Outcomes of adolescents with acute lymphoblastic leukaemia

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ABSTRACT

Introduction: Compared with young children who have acute lymphoblastic leukaemia (ALL), adolescents with ALL have unfavourable disease profiles and worse survival. However, limited data are available regarding the characteristics and outcomes of adolescents with ALL who underwent treatment in clinical trials. The aim of this study was to investigate the causes of treatment failure in adolescents with ALL.

Methods: We retrospectively analysed the outcomes of 711 children with ALL, aged 1-18 years, who were enrolled in five clinical trials of paediatric ALL treatment between 1993 and 2015.

Results: Among the 711 children with ALL, 530 were young children (1-9 years at diagnosis) and 181 were adolescents (including 136 younger adolescents [10-14 years] and 45 older adolescents [15-18 years]). Compared with young children who had ALL, adolescents with ALL were less likely to have favourable genetic features and more likely to demonstrate poor early response to treatment. The 10-year overall survival and event-free survival rates were significantly lower among adolescents than among young children (77.9% vs 87.6%, P=0.0003; 69.7% vs 76.5%, P=0.0117). There were no significant differences in the 10-year cumulative incidence of relapse, but the 10-year cumulative incidence of treatment-related death (TRD) was significantly greater among adolescents (7.2%) than among young children (2.3%; P=0.002). Multivariable analysis showed that both younger and older adolescents (vs young children) had worse survival and greater incidence of TRD.

Conclusion: Adolescents with ALL had worse survival because they experienced a greater incidence of TRD. There is a need to investigate optimal treatment adjustments and novel targeted agents to achieve better survival rates (without excessive toxicity) among adolescents with ALL.

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New knowledge added by this study

- Compared with young children who had acute lymphoblastic leukaemia (ALL), adolescents with ALL were more likely to have a T-cell immunophenotype and less likely to have favourable genetic features (high hyperdiploidy and *ETV6-RUNX1*).
- A greater proportion of adolescents with ALL had poor day 8 prednisone response and did not achieve complete remission.
- Adolescents with ALL had worse survival and a greater incidence of treatment-related death.

Implications for clinical practice or policy

- There is a need to investigate optimal treatment adjustments and novel targeted agents to achieve better survival rates (without excessive toxicity) among adolescents who receive paediatric ALL treatment protocols.
- Novel targeted agents for patients with poor early response to ALL treatment may overcome treatment resistance and improve clinical outcomes.

青少年急性淋巴細胞白血病的結局

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引言：與急性淋巴細胞白血病（ALL）幼兒患者相比，ALL青少年患者的疾病特徵和存活率較低。然而，有關臨床試驗中接受治療的ALL青少年患者的特徵和結局的數據有限。本研究旨在檢視青ALL青少年患者治療失敗的原因。

方法：回顧分析1993年至2015年間參與5項ALL兒童治療臨床試驗的711名1歲至18歲ALL患者的結局。

結果：研究納入711名ALL兒童，包括530名兒童（診斷時1-9歲）和181名青少年（136名10-14歲及45名15-18歲青少年）。與ALL幼兒患者相比，ALL青少年患者較低機會具有良好遺傳特徵，並且更有可能表現出對治療的早期反應不佳。ALL青少年患者的10 年總存活率和無事件存活率顯著低於幼兒患者（77.9% vs 87.6%，P=0.0003；69.7% vs 76.5%，P=0.0117）。10年累積復發率無顯著差異，但青少年患者的10年累積與治療相關死亡的發生率顯著高於幼兒患者（7.2%比2.3%；P=0.002）。多變量分析表明，與幼兒相比，10-14歲和15-18歲青少年患者的存活率較低，與治療相關死亡的發生率較高。

結論：ALL青少年患者的存活率較低，這與其治療相關死亡的發生率較高相關。有必要研究最佳治療調整和新標靶藥物，使ALL青少年患者的存活率在接受沒有過度毒性的治療下能有所改善。

