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Research Article

Clinical and Prognostic Analysis of Adult Acute Lymphoblastic Leukemia

Zheng Shi and Bao-An Chen*

Department of Hematology and Oncology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, People's Republic of China

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ABSTRACT

Objective: To analyse clinical characteristics of adult patients with acute lymphoblastic leukemia (ALL) and explore prognostic factors to provide evidence for the stratification of prognostic risk and the formulation of individualized therapy.

Methods: A total of 65 adult patients with newly diagnosed ALL were reviewed. Their clinical data were collected, and their overall survival was followed up. We compared the effects of different clinical features on therapeutic efficacy and long-term prognosis. Data analysis was conducted by SPSS 25.0 statistical software. $P < 0.05$ was considered statistically significant.

Results: A total of 65 adult patients with newly diagnosed ALL, including 31 males and 34 females, were enrolled in this study, with a median onset age of 48 (range, 18-85) years. After 1 course of induction therapy, bone marrow puncture was performed to evaluate, and further demonstrate that 49 patients achieved complete response (CR), with a total CR rate (CRR) of 75.4%. Among 65 patients, the median overall survival was 15.5 (range,1.0-100.0) months, and the median disease-free survival was 9.0 (range, 0.0-99.0) months. Survival analysis showed that worse long-term outcome was associated with age (≥60 years), haemoglobin (Hb<60g/L), platelet (PLT<30×10^9/L), lactic dehydrogenase (LDH≥400U/L) at initial diagnosis, CD10 negative, and failure to reach CR within 4 weeks after induction therapy, whereas timely hematopoietic stem cell transplantation (HSCT) significantly improved the survival of patients. Univariate analysis suggested that age at onset, the initial level of low PLT and high LDH, and HSCT were risk factors for 2-year OS and 2-year DFS of adult ALL patients. Moreover, multivariate analysis showed that initial PLT level was an independent risk factor for the prognosis of adult ALL patients, and CR within 4 weeks after induction and HSCT could improve patients' overall survival.

Conclusion: Long-term outcome for adult ALL patients is poor. Clinical characteristics, including elder age, severe anemia, low PLT level, high LDH level, CD10 negative and so on, make poor clinical induction effect on such patients. However, achieving CR within 4 weeks and actively accepting HSCT can significantly improve the prognosis of adult ALL.

Introduction

Acute lymphoblastic leukemia (ALL) is a hematological malignancy caused by the abnormal proliferation and accumulation of immature lymphocytes in bone marrow, peripheral blood and/or extramedullary organs. Clinical manifestations are not specific, but most patients come to the hospital because of fever, fatigue, gingival bleeding, skin petechiae and ecchymosis, or abnormal blood count in the physical examination as their first symptoms. Enlargement of liver, spleen, or lymph nodes could be found in more than 60% of the patients. This disease is more common in children, and there will be a second peak in those over 60 years old [1].

ALL is a critical disease with rapid progression and high mortality. The natural course of the disease is only a few weeks to months. Once diagnosed, treatment should be started as soon as possible. At present, therapy for ALL is still based on multi-drug combined chemotherapy,

**Correspondence to: Bao-An Chen, Department of Hematology and Oncology, Zhongda Hospital, School of Medicine, Southeast University, Dingjiaqiao 87, Gulou District, Nanjing, Jiangsu Province 210009, People's Republic of China; Tel: +862583272006; Fax: +862583272011; E-mail: cba8888@hotmail.com*

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and includes an induction course, consolidation and intensive course and maintenance course. With the continuous research of molecular biology and cytogenetics, as well as the development of testing methods, our understanding of ALL is deepening. At the same time, the rapid development of various new drugs, targeted medicine, and the maturity of hematopoietic stem cell transplantation（HSCT）have significantly improved the efficacy of ALL [2].

