HK J Paediatr (new series) 2022;**27**:249-258

Original Article

Long-term Outcome for Chinese Adolescents with Acute Lymphoblastic Leukaemia Treated with Paediatric Regimen of CCLG-ALL 2008 Protocol

JL **YU**, YY **ZHANG**, W **LIN**, Y **WU**, XL **ZHENG**, HB **HE**, PJ **QI**, J **FAN**, SY **CAI**, RD **ZHANG**, HY **ZHENG**

Abstract ***Background:*** Adopting paediatric-based protocol for adolescent acute lymphoblastic leukaemia (ALL) patients has been reported leading to superior prognosis, however, large group of study in Chinese population has not been documented. ***Purpose:*** To analyse the clinical characteristics, prognostic factors and outcome of adolescent patients with newly diagnosed ALL treated with paediatric-based protocol in a tertiary centre in China. ***Methods:*** We summarised our data of 121 adolescent ALL (aged 10-16 years) treated with Chinese Children's Leukemia Group (CCLG-ALL 2008) protocol from 2008 to 2013. ***Results:*** During 2008-2012, a total of 121 adolescent patients with ALL were enrolled in our study. The 5-year overall survival rate (OS) and event-free survival rate (EFS) was 82.64% and 80.78%, respectively. The 5-year EFS rate was 89.05% in intermediate risk patients, whereas, it was significantly lower for the high risk group (59.54%). High initial leukocyte count (WBC >50 x 10^9/L), T-immunophenotype, *BCR/BAL* and poor response to prednisone at Day 8 were associated with inferior prognosis. ***Conclusions:*** Adolescent ALL patients achieved satisfactory outcome using paediatric-based protocol of CCLG-ALL 2008.

Key words *Acute lymphoblastic leukaemia; Adolescent; Outcome; Prognostic factors*

Beijing Key Laboratory of Pediatric Hematology Oncology, National Key Discipline of Pediatrics (Capital Medical University), Key Laboratory of Major Diseases in Children, Ministry of Education, Hematology Center, Capital Medical University, National Center for Children's Health, Beijing Children's Hospital, 56 Nanlishi Road, Beijing 100045, China

JL **Yu**(于皎樂) *MD, PhD*
YY **Zhang**(張元元) *MD*
W **Lin**(林巍) *MD, PhD*
Y **Wu**(吳穎) *MD*
XL **Zheng**(鄭雪岭) *MD*
HB **He**(何紅波) *MD*
PJ **Qi**(漆佩靜) *MD, PhD*
J **Fan**(范佳) *MD*
RD **Zhang**(張瑞東) *MD, PhD*
HY **Zheng**(鄭胡鏞) *MD, PhD*

Clinical Epidemiology and Evidence-Based Medicine Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, 56 Nanlishi Road, Beijing, China

SY **Cai**(蔡思雨) *MMedSc*

Correspondence to: Dr HY **Zheng**, Dr RD **Zhang**
Email: zhenghuyong@bch.com.cn; zhangruidong@vip.sina.com

Received December 14, 2021

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common cancer diagnosed in children, accounting for approximately 25% of paediatric cancers. With the optimisation of risk stratification, risk-based therapeutic regimen, treatment response monitoring and supportive care, event-free survival (EFS) rates for childhood ALL exceed 80% and overall survival (OS) rates are approximately 90%.[1] Compared with childhood ALL, the outcome of adolescent and young adult (AYA) ALL is significantly inferior. To circumvent this adversity, adolescent ALL attracts emerging interest due to their unique disease characteristics. Recently, paediatric-based regimens have been shown to lead to superior prognosis,[2] however, relevant study in Chinese population has not been well documented and existing data included only relatively small patient number.[3] We summarised our data of 121 adolescent ALL treated with Chinese Children's Leukaemia Group (CCLG-ALL 2008) protocol and focused on the clinical features, prognostic factors and long-term outcome.

Methods

Patients

During February 1, 2008 to December 31, 2013, 121 patients (10- to 16-year) with newly diagnosed ALL were admitted in Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University. Diagnosis was confirmed by the examinations of morphology, immunology, cytogenetic and molecular studies. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies was implemented in this study.

Risk Stratification

Patients were assigned to intermediate risk (IR) and high risk (HR) based on presenting leukocyte count, immunophenotype, prednisone treatment response at Day 8; remission status at Day 15 and Day 33, minimal residual disease (MRD) at Day 33 (end of remission induction) and Day 84 (beginning of consolidation) by flow cytometry, cytogenetic abnormalities and central nervous system (CNS) status according to the risk-stratification criteria of CCLG-ALL 2008 protocol (Table 1).

Treatment

All patients received the treatment of CCLG-ALL 2008 protocol consisting of remission induction, early intensification, consolidation, delayed intensification and continuation courses. Duration of therapy was 24 months for IR female, 30 months for IR male, and 36 months for HR patients, respectively. The treatment protocol of CCLG-ALL 2008 was described previously[4] and the schema was briefly shown in Figure 1. Written informed consent was obtained under the approval of the Beijing Children's Hospital Ethical Committee.