Introduction

Despite dramatic improvement in the prognosis of paediatric acute lymphoblastic leukaemia (ALL), the age at diagnosis remains a major prognostic factor: adolescents with ALL have worse outcomes than their younger counterparts.[1-4] This is partly related to differences in disease biology, such that older children with ALL more frequently have a T-cell phenotype and less frequently have high hyperdiploidy or *ETV6-RUNX1* translocation.[4-9] Therefore, older children constitute a distinct subgroup for which an optimal treatment strategy has not been determined. Although intensive treatment protocols for paediatric ALL reportedly improve outcomes among adolescents,[3,5,10-12] limited data are available from East Asian countries regarding the characteristics of adolescents with ALL who underwent treatment in clinical trials.[13] The National Cancer Institute criteria, used for risk stratification in most international ALL trials, define age ≥10 years as a risk factor for B-cell precursor ALL[1-5,10-12,14]; however, most treatment-related toxicities occur with significantly greater frequency in older adolescents (aged ≥15 years).[1-5,10-12,14] To our knowledge, there is limited available information regarding the differences in clinical characteristics and long-term treatment outcomes between adolescents (younger adolescents aged 10-14 years and older adolescents aged 15-18 years) and young children (aged 1-9 years) who receive intensive paediatric treatment protocols for ALL.[13,15] Additionally, because ALL is a comparatively uncommon disorder in older adolescents, specific treatment outcome data for such patients are limited. We aimed to study the territory-wide outcome of adolescents with ALL treated by uniform chemotherapy protocols in Hong Kong, and tried to identify the treatment response and toxicity profile in the adolescents, and also the causes of treatment failure in particular older adolescents who shared similar characteristics of young adults.

Methods

Patients

In total, 711 patients (aged 1-18 years) newly diagnosed with ALL were enrolled in consecutive clinical trials during the period from 1993 to 2015; these trials were HKALL 93[16] (1993-1997, n=144), HKALL 97[17] (1997-2002, n=170), ALL IC-BFM 2002[18] (2003-2008, n=169), CCLG-ALL 2008[19] (2008-2015, n=221), and EsPhALL[20] (2008-2014, n=7).

Risk classification and treatment

Detailed treatment stratification and therapy protocols used in the five trials have been described elsewhere. Briefly, stratification in the HKALL 93, HKALL 97, and ALL IC-BFM 2002 trials was performed using the following information: initial white blood cell count, central nervous system (CNS) status, immunophenotype, age at diagnosis, molecular-genetic abnormalities (t[9;22]/*BCR-ABL1*, *ETV6-RUNX*1, t[1;19]/*TCF3-PBX1*, and *KMT2A*-rearranged), and early response to chemotherapy (day 8 prednisone response and post-induction bone marrow status). Thus, patients were stratified into three risk groups within the respective trials: standard-risk, intermediate-risk, and high-risk. In the CCLG-ALL 2008 trial, therapy stratification was performed using flow cytometry and polymerase chain reaction–based analyses of minimal residual disease (MRD).[19] Definitive risk assignment (for provisional standard- or intermediate-risk cases based on presenting features) was performed after MRD evaluation during therapy. In the EsPhALL trial, patients were stratified into good and poor risk groups according to their early response to induction therapy (day 8 prednisone response and post-induction bone marrow status).

Statistical analysis

Characteristics were compared among age-groups using the Chi squared test or Fisher's exact test for categorical variables; the Wilcoxon rank-sum test was used for comparisons of continuous variables. We used the following age-group definitions:

young children were patients aged 1 to 9 years and adolescents were patients aged 10 to 18 years; younger adolescents were patients aged 10 to 14 years and older adolescents were patients aged 15 to 18 years. Complete remission (CR) was defined as <5% bone marrow lymphoblasts and the absence of peripheral lymphoblasts or extramedullary disease. Event-free survival (EFS) was defined as the length of time from diagnosis to the last follow-up or first event (relapse, secondary malignancy, or death from any cause). Overall survival (OS) was defined as the length of time from diagnosis to the last follow-up or death from any cause. The probabilities of EFS and OS were estimated by Kaplan–Meier analysis; they were compared between groups using the log-rank test. Time to relapse was defined as the length of time from the end of remission induction chemotherapy (for patients who achieved CR) to relapse. The cumulative incidence of relapse was estimated according to time period; death from any cause before relapse was regarded as a competing event. Time to treatment-related death (TRD) was defined as the length of time from the date of diagnosis until death from non-progressive disease. The cumulative incidence of TRD was estimated by regarding leukaemia-related death and relapse as competing risk factors. Gray's methods were used to assess the effects of age-group on the cumulative incidences of relapse and TRD. Univariable and multivariable Cox proportional hazard regression models were used to identify predictors of survival; univariable and multivariable competing risks regression models were used to identify predictors of TRD. Predictors with P values <0.1 in univariable analyses were included in the corresponding multivariable model. All tests were two-sided, and P values <0.05 were considered statistically significant. Stata Statistical Software (version 12.0; StataCorp, College Station [TX], United States) was used for all statistical analyses. The STROBE checklist was followed to ensure standardised reporting.