The experience of treating pediatric ALL tells a successful story in oncology. Nowadays, based on risk stratification, the complete remission rate（CRR）of pediatric patients can reach 95% under suitable diagnosis and treatment. The rate of 5-year event-free survival（EFS）and 5-year overall survival（OS）has been improved to more than 80% and 90%, respectively, and some patients even have the possibility of being cured [3-7]. Due to the higher incidence of chromosomal abnormalities associated with poor prognosis and lower tolerance to chemotherapy in adult patients, although the vast majority of this group can achieve CR after treatment, their long-term prognosis is far from satisfactory, and the 5-year survival rate is only 35-45% [8-10].

ALL is highly heterogeneous and varies greatly among individuals. Exploring factors affecting the prognosis of adult ALL patients and performing risk stratification is of great significance to formulate individualized strategies and improve treating efficacy, which helps to better guide clinical work. In this study, clinical data and related indicators of patients who were initially diagnosed and treated in the Department of Hematology, Zhongda Hospital, affiliated to Southeast University, were collected and followed up. To explore the clinical characteristics, treatment regimens and effects of newly diagnosed adult ALL patients in our hospital, and to explore the independent prognostic risk factors. The aim of this study is to analyse clinical characteristics, treatment options and outcomes of newly diagnosed adult ALL patients in this hospital, and to explore independent prognostic risk factors.

Methods

I Patient Data

A total of 65 ALL patients hospitalized in the Department of Hematology, Zhongda Hospital, affiliated to Southeast University, from July 2012 to December 2019 were selected as the research objects, including 31 males and 34 females, who were all older than 18 years old. All patients were classified according to Morphology, Immunology, Cytogenetics and Molecular biology (MICM), and received at least 1 course of induction therapy after diagnosis.

II Treating Strategy

Induction chemotherapy regimen includes: VDCLP regimen: vincristine+ daunorubicin+ cyclophosphamide+ L-asparaginase+ prednisone; DVLP regimen: vincristine+ daunorubicin+ L-asparaginase+ prednisone; DVCP regimen: vincristine+ daunorubicin+ cyclophosphamide+ prednisone; VP regimen: vincristine+ prednisone; Hyper-CVAD regimen: cyclophosphamide+ doxorubicin + vincristine+ dexamethasone.

III Efficacy Evaluation

After one course of induction, bone marrow was re-evaluated. Complete remission (CR) mainly refers to: (1) disappearance of clinical symptoms and signs; (2) no blasts in peripheral blood or extramedullary leukemia; (3) recovery of hematopoietic function, with <5% primitive cells; (4) absolute neutrophil count (ANC) $>1.0\times10^9$ /L; (5) PLT$>100\times10^9$ /L. Relapse refers to the re-emerging of >5% blasts in peripheral blood or bone marrow after CR or extramedullary infiltration of leukemia.

IV Follow-up

Patients were followed up in the outpatient department or by telephone from the date of diagnosis until death or December 31, 2020, the cutoff date of this study. OS was defined as the period from the date of diagnosis to death of any cause or the cutoff date; cases abandoned or lost were followed up to the date of abandonment or loss. DFS was defined as the period from the acquisition of CR1 to the first recurrence of disease, or death in CR status, or date of loss.

V Statistical Analysis

Chi-square test or Fisher exact test was used to compare clinical characteristics and treatment effects. Kaplan-Meier survival curve was used to evaluate survival analysis. Log-rank was used to analyse the possible prognostic factors. Valuable predictive factors were further screened out by using least absolute shrinkage and selection operator (LASSO) regression and incorporated into Cox regression model for multivariate analysis. $P < 0.05$ was considered statistically significant.

Results

I Clinical Features

A total of 65 newly diagnosed adult ALL patients were included in this study, involving 31 males and 34 females. The median age of onset was 48 (18-85) years old. At initial diagnosis, the median WBC count was 15.56 (0.60-265.57)$\times10^9$/L, including 22 cases with WBC$\geq30\times10^9$/L and 5 cases with WBC$\geq100\times10^9$/L; the median Hb was 86 (30-160) g/L, including 13 cases with Hb < 60g/L; the median PLT count was 49 (1-287) $\times10^9$ /L, including 21 cases with PLT < 30 $\times10^9$/L and 9 cases with PLT < 10 $\times10^9$/L, the median LDH level was 516 (138-15525) U/L, including 36 cases with LDH ≥400 U/L and 16 cases with LDH ≥1000U/L.