Response

Treatment response was evaluated according to prednisone response at Day 8; bone marrow morphology study at Day 15, Day 33 and Day 84; MRD and cytogenetic

Table 1 Risk stratification

Risk group	Stratification criteria
Standard Rick (SR)	Age: ≥1, <10 years +WBC count >50x10^9/L +B-cell ALL +Absence of t(9;22) or t(1;19) or *MLL* rearrangement +Non CNS3 +Prednisone good response +Bone marrow blasts <5% by cytological study at Day 15 of induction +MRD <10^{-4} at Day 33 of induction
Intermediate Risk (IR)	Age: <1 year or ≥10 years or WBC count ≥50x10^9/L or T-cell ALL or t(1;19) +Absence of t(9;22) or *MLL* rearrangement +Prednisione good response +Bone marrow blasts <25% at Day 15 wiht IR protocol or <5% with SR protocol +MRD <10^{-2} at Day 33 of induction +MRD <10^{-3} at the beginning of consolidation
High Risk (HR)	t(9;22) or *MLL* rearrangement or Prednisone poor response or Bone marrow blasts ≥25% at Day 15 wiht IR induction or >5% at Day 33 of induction or MRD ≥10^{-2} at Day 33 of induction or MRD ≥10^{-3} at the beginning of consolidation

WBC, white blood cell; ALL, acute lymphoblastic leukaemia; CNS, central nerve system; MRD, minimal residual disease