Results

Patient characteristics

The characteristics of the 711 patients analysed in this study are shown in Table 1. There were 530 young children, 136 younger adolescents, and 45 older adolescents. Sex distribution did not differ between young children and adolescents, but the proportion of male patients tended to be higher among older adolescents. The proportion of patients with white blood cell count ≥50 × 10^9/L at presentation was greater among adolescents than among young children (29.8% vs 19.8%, P=0.005). The proportion of patients with a B-cell immunophenotype was greater among young children (91.3% vs 72.9%), while the proportions of patients with a T-cell immunophenotype were significantly greater among older and younger adolescents than among young children (31.1% vs 23.5% vs 7.5%, P<0.001). The incidences of CNS involvement at diagnosis (CNS2/3 status) were 11.1%, 4.4%, and 4.2% among older adolescents, younger adolescents, and young children, respectively; these values did not significantly differ (P=0.102). Concerning the karyotypes of leukaemic cells, the proportion of patients with high hyperdiploidy (≥51 chromosomes) was significantly greater among young children than among older or younger adolescents (P=0.001). *ETV6-RUNX1* fusion was also significantly more common among young children (P<0.001).

In total, 471 patients underwent evaluations of blast count in peripheral blood after 7 days of prednisone therapy. The proportion of patients with poor prednisone response (blast count >1.0 × 10^9/L after 7 days of prednisone therapy) was greater among older adolescents than among younger adolescents or young children (22.9% vs 13.5% vs 6.9%, P=0.003). Additionally, the CR rate was significantly lower among older adolescents than among younger adolescents or young children (80.0% vs 92.6% vs 98.3%, P<0.001). The early death rate during induction therapy was higher among older adolescents than among younger adolescents or young children (6.7% vs 0.7% vs 1.1%, P=0.008). In total, 288 patients underwent MRD assessment at the end of remission induction; the proportion of patients with MRD ≥1% was greater among adolescents than among young children (16.7% vs 5.2%), while the proportion of patients with MRD <0.01% was lower among adolescents than among young children (47.4% vs 70.5%, P<0.001). However, MRD response did not differ between younger adolescents and older adolescents.

Treatments and outcomes of 45 older adolescents with lymphoblastic leukaemia

The treatments and outcomes of older adolescents with ALL are shown in the online supplementary Figure. Three patients died during induction (two had TRD and one had leukaemia-related death). Among the 36 older adolescents who achieved CR, three patients underwent allogeneic haematopoietic stem cell transplantation (HSCT) during CR1; one died of transplant-related infection, one relapsed (they achieved CR2 after salvage chemotherapy and remained in continuous CR), and one remained in continuous CR. The remaining 33 patients received only chemotherapy; 28 remained in continuous CR, one died of treatment-related infection, and five relapsed. Among the patients who relapsed, one was lost to follow-up, two died of progressive leukaemia, and two received allogeneic HSCT during CR2; one of the two transplant patients died of transplant-related infection, while the other remained in continuous CR.