Flow cytometry analysis showed 57 patients with B cell-acute lymphoblastic leukemia (B-ALL), 6 patients with T cell-acute lymphoblastic leukemia (T-ALL) and 2 patients with T/B bi-phenotypic ALL. Abnormal karyotype was found in 34 cases, among which positivity of Philadelphia chromosome (Ph) and/or BCR/ABL fusion gene was most common, with 29 cases in total. Complex karyotypes (≥5 abnormal chromosomes) were presented in 13 patients.

II Follow-up Results

At the end of the follow-up, the median overall survival was 15.5(0.5-100.0) months, the 2-year 0S rate was 24.6% and the 2-year DFS rate

was 20.0%. Univariate analysis showed that advanced age (≥60 years old) at onset, low PLT (< 30×10^9/L) and high LDH (≥400 U/L) at diagnosis were risk factors for 2-year OS and 2-year DFS in adult ALL patients. While HSCT was a protective factor in this group (Table 1).

Table 1: Influencing factors of OS and DFS in ALL patients.

Factors	**Cases**	**2-year OS**		**2-year DFS**	
		N（%）	***P***	**N（%）**	***P***
age					
18~39	21	10（47.6）	**0.002**	8（38.1）	
40~59	23	6（26.1）		5（21.7）	**0.005**
≥60	21	0（0.0）		0（0.0）	
gender					
male	31	9（29.0）	0.430	7（22.6）	0.619
female	34	7（20.6）		6（17.6）	
bone marrow infiltration					
yes	31	5（16.1）	0.129	5（16.1）	0.456
no	34	11（32.4）		8（23.5）	
WBC（$\times10^9$ /L）					
＜30	43	10（23.3）	0.722	7（16.3）	0.471
≥30	22	6（27.3）		6（27.3）	
Hb（g/L）					
＜60	13	1（7.7）	0.221	0（0.0）	0.104
≥60	52	15（28.8）		13（25.0）	
PLT（$\times10^9$ /L）					
≥30	44	15（34.1）	**0.010**	13（29.5）	**0.014**
＜30	21	1（4.8）		0（0.0）	
LDH（U/L）					
≥400	36	3（9.1）	**0.001**	3（8.3）	**0.009**
＜400	29	13（44.8）		10（34.5）	
CD34					
positive	48	10（20.8）	0.389	9（18.8）	0.944
negative	17	6（35.3）		4（23.5）	
CD10					
positive	46	14（30.4）	0.168	11（23.9）	0.375
negative	19	2（10.5）		2（10.5）	
with myeloid antigen					
yes	29	6（20.7）	0.510	6（20.7）	0.901
no	36	10（27.8）		7（19.4）	
karyotype					
normal	31	7（22.6）	0.716	6（19.4）	0.901
abnormal	34	9（26.5）		7（20.6）	
Ph chromosome					
positive	29	7（24.1）	0.936	6（20.7）	0.901
negative	36	9（25.0）		7（19.4）	
treating efficacy					
do not achieve CR	16	1（6.3）	0.103	1（6.3）	0.221
achieve CR	49	15（30.6）		12（24.5）	
HSCT					
yes	24	13（54.2）	**0.000**	11（45.8）	**0.000**
no	41	3（7.3）		2（4.9）	

III Survival Analysis

Survival analysis showed that advanced age (≥60 years old), low Hb (< 60 g/L), low PLT (< 30×10^9/L) and high LDH (≥400 U/L) at diagnosis were risk factors affecting the long-term prognosis of adult ALL patients. CD10 expression, CR within 4 weeks after 1 course of induction therapy, and HSCT acceptance were protective factors affecting the long-term prognosis of adult ALL patients (Figure 1).

