)	1.1 (0.7-1.9)	0.62	-	-
CNS status					
CNS1	112 (83.6)	1		-	-
CNS2	5 (3.7)	0.9 (0.2-3.5)	0.84	-	-
CNS3	2 (1.5)	1.0 (0.1-7.4)	0.98	-	-
Traumatic	15 (11.2)	1.5 (0.8-3.1)	0.23	-	-
WBC, x10^9/L					
<100	78 (58.2)	1	-	-	-
≥100	56 (41.8)	1.7 (1.0-2.7)	0.09	-	-
<300	119 (88.8)	1	-	-	-
≥300	15 (11.2)	1.8 (0.9-3.7)	0.10	-	-
Day 5 blast, x10^9/L, DEX response					
Good response, blast <1	63 (73.3)	1	-	-	-
Poor response, blast ≥1	23 (26.7)	1.8 (0.9-3.4)	0.09	-	-
Day19 MRD					
<0.01%	67 (57.3)	1	-	1	-
≥0.01%	50 (42.7)	2.4 (1.4-4.3)	0.002	3.8 (1.8-8.2)	<0.001
Day 46 MRD					
<0.01%	88 (87.1)	1	-	1	-
≥0.01%	13 (12.9)	3.0 (1.4-6.7)	0.006	1.3 (0.5-3.3)	0.59

CI: confidence interval; *KMT2A*-g: *KMT2A*-germline; K*MT2A*-r: *KMT2A*-rearranged; DEX: dexamethasone; HR: high-risk; IR: intermediate-risk; mth: months; CNS: central nervous system; MRD: minimal residual disease; WBC: white blood cell count.

our cohort, with 10 fatal infections (7.5%) occurring in the induction period; this rate surpasses that reported in the Interfant-99 protocol (3.8%).[2] Recognizing the critical role of supportive care in the early phase of therapy is essential for enhancing outcomes, particularly in developing countries. Implementing dose modification during the induction could also contribute to reducing early mortality.[9] To mitigate TRM during the early intensive phase, we developed a dedicated Infant ALL study with an age-adjusted dose approach and blinatumomab.

Blinatumomab, recently investigated in a pilot study based on the Interfant regimen, demonstrated remarkable early results.[10] CAR-T therapy, performed in patients with relapsed or refractory ALL, raises concerns about lineage switch, particularly in patients with mixed-phenotype acute leukemia, where the B-lineage is the target.[11,12] Instances of myeloid leukemia have been reported in infants after achieving remission with ALL treatment post blinatumomab or CAR-T therapy.[13-15] Consolidative HSCT after CAR-T therapy has shown success in our cohorts. In conclusion, the CCCG-2015-Study had a low percentage of infant patients as well as *KMT2A*-r. Despite high TRM, the relapse rate was not excessively high.

Table 2. Treatment outcome according to selected clinical and biological characteristics in infants with *KMT2A*-r acute lymphoblastic leukemia.

	N (%)	5-year EFS (95% CI)	*P*	5-year OS (95% CI)	*P*
KMT2A subtype					
AFF1+ *MLLT1*	42 (59.2)	34.4 (22.5-52.7)	0.4	56.1 (42.8-73.6)	0.3
MLLT3 + *MLLT10* + others	29 (40.8)	38.3 (23.6-62.2)	0.4	60.6 (43.6-84.0)	0.3
A*FF1*	32 (45.1)	35.9 (22.4-57.5)	0.9	59.4 (44.6-79.1)	0.9
MLLT1+ *MLLT3* + *MLLT10* + others	39 (54.9)	35.6 (22.7-55.6)	0.9	56.7 (41.8-76.8)	0.9
Age					
<3 mth	2 (2.8)	0	0.02	0	<0.001
≥3 mth	69 (97.2)	36.7 (26.5-50.8)	0.02	59.8 (48.8-73.3)	<0.001
< 6 mth	19 (26.8)	36.8 (20.4-66.4)	0.9	50.0 (31.5-79.4)	0.4
≥ 6 mth	52 (73.2)	35.6 (24.2-52.2)	0.9	61.2 (48.7-76.8)	0.4
< 9 mth	54 (76.1)	35.3 (24.4-51.0)	0.3	57.4 (45.3-72.6)	0.4
≥9 mth	17 (23.9)	39.2 (21.1-72.8)	0.3	62.3 (42.2-92.0)	0.4
Final risk group					
IR	64 (90.1)	37.9 (27.3-52.8)	0.06	61.4 (50.0-75.4)	0.01
HR	7 (9.9)	14.3 (2.3-87.7)	0.06	28.6 (8.9-92.2)	0.01
Sex					
Male	33 (46.5)	36.7 (22.8-58.9)	0.8	57.9 (42.6-78.7)	0.8
Female	38 (53.5)	35.1 (22.6-54.6)	0.8	58.9 (44.9-77.3)	0.8
CNS status					
CNS1	57 (80.3)	37.3 (26.1-53.4)	0.3	62.7 (50.7-77.5)	0.02
CNS2	4 (5.6)	50.0 (18.8-100)	0.3	75.0 (42.6-100)	0.02
CNS3	1 (1.4)	0	0.3	0	0.02
Traumatic	9 (12.7)	11.1 (1.8-70.5)	0.3	11.7 (2.0-78.2)	0.02
WBC, x10^9/L					
≥100	36 (50.7)	37.5 (24.2-58.1)	0.9	59.0 (44.6-78.1)	0.8
<100	35 (49.3)	33.5 (20.6-54.5)	0.9	56.0 (40.4-77.6)	0.8
≥300	12 (16.9)	33.3 (15.0-74.2)	0.3	38.1 (17.9-81.1)	0.02
<300	59 (83.1)	35.8 (24.9-51.1)	0.3	62.0 (50.1-76.6)	0.02
Day 5 blast, x10^9/L, DEX response					
Good response, blast <1	30 (78.9)	33.0 (19.7-55.2)	0.3	55.6 (40.1-76.9)	0.7
Poor response, blast ≥1	8 (21.1)	25.0 (7.5-83.0)	0.3	50.0 (25.0-100)	0.7
Day 19 MRD					
<0.01%	34 (54.8)	59.3 (44.0-79.9)	0.001	75.8 (62.5-91.9)	0.07
≥0.01%	28 (45.2)	15.2 (6.2-37.3)	0.001	50.8 (34.9-74.1)	0.07
Day 46 MRD					
<0.01%	39 (83.0)	58.9 (44.6-77.8)	0.001	87.0 (76.9-98.3)	0.001
≥0.01%	8 (17.0)	12.5 (2.0-78.2)	0.001	37.5 (15.3-91.7)	0.001

DEX: dexamethasone; EFS: event-free survival; HR: high-risk; IR: intermediate-risk; mth: months; CNS: central nervous system; MRD: minimal residual disease; OS: overall survival; WBC: white blood cell count.

Dexamethasone prophase may offer protection against CNS relapse in infants. CAR-T therapy followed by allogeneic HSCT should be explored in future studies.

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Disclosures

No conflicts of interest to disclose.

Contributions

C-KL, C-HP and JG conceived and performed the research, discussed data and wrote the paper. AWKL, JC and ZW collected data and provided statistical analysis. All authors contributed to the manuscript and to the interpretation of the data, and approved the final version for publication.

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Data-sharing statement

The original data and protocols are available to other investigators on reasonable request to the corresponding author.

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