TABLE 1. Patient characteristics and early treatment response parameters*

	Young children (aged 1-9 y)	Adolescents (aged 10-18 y)	Younger adolescents (aged 10-14 y)	Older adolescents (aged 15-18 y)	P value†	P value‡
Total No.	530	181	136	45		
Age, median (interquartile range), y	4.1 (2.7-5.9)	13.8 (11.6-15.0)	12.8 (11.2-14.1)	16.3 (15.8-16.9)	N/A	N/A
Study					0.510	0.006
HKALL 93	115 (21.7%)	29 (16.0%)	28 (20.6%)	1 (2.2%)		
HKALL 97	128 (24.2%)	42 (23.2%)	35 (25.7%)	7 (15.6%)		
ALL IC-BFM 2002	123 (23.2%)	46 (25.4%)	33 (24.3%)	13 (28.9%)		
CCLG-ALL 2008	159 (30.0%)	62 (34.3%)	40 (29.4%)	22 (48.9%)		
EsPhALL	5 (0.9)	2 (1.1%)	0	2 (4.4%)		
Time period					0.030	<0.001
Early (1993-2001)	221 (41.7%)	59 (32.6%)	54 (39.7%)	5 (11.1%)		
Late (2002-2015)	309 (58.3%)	122 (67.4%)	82 (60.3%)	40 (88.9%)		
Sex					0.501	0.082
Male	308 (58.1%)	100 (55.2%)	69 (50.7%)	31 (68.9%)		
Female	222 (41.9%)	81 (44.8%)	67 (49.3%)	14 (31.1%)		
Diagnosis					<0.001	<0.001
B-cell ALL	484 (91.3%)	132 (72.9%)	101 (74.3%)	31 (68.9%)		
T-cell ALL	40 (7.5%)	46 (25.4%)	32 (23.5%)	14 (31.1%)		
Biphenotypic ALL	6 (1.1%)	3 (1.7%)	3 (2.2%)	0		
WBC count at presentation (× 10^9/L)					0.005	0.017
<50	425 (80.2%)	127 (70.2%)	95 (69.9%)	32 (71.1%)		
≥50	105 (19.8%)	54 (29.8%)	41 (30.1%)	13 (28.9%)		
CNS involvement					0.431	0.204
CNS1	508 (95.8%)	170 (93.9%)	130 (95.6%)	40 (88.9%)		
CNS2	18 (3.4%)	10 (5.5%)	6 (4.4%)	4 (8.9%)		
CNS3	4 (0.8%)	1 (0.6%)	0	1 (2.2%)		
Cytogenetics§	390	149	107	42		
Normal	103 (26.4%)	52 (34.9%)	38 (35.5%)	14 (33.3%)	0.051	0.145
High hyperdiploidy	86‖ (22.1%)	13 (8.7%)	8 (7.5%)	5 (11.9%)	<0.001	0.001
t(9;22)/*BCR-ABL1*	11 (2.8%)	6 (4.0%)	3 (2.8%)	3 (7.1%)	0.474	0.305
t(1;19)/*E2A-PBX1*	17‖ (4.4%)	9 (6.0%)	9 (8.4%)	0	0.415	0.070
t(12;21)/*ETV6-RUNX1*	91‖ (23.3%)	11 (7.4%)	9 (8.4%)	2 (4.8%)	<0.001	<0.001
Others	84 (21.5%)	58 (38.9%)	40 (37.4%)	18 (42.9%)	<0.001	<0.001
Day 8 prednisone response¶	347	124	89	35	0.002	0.003
Good	323 (93.1%)	104 (83.9%)	77 (86.5%)	27 (77.1%)		
Poor	24 (6.9%)	20 (16.1%)	12 (13.5%)	8 (22.9%)		
Early death during induction	6 (1.1%)	4 (2.2%)	1 (0.7%)	3 (6.7%)	0.288	0.008
Response to remission induction**					<0.001	<0.001
CR	521 (98.3%)	162 (89.5%)	126 (92.6%)	36 (80.0%)		
Non-CR	3 (0.6%)	14 (7.7%)	8 (5.9%)	6 (13.3%)		
Not evaluated	0	1 (0.6%)	1 (0.7%)	0		
MRD after induction††	210	78	51	27	<0.001	<0.001
<0.01%	148 (70.5%)	37 (47.4%)	25 (49.0%)	12 (44.4%)		
0.01%-0.09%	23 (11.0%)	4 (5.1%)	3 (5.9%)	1 (3.7%)		
0.1%-0.99%	28 (13.3%)	24 (30.8%)	15 (29.4%)	9 (33.3%)		
≥1%	11 (5.2%)	13 (16.7%)	8 (15.7%)	5 (18.5%)		

Abbreviations: ALL = acute lymphoblastic leukaemia; CNS = central nervous system; CR = complete remission; EsPhALL = European intergroup study of post-induction treatment of Philadelphia-chromosome-positive acute lymphoblastic leukaemia; MRD = minimal residual disease; N/A = not applicable; WBC = white blood cell

* Data are shown as No. (%) or median (interquartile range), unless otherwise specified

† Comparison between young children and adolescents

‡ Comparison among young children, younger adolescents, and older adolescents

§ Analysis only includes 539 patients with positive results

‖ One patient had both t(1;19)/*E2A-PBX1* and t(12;21)/*ETV6-RUNX1*, while one patient had both high hyperdiploidy and t(12;21)/*ETV6-RUNX1*

¶ Analysis only includes 471 patients with evaluable prednisone response

** Excluding early deaths

†† Analysis only includes 288 patients with MRD evaluation

Among the six patients who failed to achieve CR after remission induction chemotherapy, two died of progressive leukaemia, while four achieved CR after salvage chemotherapy. Among the four patients who achieved CR, three received allogeneic HSCT during CR1 and remained in continuous CR; the other patient relapsed and received allogeneic HSCT after achievement of CR2, then died of transplant-related infection. In summary, six of the 11 deaths among older adolescents were treatment-related; the main cause of TRD was infection.

Overall outcome analysis

The median follow-up interval (for all groups) was 12.78 years (interquartile range=6.73-19.09). Young children had significantly better 10-year OS and EFS rates, compared with adolescents (87.6% [95% confidence interval (CI)=84.4%-90.2%] vs 77.9% [95% CI=71.0%-83.4%], P=0.0003; 76.5% [95% CI=72.6%-79.9%] vs 69.7% [95% CI=62.3%-76.0%], P=0.0117; Fig 1a and b). Ten-year relapse rates were similar between young children and adolescents: 20.6% (95% CI=17.3%-24.4%) for young children vs 22.8% (95% CI=16.9%-30.4%) for adolescents (P=0.479; Fig 1c). The 10-year incidence of TRD was significantly greater among adolescents (7.2% [95% CI=4.1%-12.4%]) than among young children (2.3% [95% CI=1.2%-4.1%]) [P=0.002; Fig 1d]. Subgroup analysis revealed that OS and EFS rates, as well as cumulative incidences of relapse and TRD, were similar between younger adolescents and older adolescents (Fig 2).