IV Factor Screening

Possible factors that may affect OS were included in the analysis model for further screening by the use of Lasso regression. Lasso coefficient

profiles were drawn according to log (λ) sequence (Figure 2A). At the same time, 10-fold cross-validation was used to determine the optimal penalty coefficient on the basis of the minimum quasi-test (Figure 2B). The left vertical dashed line represents the minimum model error, and the right vertical dashed line is drawn according to one standard error criterion. To establish a simplified and regularized model, four factors with non-zero coefficients at λ1se=0.2083 were selected as significant predictors, including age at onset, PLT level at diagnosis, CR within 4 weeks of induction therapy, and subsequent HSCT.

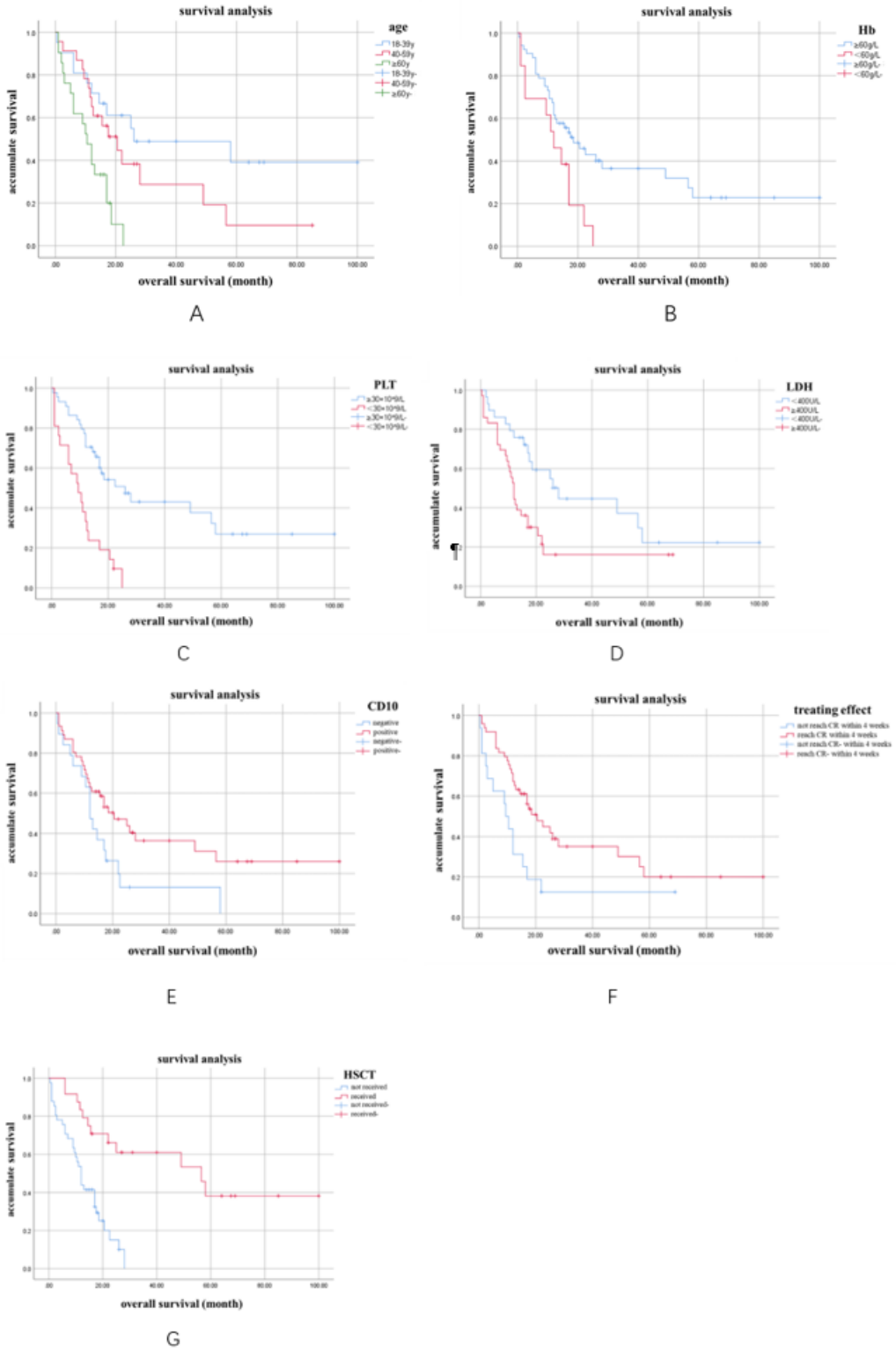

Figure 1: OS in ALL patients affected by **A)** age, **B)** Hb, **C)** PLT, **D)** LDH, **E)** CD 10 expression, **F)** treating effect, and **G)** HSCT.

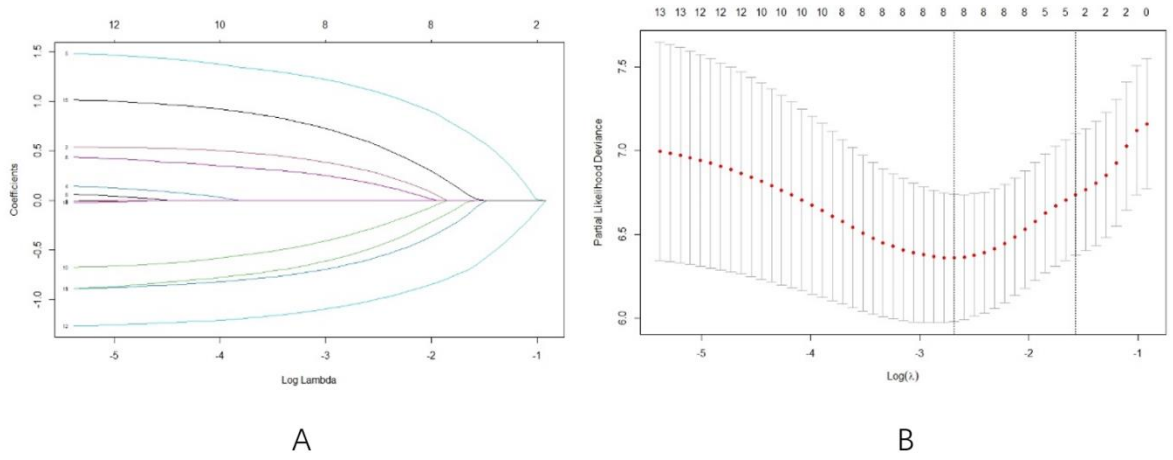

Figure 2: A & B) Lasso regression analysis.

V Efficacy Analysis in the Long-Term

According to Lasso regression analysis, indicators with predictive value were included in the COX regression model. Multivariate analysis showed that: PLT level at initial diagnosis (P < 0.001) was an independent risk factor for OS in adult ALL patients, while CR within 4 weeks of treatment (P=0.007) and HSCT therapy (P < 0.001) were protective factors for OS in adult ALL patients (Table 2). Among the 65 patients included in this study, 5 achieved long-term survival for more than 5 years. Their clinical characteristics were summarized as follows (Table 3).

Table 2: Multivariate COX regression analysis of prognostic factors in ALL patients.

Risk factors	B	SE	Exp(B)	95.0% CI	P
age at onset	0.162	0.433	1.175	0.503~2.746	0.709
PLT level	1.336	0.335	3.802	1.972~7.330	**0.000**
CR within 4 weeks	-0.947	0.349	0.388	0.196~0.768	**0.007**
HSCT	-1.667	0.463	0.189	0.076~0.468	**0.000**

Table 3: Patients with long-term survival.