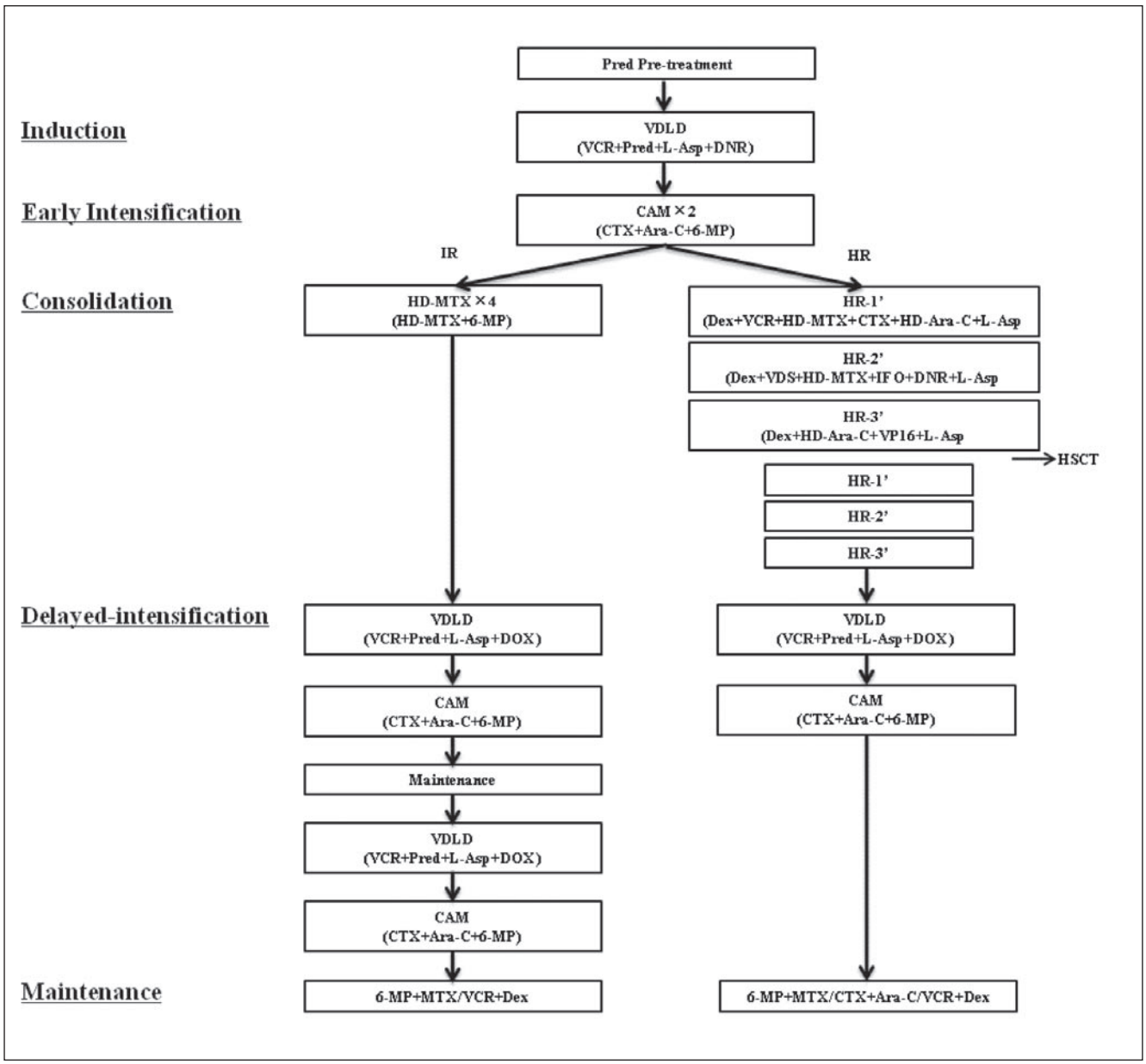

Figure 1 Treatment schema of CCLG-ALL 2008 protocol. Abbreviations: IR, intermediate risk; HR, high risk; Pred, prednisone; VCR, vincristine; L-Asp, L-asparaginase; DNR, daunorubicin; CTX, cyclophosphamide; Ara-C, cytarabine; 6-MP, 6-mercaptopurine; MTX, methotrexate; DEX, dexamethasone; VDS, vindesine; IFO, ifosfamide; VP16, etoposide; DOX, doxorubicin; HSCT, haematopoietic stem cell transplantation.

results. Peripheral blast >1.0x10^9/L at Day 8 after initial prednisone treatment was considered as poor response. The presence of blast in bone marrow <5% by cytological study was defined as complete remission. Patients with MRD >1x10^{-2} at Day 33 or MRD >1x10^{-3} at Day 84 by flow cytometry were upstaged to HR.

Statistical Analysis

The endpoints of this study were overall survival (OS) and event-free survival (EFS). OS was defined as the time from diagnosis to death or the last follow-up from any cause. EFS was defined as the time from diagnosis to the date of either the first adverse event or the last follow-up. Adverse events were relapse, death, the development of secondary malignant neoplasm and loss of follow up. Survival rate was evaluated and represented with Kaplan-Meier plots. Comparison between groups was performed with Log-rank test. A value of 2-tailed *p*-value <0.05 was considered statistically significant. All statistical analyses were performed with SAS JMP 14.0 software.