Predictors of OS and EFS are shown in Tables 2 and 3, respectively. Univariable analysis showed that both younger and older adolescent age-groups (vs young children) were associated with poor OS (P=0.003 and P=0.009). Additionally, univariable analysis showed that more recent time periods and treatment protocols (ALL IC-BFM 2002 and CCLG-ALL 2008), as well as favourable cytogenetics (high hyperdiploidy and/or *ETV6-RUNX1*), were significantly associated with better OS. After adjustments for parameters with P values <0.1 in univariable analysis, multivariable Cox regression analysis revealed that both younger

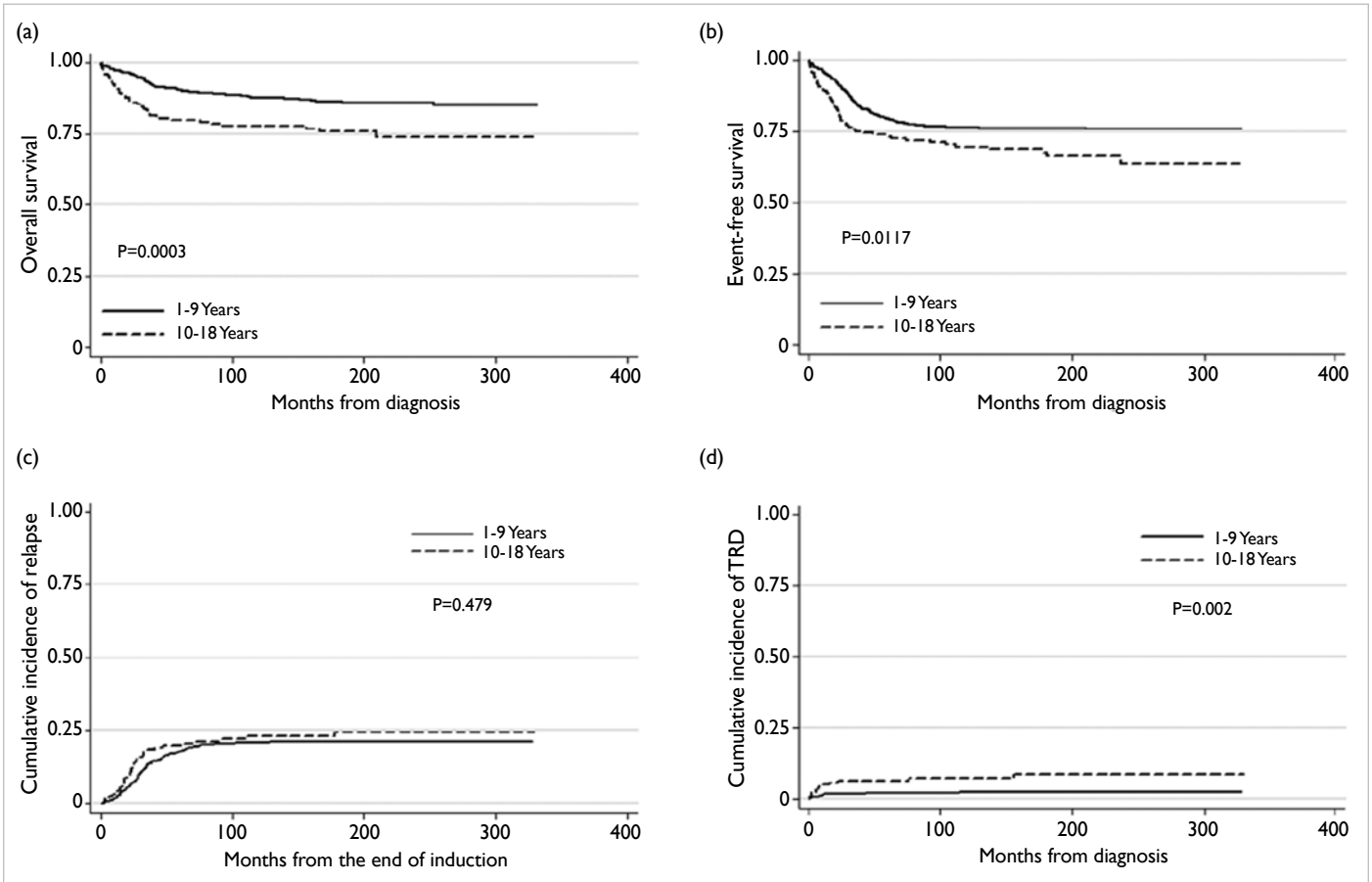

FIG 1. Survival probability and cumulative incidences of relapse and treatment-related death (TRD) in two age-groups (young children and adolescents) of children with acute lymphoblastic leukaemia: (a) overall survival; (b) event-free survival; (c) cumulative incidence of relapse; (d) cumulative incidence of TRD