	Case 1	Case 2	Case 3	Case 4	Case 5
gender	male	male	female	male	male
age	19	24	24	30	48
main complain	fatigue	fever	Fever, lymph node enlargement	fatigue	recurrent abdominal pain
WBC（/L）	102.77×10^9	71.4×10^9	107.73×10^9	4.03×10^9	27.8×10^9
Hb（g/L）	60	125	61	86	93
PLT（/L）	59×10^9	230×10^9	56×10^9	37×10^9	106×10^9
marrow blast	94%	71.5%	77%	90.4%	95.5%
Flow cytometry analysis	CD58，CD66，CD34，CD10，CD19，CD45	HLA-DR，CD10，CD19，CD20，CD22，CD38，CD123，CD79a，TdT	CD19，CD10，CD33，CD38，CD22，CD79a，HLA-DR	CD79a，CD22，CD19，CD10，	CD34，CD79a，CD19，CD10
chromosome	41-46，XY，9P-[CP7]/45，XY，9P-/46，XY	46，XY，t（9，22）（q34；q11.2）	47，XX，t（1:11）（p36.1:q21），+21[8]/46，XX[1]	44，XY，-7，t(9;22)(q34;q11)，-13[15]/46，XY[5]	46，XY，t（9，22）（q34；q11.2）
gene		BCR/ABL（p210）		BCR/ABL（p190）	BCR/ABL
induction therapy	VDCLP	VDCP+ dasatinib	VDCLP	hyper-CVAD+ imatinib	VDCLP+ dasatinib
HSCT	umbilical cord blood transplantation was performed 4.5 months after diagnosis during CR1	allo-HSCT was performed 5 months after diagnosis during CR1	allo-HSCT was performed 3 months after diagnosis during CR1	allo-HSCT was performed 4.5 months after diagnosis during CR1	allo-HSCT was performed 4.5 months after diagnosis during CR1

Discussion

ALL is a malignant hematologic disease caused by abnormal proliferation and differentiation of lymphoblast cells. Adult patients suffering from this disease are difficult to treat and have a poor long-term prognosis. Early risk stratification is helpful in determining outcome and guide treatment strategy. However, there is no consensus on the independent risk factors affecting the long-term prognosis of adult patients.

Age has always been considered an independent prognostic factor for adult ALL. CRR, OS, and DFS of patients showed a downward trend with the increase of onset age, and the prognosis of elderly patients over 60 years old was worse [11-13]. It may be that adult ALL patients were more likely to have high-risk molecular abnormalities such as BCR-ABL1 rearrangement and Ph-like chromosomes, while the probability of low-risk subtypes such as hyperdiploidy and ETV6-RUNX1 was low. Regimens of lower intensity were often applied in adult patients, considering their low tolerance to chemotherapy [14-16]. Adolescents and young adults younger than 40 years old were referred to as AYAs in many clinical studies, and 40 years old was used as the cut-off point for prognosis [9, 17]. In this study, patients were divided into three groups according to their age: 18-39 years old, 40-59 years old and ≥60 years old. With the increase in age, patients' OS, 2-year OS rate and 2-year DFS rate all decreased, and the differences were statistically significant, which was consistent with literature reports [12, 15, 16].

Laboratory tests at the first time could often predict prognosis. In a large retrospective study MRC UKALL XII/ECOG E2993, researchers found that WBC>30×10^9/L (B-ALL) or >100×10^9 / L (T-ALL) at initial diagnosis was an independent prognostic factor affecting DFS and OS [9]. In addition, multiple studies have regarded high WBC as a high-risk factor for poor prognosis [17-19]. In this study, there were 22 patients with high WBC and 43 patients without high WBC. There was no significant difference in CRR, OS and DFS between the two groups, which was inconsistent with most studies [9, 17-19]. Possible reasons included small sample size, difference in induction protocol, consolidation therapy, subsequent HSCT and so on. Large studies analysed other laboratory measures, such as Hb, platelet level, and LDH were few.