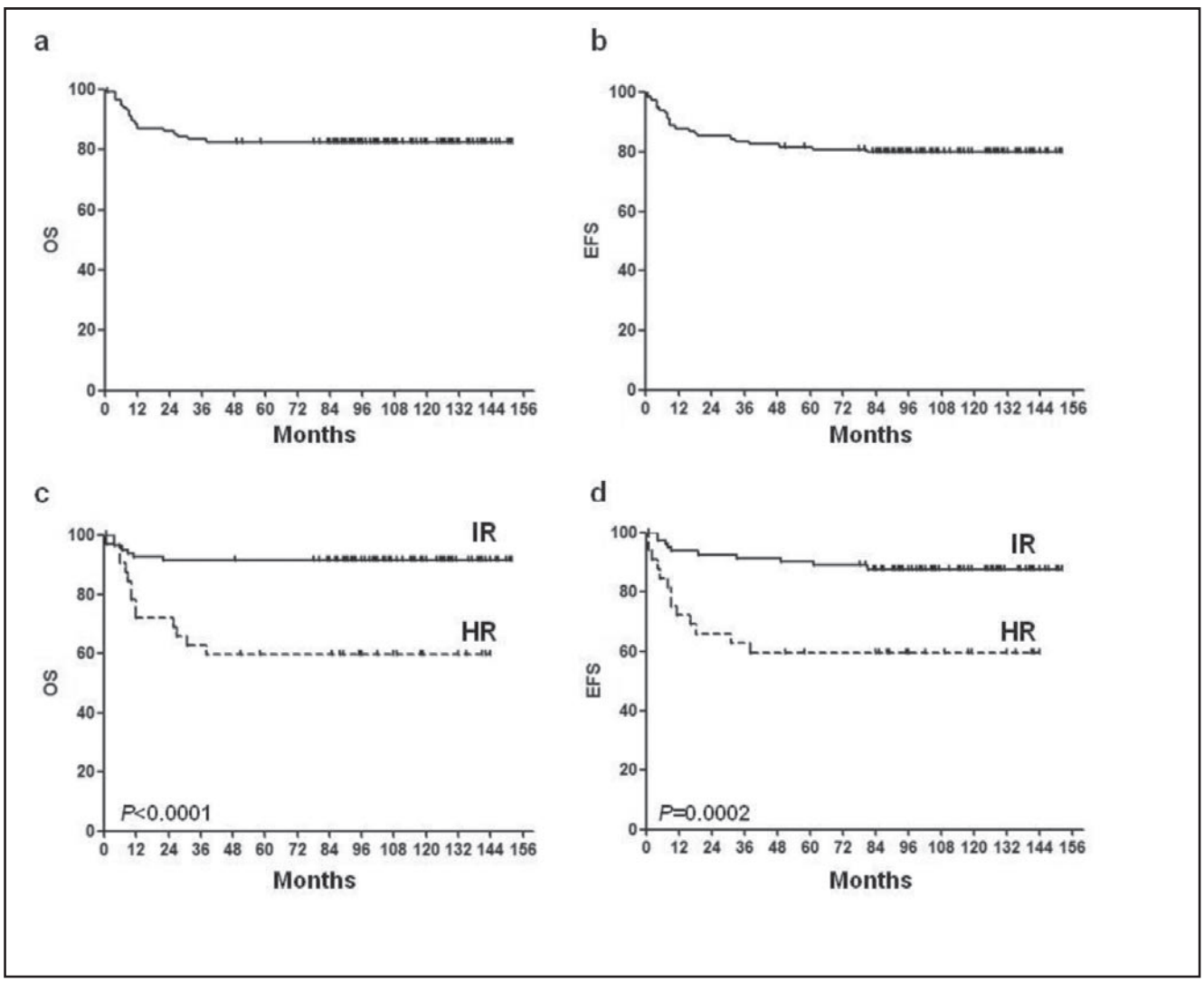

Figure 2 Five-year overall survival (a) and Event-free survival (b) for the whole group of patients, intermediate risk (IR) and high risk (HR) patients, respectively. (c) 5-year OS rate was 91.57% in IR patients, whereas, significantly decreased in HR patients 59.71%. (d) Similarly, the 5-year EFS rate was dramatically declined in HR (59.54%).

Results

Patient Characteristics

A total of 121 adolescent patients with newly diagnosed ALL were enrolled on CCLG-ALL 2008 protocol between February 1, 2008 to December 31, 2013. Median age at diagnosis was 11.5 years (range, 10-15.8 years) and mean age was 11.8 years including 72 males and 49 females. The median follow-up is 8.5 years. The clinical characteristics were summarised in Table 2.

Approximately one third of patients were assigned to HR group based on the risk-classification criteria. The frequency of high initial leukocyte count (>50x10^9/L) was 29.8%. B cell immunophenotype (81%) was more frequent than T-ALL (17.4%). Nine patients (7.4%) had *BCR/ABL* signature and 11 patients had *ETV6-RUNX1*. The incidence of *MLL* rearrangement was low (2.5%) (Table 2). Molecular genetic data were not available in a few of patients. However, relevant techniques have developed and already been used routinely in our patients during the past ten years.

Treatment Response and Outcome

In the whole cohort of patients, 10.7% of adolescent patients had poor response to prednisone at Day 8. The complete remission rate was 88.4% by morphology study. Fifteen patients did not achieve complete remission after induction phase. The 5-year OS was 82.64% and EFS was 80.78%, respectively (Figure 2). The relapse rate was 10.7% and death rate was 17.4% (Table 3). Three patients relapsed within 6 months. One patient relapsed twice. A total of 21 patients died. Twenty patients died after achieved the first CR. Only one patient died during induction phase due to severe infection. Total 11 patients died due to

Table 2 Characteristics of patients

	Number (%)
Total N=121	
Gender	
Female	72 (59.5)
Male	49 (40.5)
Risk Group	
IR	85 (70.2)
HR	36 (29.8)
WBC Count	
Median (x10^9/L)	14.15
Range (x10^9/L)	0.17-732
>50x10^9/L	36 (29.8)
<50x10^9/L	85 (70.2)
Immunophenotype	
B-lineage	98 (81.0)
T-lineage	21 (17.4)
Mixed Lineage	2 (1.7)
Cytogenetics	
ETV6-RUNX1	11 (9.1)
BCR/ABL	9 (7.4)
TCF3/PBX1	9 (7.4)
MLL rearrangement	3 (2.5)

IR, intermediate risk; HR, high risk; WBC, white blood cell.

Table 3 Treatment response and outcome

	Number (%)
Day 8 Peripheral Blood Blast Count	
<1x10^9/L	108 (89.3)
>1x10^9/L	13 (10.7)
Day 33 BM with <5% Blast	
CR	107 (88.4)
Day 33 MRD	
<1x10^{-2}	92 (84.4)
>1x10^{-2}	17 (15.6)
Day 84 MRD	
<1x10^{-3}	95 (91.3)
>1x10^{-3}	9 (8.7)
Death	
Death (Total)	21 (17.4)
Induction Death	1 (0.8)
Death after Achieved CR	20 (16.5)
Death after Relapse	11 (9.1)
Death due to Severe Infection	5 (4.1)
Death after HSCT	8 (6.6)
Relapse	
	13 (10.7)

BM, bone marrow; CR, complete remission; MRD, minimal residual disease; HSCT, haematopoietic stem cell transplantation.

disease relapse. Among these 11 patients, four patients (4/11) died due to the progressive Leukaemia, five patients (5/11) died of haematopoietic stem cell transplantation (HSCT) complications, and two patients (2/11) died due to the abandonment of treatment. Six HR patients received HSCT after CR1 and three of them (without relapse) died due to the complications of HSCT. Severe infection including septicemia and fungal infection was the major cause leading to non-relapse death (5/21). Two patients died due to the abandonment of treatment. Secondary neoplasm, pancreatitis and severe osteonecrosis were not observed during the follow up period.