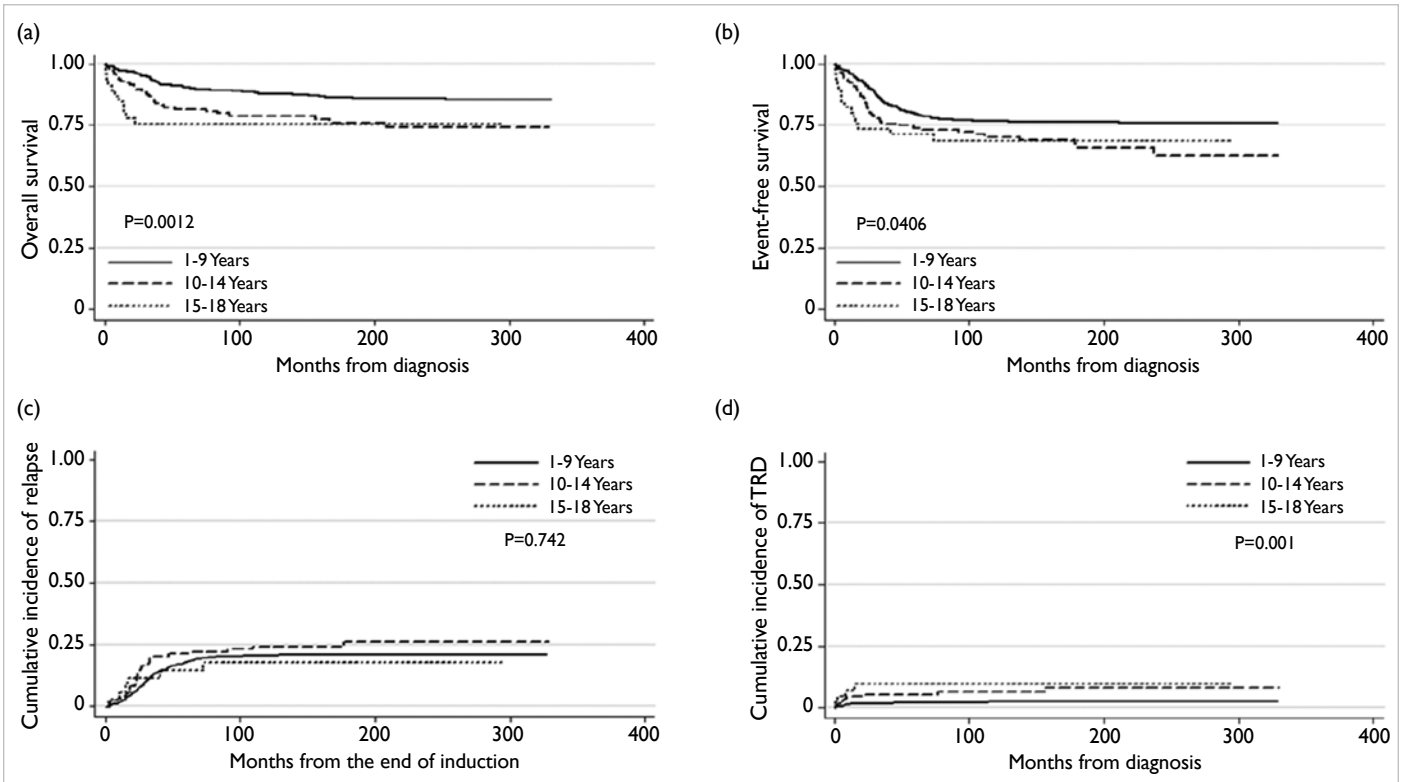

FIG 2. Survival probability and cumulative incidences of relapse and treatment-related death (TRD) in three age-groups (young children, younger adolescents, and older adolescents) of children with acute lymphoblastic leukaemia: (a) overall survival; (b) event-free survival; (c) cumulative incidence of relapse; (d) cumulative incidence of TRD

and older adolescent age-groups remained independent predictors of OS (hazard ratio=1.79 [95% CI=1.07-3.00], P=0.026; hazard ratio=2.98 [95% CI=1.41-6.30], P=0.004). Favourable cytogenetics also remained an independent predictor of OS (P=0.002). Similarly, univariable analysis showed that the younger adolescent age-group (vs young children) was significantly associated with poor EFS (P=0.029); the older adolescent age-group (vs young children) tended to show an association with poor EFS, although this was not statistically significant (P=0.111). Upon inclusion of all parameters with P values <0.1 in univariable analysis, multivariable Cox regression analysis revealed that both younger and older adolescent age-groups (vs young children) were significantly associated with poor EFS (hazard ratio=1.57 [95% CI=1.02-2.41], P=0.039; hazard ratio=2.18 [95% CI=1.16-4.09], P=0.016).