In terms of the choice of chemotherapy regimen, for Ph- patients, guidelines recommend at least vincristine, anthracyclines (e.g., daunorubicin) and glucocorticoid (prednisone or dexamethasone) in induction therapy, asparaginase and/or cyclophosphamide were also recommended for combination. In this study, after one course of induction therapy, the CRR of patients using VDLP regimen and VDCLP regimen was 75.0% and 70.6%, respectively. The therapeutic effect was obvious. Meanwhile, guidelines also recommended the use of hyper-CVAD regimen. A non-randomized study conducted by MD Anderson Cancer Center for AYA patients showed that the period of 5-year CR reached 53% and the 5-year OS rate reached 60% in patients accepting Hyper-CVAD treatment [20]. In our study, 4 out of 5 patients treated with Hyper-CVAD regimen achieved CR, but due to the small sample size, further statistical analysis could not be performed.

Ph+ ALL accounted for 20%-30% of adult ALL patients, and this proportion increased with age, even up to 40% in elderly patients. Ph+ was often considered a high-risk factor for poor prognosis. In the past, the prognosis of patients with Ph+ ALL was very poor, and the 5-year OS rate was only 5%-20%. Timely allo-HSCT was the only hope for the cure. But the emergence and application of TKI significantly improved the outcome of this subgroup of patients [21, 22]. Some studies even believed that Ph+ maybe a factor conducive to long-term prognosis for newly diagnosed elderly ALL patients [23].

The combination of first-generation TKI, imatinib, with standard chemotherapy, could increase the CR rate to 90%-95% and the long-term survival rate to 40%-50%, but cases with central nervous system recurrence were common [24-26]. The second-generation TKI, such as dasatinib, could better penetrate into the central nervous system [27]. Studies have shown that chemotherapy combined with dasatinib can also make more than 90% of patients achieve CR. The 2-year DFS and OS of patients with dasatinib combined with Hyper-CVAD were 60% and 64%, respectively, which was further improved compared with the efficacy of imatinib [28, 29].

In our study, 29 Ph+ patients (except 2 patients) were treated with TKI. Compared with Ph- patients, after 1 course of induction therapy, the CRR of Ph+ group was even slightly higher, while there was no significant difference in the median OS, 2-year OS rate and 2-year DFS rate between the two groups. Ph+ did not indicate poor prognosis in our study, meaning that the application of TKI significantly improved the overall therapeutic effect of this subgroup of patients. Side effects of asparaginase, especially liver toxicity, were more obvious when combined with TKI, which could increase the treatment-related mortality and the incidence of serious adverse events. Therefore, the application of asparaginase was not emphasized in the current guidelines [30].

For elderly patients, reducing the intensity of chemotherapy could reduce the risk of treaty-related toxicity and death. Glucocorticoid alone combined with TKI without chemotherapy could also achieve a satisfactory CRR. 5 elderly patients treated with dexamethasone or prednisone combined with TKI in our hospital all achieved CR within 4 weeks [31-33]. Currently, clinical studies are underway to investigate whether the addition of monoclonal antibodies can further improve the efficacy of elderly patients without increasing chemotherapy-related adverse events, such as NCT03263572, NCT02143414, NCT02744768, and NCT02311998.

Allo-HSCT was recommended during CR1 for patients highly likely to suffer from recurrence. High-risk indicators included low diploid/near triploid, t(4; 11), t(9; 22), complex karyotype, Ph-like ALL, early precursor T-lymphocytic leukemia, and MRD positive after induction therapy [34-37]. For Ph+ patients, HSCT was previously recommended as the first-line consolidation regimen to obtain a better prognosis, but the addition of TKI made researchers question the benefit of transplantation. Many clinical studies have found that patients with molecular remission after induction could obtain long-term survival without subsequent transplantation therapy [38-40].

In conclusion, adult ALL patients are prone to relapse after remission and have poor long-term survival. Early risk stratification is helpful in predicting the prognosis and guide clinical individualized treatment.

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