The outcome of HR patients was notably inferior to IR patients. The OS was 91.57% in IR group, whereas, significantly lower in HR group (59.71%, p<0.0001). Similarly, the 5-year EFS was dramatically worse in HR patients (59.54% vs. 89.05%, p=0.0002) (Figure 2). The cumulative incidence of relapse (CIR) of HR patients was remarkably higher than IR patients (26.4% vs. 5.1%). High initial leukocyte count and poor response to prednisone at Day 8 were strongly related to inferior prognosis. The 5-year EFS was significantly declined in patients with high presenting leukocyte count (61.77% vs. 88.89%, p=0.0021). Compared to the other patients (84.25%), the 5-year EFS of patients with poor response to prednisone was 46.15% (p=0.0006). T cell immunophenotype was considered as unfavourable factor. The EFS rates of T-ALL trended to be much lower than B cell immunophenotype (66.67% vs. 83.65%, p=0.1306). Both of two patients with mixed lineage ALL survived. One patient was treated with HR protocol and the other patient achieved complete remission after HSCT. For the cytogenetic analysis, 5-year EFS rate was significantly worse in *BCR/BAL* positive patients (54.55% vs. 82.6%, p=0.011). Although the difference was not significant, there was a notable trend towards the correlation between *ETV6-RUNX1* and better outcome, being 100% and 77.76% in with or without *ETV6-RUNX1* ALL (p=0.0884). Significant superior outcome was observed in MRD $<1x10^{-2}$ group at Day 33 (86.54% vs. 50.68%) and MRD $<1x10^{-3}$ group at Day 84 (85.52% vs. 44.44%) (Table 3 & Figure 3). For HR group, 45.16% of patients were observed with MRD lower than $1x10^{-2}$ at Day 33 and 60.97% of patients' MRD at Day 84 was lower than $1x10^{-3}$.

Discussion

The incidence of ALL is more common in early childhood. It peaks at 3-5 years and declines dramatically afterwards. However, it remains the predominant subtype of Leukaemia among adolescents and is among the leading causes of cancer-related death in AYA.[5] The clinical characteristics, treatment response and outcome of adolescent ALL are distinct from paediatric ALL.

Historically, the outcome of adolescent ALL patients has been inferior to childhood patients. This discrepancy could partially explained by the unique feature of the host and ALL biology. The disparities in disease biology between adolescent ALL and paediatric ALL has been documented in some retrospective studies, however, the disease profile of Chinese adolescent patients has not been reported. Twenty-one patients (17.1%) had T-immnunophenotype and is higher than that of the younger children (usually <10%). In addition, high initial leukocyte count ($>50x10^9$/L) was present in 29.8% of patients which is again a higher proportion than younger children. This is in consistent with previous studies, which found the incidence of unfavourable factors, such as high leukocyte count at initial diagnosis, T-cell immunophenotype, *BCR/ABL* and *MLL* rearrangement were more frequent in adolescent patients. In contrary, favourable cytogenetic abnormalities (e.g., *ETV6-RUNX1*) were less frequent in adolescent ALL, when compared with our large multi-centre data for patients aged 0-18 years old.[4]

Recent improved treatment in childhood ALL has extended to adolescent patients. Paediatric-based regimen has been reported leading to much better outcome for adolescent patients compared with those enrolled in adult protocols. Retrospective study from UK reported that 5-year EFS of AYA patients treated by MRC ALL97 was 65% versus 49% for those treated on adult UKALLXII/E2993 protocol.[6] Recent published prospective cooperative study in US addressed the tolerance and better outcome of using paediatric treatment regimen in 318 AYAs patients aged 17-39 years.[7] Seventy-eight percent EFS was reported in 58 patients aged 15 to 18 years from Dana-Farber Cancer Institute.[8] Similarly, St. Jude Children's Research Hospital Total XV demonstrated excellent results in adolescent patients with 5-year EFS of 71.5%.[9] Several potential factors are contributing to such improvement. The combination of myelosuppressive and non-myelosuppressive regents are commonly utilised during the induction phase and asparaginase is only used in paediatric based ALL regimen.[10] Intrathecal treatment is taken early after the diagnosis and high-dose methotrexate treatment dramatically reduces the risk of CNS disease. Cranial irradiation has been eliminated in current paediatric