Predictors of the cumulative incidence of TRD are shown in Table 4. Univariable analysis showed that only younger and older adolescent age-groups (vs young children) were significantly associated with a greater incidence of TRD (hazard ratio=3.25 [95% CI=1.35-7.83], P=0.009; hazard ratio=4.50 [95% CI=1.43-14.13], P=0.010). Furthermore, favourable cytogenetics (high hyperdiploidy and/or *ETV6-RUNX1*) tended to show an association with lower incidence of TRD, although this was not statistically significant (P=0.088). After adjustments for parameters with P values <0.1 in univariable analysis, multivariable competing risks regression analysis revealed that both younger and older adolescent age-groups remained independent predictors of a greater incidence of TRD [hazard ratio=3.16 (95% CI=1.11-9.01), P=0.031; hazard ratio=4.69 (95% CI=1.28-17.20), P=0.020].

Discussion

In this retrospective study, we combined five clinical trials of paediatric ALL treatment in Hong Kong to compare characteristics and outcomes among young children, younger adolescents, and older adolescents with ALL; we specifically focused on the outcomes of older adolescents. Among the overall cohort of patients with ALL in this study, which covered a 20-year period and included 711 non-infant patients, 6.3% were older adolescents; this proportion was comparable with the findings in previous studies.[1,4,8,21,22] Additionally, our results are consistent with published literature in that

TABLE 2. Univariable and multivariable analyses of overall survival

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, y				
1-9	1		1	
10-14	1.90 (1.24-2.90)	0.003	1.79 (1.07-3.00)	0.026
15-18	2.33 (1.23-4.41)	0.009	2.98 (1.41-6.30)	0.004
Study				
HKALL 93	1		1	
HKALL 97	0.74 (0.46-1.19)	0.217	0.45 (0.23-0.89)	0.022
ALL IC-BFM 2002	0.57 (0.34-0.96)	0.034	0.63 (0.16-2.53)	0.520
CCLG-ALL 2008	0.35 (0.20-0.63)	<0.001	0.27 (0.07-1.14)	0.076
Time period				
Early (1993-2001)	1		1	
Late (2002-2015)	0.56 (0.38-0.82)	0.003	0.57 (0.17-1.92)	0.362
Sex				
Male	1			
Female	0.83 (0.56-1.21)	0.330		
Diagnosis				
B-cell ALL	1			
Non-B-cell ALL	1.47 (0.90-2.42)	0.123		
WBC count at presentation, × 10^9/L				
<50	1			
≥50	1.35 (0.89-2.06)	0.157		
CNS involvement				
CNS1/2	1			
CNS3	1.26 (0.18-9.04)	0.817		
Karyotypes*				
High hyperdiploidy and/or *ETV6-RUNX1*	1		1	
Others	3.53 (1.91-6.53)	<0.001	2.75 (1.46-5.18)	0.002

Abbreviations: 95% CI = 95% confidence interval; ALL = acute lymphoblastic leukaemia; CNS = central nervous system; HR = hazard ratio; WBC = white blood cell

* Analysis only includes 539 patients with positive results

adolescents with ALL were more likely to have a T-cell immunophenotype and less likely to have favourable genetic features (eg, high hyperdiploidy or *ETV6-RUNX1*), compared with young children who had ALL.[1,4-9,13] These findings are consistent with the results of previous studies conducted in Western countries.[1,4-9]

Over the past two decades, several comparative analyses have shown that adolescents with ALL experience better outcomes when they receive paediatric treatment protocols, rather than adult treatment protocols.[6,10,23,24] Adult protocols for ALL (eg, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) only achieved 5-year OS rates of 40% to 60% in adolescents and young adults with ALL.[25] Although most adult treatment programmes for ALL have evolved from the multi-agent approach used in paediatric protocols, there are some notable differences in treatment design. Paediatric ALL protocols generally use more intensive dosing of several key therapeutic agents, including corticosteroids, vincristine, asparaginase/PEG-asparaginase, and anti-metabolites (eg, methotrexate and 6-mercaptopurine); they also use more intensive and prolonged CNS prophylaxis with intrathecal chemotherapy.[25-27] In the present study, the 10-year EFS (70.2% vs 68.6%) and OS (78.8% vs 75.4%) rates for younger and older adolescents confirm the favourable outcomes of paediatric ALL protocols for adolescents aged ≤18 years.[4,13,15,21,22,28-30] There are some important challenges involved in the treatment of adolescents with intensive