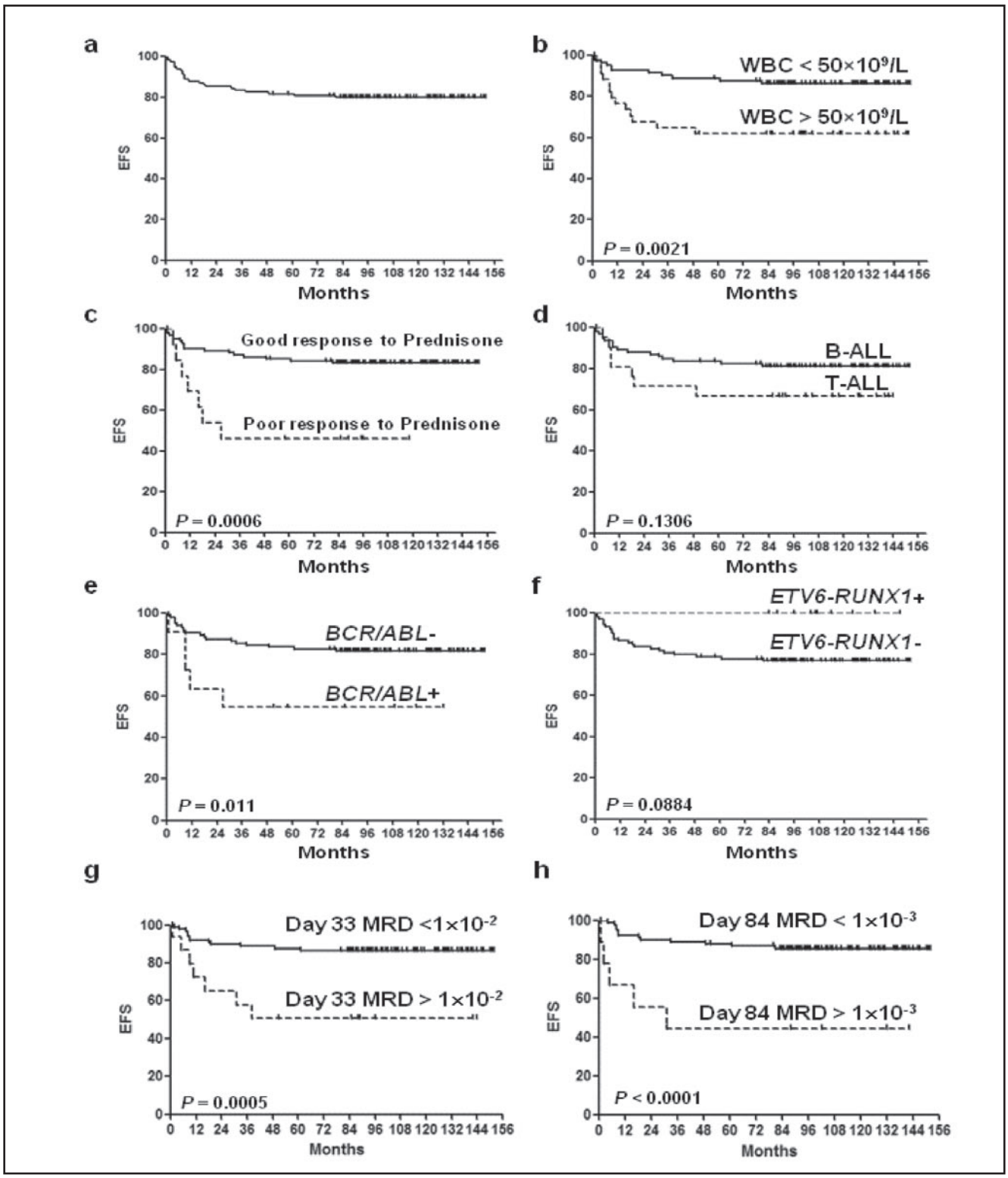

Figure 3 Five-year event-free survival (EFS) data according to prognostic factors. (a) 5-year EFS rate for whole cohort of patients was 80.78%. (b) High initial leukocyte count and (c) poor response to prednisone at Day 8 were strongly related with inferior prognosis. (d) EFS rates of T-ALL trended to be lower than B cell immunophenotype, however, without statistical difference. (e) 5-year EFS rate was significantly worse in *BCR/BAL* positive patients. (f) The outcome of patients with *ETV6-RUNX1* tended to be improved. (g) 5-year EFS was significantly higher in MRD $<1x10^{-2}$ at Day 33 and (h) MRD $<1x10^{-3}$ at Day 84, respectively.

ALL regimen unless in relapsed CNS disease, which remarkably decreases the occurrence of secondary brain tumor and improve the quality of life. Bone marrow transplantation is usually administered once patients achieving the first CR in adult protocol, however, majority of patients treated on paediatric regimen could achieve long-term remission with chemotherapy alone, which markedly decreases the transplant-related death. Moreover, unlike the adult regimen, paediatric protocol contains maintenance therapy which is beneficial to the long-term disease remission. Our study is the largest prospective study of Chinese adolescent ALL with median 8.5 years follow-up. We demonstrated that adolescents aged 10 to 18 years, treated with CCLG-ALL-2008 protocol had comparable and ever better 5-year EFS and OS compared with other published reports. The 5-year OS rate for whole cohort of patients was 82.64% and EFS was 80.78%. The death rate and relapse rate was also comparable with previous paediatric studies. Early death was only 0.83%. This improved outcome is mainly due to the precise risk-stratification, strict treatment response monitoring and timely response-adopted adjustment. And importantly, patients treated in our centre were provided with multi-disciplinary support and have strict adherence to therapy.

Despite of the improvement, the outcome of adolescents remains unsatisfactory particularly in HR group. Significant worse outcome was noted in HR patient in this study compared with IR patients. Regarding prognostic predictors, our study indicated that high initial white blood cell count, poor response to prednisone at Day 8 and *BCR/ABL* were strongly related with inferior prognosis. Since the study was started as early as 2008, we did not routinely treat the *BCR/ABL* patients with Tyrosine kinase inhibitors (TKI) at that period. However, the TKI has been regularly used to treat *BCR/ABL* patients in our current ALL protocol. Although without statistical difference, obvious trend associated with poor outcome was noted in T-immunophenotype, *TCF3/PBX1* and *MLL* rearrangement. *ETV6-RUNX1* was considered as a favourable factor and was also noted to be related with better outcome in this study. Currently, more and more novel cytogenetic abnormalities emerge as promising prognostic predictors. Philadelphia chromosome-like (Ph-like) is identified with similar gene profile with *BCR/ABL-1* in B-lineage ALL and high frequency of *IKZF-1* mutation by genome wide analysis.[11-15] The prevalence of Ph-like ALL increases significantly with age. It represents 10-15% among childhood ALL, higher than 20% in adult ALL, and with a peak of 25-30% in AYA ALL. Ph-like ALL patients have poor outcome and high risk of relapse rate. Five-year EFS of Ph-like patients was significantly inferior to Ph-like negative patients (63% *vs.* 85%).[16] In addition, compared with paediatric ALL, *IKZF* deletion, *MEF2D* rearrangement and intrachromosomal amplification of chromosome 21 (iAMP21) also has higher frequency in AYA patients and is associated with dismal outcome.[13] Screening of genetic abnormalities including Ph-like, *IKZF* deletion, *CRLF2* and iAMP21 will be beneficial to precisely identify AYA patients with high-risk features and improve their outcome by early interventions. Since those genetic marker were gradually recognised throughout the study period, only few of patients were screened with *IKZF1*, Ph-like, *CRLF2* and iAMP21, however, such genetic predictors have been adopted in new risk stratification criteria of our current multi-centre clinical trial.

Currently, there is no universal consensus on the administration of HSCT in high-risk group of patients. Previously, HSCT in first complete remission (CR1) is commonly used in adult based protocol. A meta-analysis reported survival benefit in AYA patients with HSCT comparing with chemotherapy alone.[17] MRC and ECOG supported the benefit of matched sibling allogeneic transplantation HSCT in standard-risk adult patients in CR1, with OS 53%. However, this study did not show any significant advantage of HSCT in high-risk patients. Moreover, this trial demonstrated the poor outcome of AYA patients, with OS 44% of patients younger than 20 years and 45% of patients aged 20-29 years, suggesting the limited role of HSCT in CR1 AYA patients.[10,18] Importantly, such studies were limited to adult chemotherapy regimen but not to the paediatric-based chemotherapy treatment. Recently, the role of HSCT in AYA patients after CR1 is controversial. More evidence argued the role of upfront HSCT in AYA patients' treatment. Study from US and Canada demonstrated paediatric-based therapy achieved 71% OS compared with 40% OS in patients with HSCT after CR1 and with significant lower treatment-related mortality (6% vs. 37%).[19] Moreover, AYA patients were presented with higher susceptibility to graft-versus-host disease induced by HSCT.[20] These evidence support the general consensus that paediatric-based therapy is superior and well tolerated by adolescent patients,[21] and HSCT is recommended only for very high-risk patients and relapsed patients.[22,23] Instead of HSCT, increasing treatment options have been emerging during the past decade. Targeted

therapy and immune therapy based on the precise genotyping and comprehensive treatment provide promising chance for some refractory adolescent ALL patients. In our patients with *BCR/ABL* fusion gene, the outcome was significant inferior than *BCR/ABL* negative patients during the study period, however, with the adoption of tyrosine kinase inhibitors in our regimen during past years, the prognosis of such patients has been dramatically improved and HSCT has not been considered as the first choice.

Adolescent ALL patients face the great developmental challenges and experience the transition from child to adult. In addition to health services, age-appropriate social and emotional support is equally essential and might impact on outcome of AYA patients. However, majority of countries have not established specific program providing multidisciplinary care for AYA cancer patients. Long-term physiological and psychological support is far from satisfactory. Patients younger than 18 years generally are treated in children cancer centre, however, patients older than 18 years have to be admitted in adult hospital. This incoherency in treatment and follow-up significantly impacts the outcome of AYA patients. Collaborative efforts among paediatric and adult haematologists are essential to overcome this hurdle.

The limitation of this study is the age limit in our centre. To overcome this limitation, currently, a multi-centre AYA-ALL clinical trial has been conducting and is leaded by our hospital in China. With the participation of both paediatric and adult centres, age-appropriate regimen designed for AYA patients will further improve the prognosis of patients.

Conclusion

Adolescent ALL patients are a unique subgroup with distinct disease biological characteristics and host features. Paediatric-based regimen could dramatically improve the outcome of adolescent ALL patients, however, the high-risk group treatment remains a challenge. With the development in precise risk-stratification, continuous monitoring of treatment response and targeted therapy, further improvement will be achieved by optimising the treatment and minimising the toxicity. Moreover, multidisciplinary collaboration between paediatric and adult cancer centres is needed to design more age-appropriate supportive care.

Funding

This work was supported by Beijing Municipal Administration of Hospitals Deng Feng Program (No. DFL20151101), Capital Health and Development of Special Grant (No. 2016-1-2091), in part supported by the National Science Foundation for Distinguished Young Scholars of China (grant number: 81400074), Beijing Hospital Authority Youth Program (QML20161202) and Capital Medical University Research Fund (PYZ19049). We thank all staff of Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University.

Ethics Approval

The CCLG-ALL 2008 protocol obtained the approval of Beijing Children's Hospital Ethical Committee, Capital Medical University, National Center for Children's Health. Written informed consent was obtained under the approval of the Beijing Children's Ethical Committee.

Declaration of Interest

The authors state no conflict of interest.

References

1. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol 2012;30:1663-9.
2. Rytting ME, Thomas DA, O'Brien SM, et al. Augmented Berlin-Frankfurt-Munster therapy in adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL). Cancer 2014;120: 3660-8.
3. Xiong H, Ha SY, Chiang AKS, Hu Q, Chan GCF. A small cohort review of the long-term prognosis for Chinese older children and adolescents with acute lymphoblastic leukaemia treated on a paediatric protocol. HK J Paediatr (new series) 2013;18:89-95.
4. Cui L, Li ZG, Chai YH, et al. Outcome of children with newly diagnosed acute lymphoblastic leukemia treated with CCLG-ALL 2008: The first nation-wide prospective multicenter study in China. Am J Hematol 2018;93:913-20.
5. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel R. Cancer statistics for adolescents and young adults, 2020. CA Cancer J Clin 2020;70:443-59.

6. Ramanujachar R, Richards S, Hann I, et al. Adolescents with acute lymphoblastic leukaemia: outcome on UK national paediatric (ALL97) and adult (UKALLXII/E2993) trials. Pediatr Blood Cancer 2007;48:254-61.
7. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood 2019;133:1548-59.
8. Barry E, DeAngelo DJ, Neuberg D, et al. Favorable outcome for adolescents with acute lymphoblastic leukemia treated on Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium Protocols. J Clin Oncol 2007;25:813-9.
9. Pui CH, Pei D, Campana D, et al. Improved prognosis for older adolescents with acute lymphoblastic leukemia. J Clin Oncol 2011; 29:386-91.
10. Place AE, NN Frederick, SE Sallan. Therapeutic approaches to haematological malignancies in adolescents and young adults. Br J Haematol 2014;164:3-14.
11. Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol 2009;10:125-34.
12. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med 2014;371:1005-15.
13. Roberts KG. Genetics and prognosis of ALL in children vs adults. Hematology Am Soc Hematol Educ Program 2018;2018:137-45.
14. Roberts KG, Reshmi SC, Harvey RC, et al. Genomic and outcome analyses of Ph-like ALL in NCI standard-risk patients: a report from the Children's Oncology Group. Blood 2018;132:815-24.
15. Reshmi SC, Harvey RC, Roberts KG, et al. Targetable kinase gene fusions in high-risk B-ALL: a study from the Children's Oncology Group. Blood 2017;129:3352-61.
16. Roberts KG, Morin RD, Zhang J, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell 2012;22:153-66.
17. Gupta V, Richards S, Rowe JM. Allogeneic, but not autologous, hematopoietic cell transplantation improves survival only among younger adults with acute lymphoblastic leukemia in first remission: an individual patient data meta-analysis. Blood 2013;121:339-50.
18. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 2005;106:3760-7.
19. Seftel MD, Neuberg D, Zhang MJ, et al. Pediatric-inspired therapy compared to allografting for Philadelphia chromosome-negative adult ALL in first complete remission. Am J Hematol 2016;91: 322-9.
20. Vignon M, Andreoli A, Dhédin N, et al. Graft-Versus-Host Disease in Adolescents and Young Adults (15-24 Years Old) After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Leukemia in First Complete Remission. J Adolesc Young Adult Oncol 2017;6: 299-306.
21. Advani AS, Larsen E, Laumann K, et al. Comparison of CALGB 10403 (Alliance) and COG AALL0232 toxicity results in young adults with acute lymphoblastic leukemia. Blood Adv 2021;5:504-12.
22. Nachman JB, Heerema NA, Sather H, et al. Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia. Blood 2007;110:1112-5.
23. Vey N, Thomas X, Picard C, et al. Allogeneic stem cell transplantation improves the outcome of adults with t(1;19)/E2A-PBX1 and t(4;11)/MLL-AF4 positive B-cell acute lymphoblastic leukemia: results of the prospective multicenter LALA-94 study. Leukemia 2006;20:2155-61.