TABLE 3. Univariable and multivariable analyses of event-free survival

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, y				
1-9	1		1	
10-14	1.47 (1.04-2.08)	0.029	1.57 (1.02-2.41)	0.039
15-18	1.57 (0.90-2.72)	0.111	2.18 (1.16-4.09)	0.016
Study				
HKALL 93	1		1	
HKALL 97	0.53 (0.36-0.78)	0.001	0.34 (0.19-0.61)	<0.001
ALL IC-BFM 2002	0.48 (0.32-0.72)	<0.001	0.32 (0.12-0.85)	0.023
CCLG-ALL 2008	0.29 (0.19-0.45)	<0.001	0.15 (0.06-0.43)	<0.001
Time period				
Early (1993-2001)	1		1	
Late (2002-2015)	0.56 (0.42-0.75)	<0.001	1.03 (0.45-2.37)	0.939
Sex				
Male	1			
Female	0.79 (0.59-1.07)	0.126		
Diagnosis				
B-cell ALL	1			
Non-B-cell ALL	1.27 (0.84-1.91)	0.255		
WBC count at presentation, $\times 10^9$/L				
<50	1		1	
≥50	1.45 (1.05-2.01)	0.026	1.34 (0.90-2.00)	0.143
CNS involvement				
CNS1/2	1			
CNS3	0.80 (0.11-5.70)	0.822		
Karyotypes*				
High hyperdiploidy and/or *ETV6-RUNX1*	1		1	
Others	2.11 (1.40-3.18)	<0.001	1.53 (0.99-2.37)	0.055

Abbreviations: 95% CI = 95% confidence interval; ALL = acute lymphoblastic leukaemia; CNS = central nervous system; HR = hazard ratio; WBC = white blood cell

* Analysis only includes 539 patients with positive results

chemotherapy protocols; these include a greater frequency of treatment-related complications (eg, liver derangement and thrombosis) than in young children who receive similar treatment. Drug compliance is also challenging in adolescents; poor adherence to long-term maintenance treatment may lead to worse outcomes.[31]

Notably, the long-term OS and EFS rates remained worse in adolescents with ALL than in young children (aged 1-9 years) with ALL. Our results indicate that this difference is not related to an increased rate of relapse; it arises from an increased risk of TRD. An age-related increase in treatment-related toxicity has been reported in almost all cohorts of patients with ALL who have received paediatric treatment protocols. Most studies have shown that, compared with young children, adolescents have greater risks of severe adverse events.[28,32] The use of paediatric intensive combination chemotherapy is effective for preventing relapse in adolescents with ALL, but these patients may not tolerate the toxicity of intensive multi-agent chemotherapy (eg, myeloablative allogeneic HSCT). For example, among older adolescents in the present study, the high incidence of TRD was mainly attributed to two TRDs in 45 patients who received remission induction chemotherapy, one TRD in 33 patients who received post-induction chemotherapy during CR1, and three TRDs in nine patients who received allogeneic HSCT during

TABLE 4. Univariable and multivariable analyses of the cumulative incidence of treatment-related death

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, y				
1-9	1		1	
10-14	3.25 (1.35-7.83)	0.009	3.16 (1.11-9.01)	0.031
15-18	4.50 (1.43-14.13)	0.010	4.69 (1.28-17.20)	0.020
Study				
HKALL 93	1			
HKALL 97	1.46 (0.43-4.97)	0.546		
ALL IC-BFM 2002	1.27 (0.36-4.50)	0.709		
CCLG-ALL 2008	0.90 (0.24-3.33)	0.871		
Time period				
Early (1993-2001)	1			
Late (2002-2015)	1.15 (0.51-2.58)	0.738		
Sex				
Male	1			
Female	0.54 (0.23-1.32)	0.177		
Diagnosis				
B-cell ALL	1			
Non-B-cell ALL	1.31 (0.45-3.85)	0.618		
WBC count at presentation, × 10^9/L				
<50	1			
≥50	1.16 (0.46-2.91)	0.755		
CNS involvement*				
CNS1/2	-			
CNS3	-	-		
Karyotypes†				
High hyperdiploidy and/or *ETV6-RUNX1*	1		1	
Others	2.95 (0.85-10.27)	0.088	2.00 (0.55-7.27)	0.295

Abbreviations: 95% CI = 95% confidence interval; ALL = acute lymphoblastic leukaemia; CNS = central nervous system; HR = hazard ratio; TRD = treatment-related death; WBC = white blood cell

* Univariable competing risks regression model to examine CNS involvement as a potential predictor for cumulative incidence of TRD was hampered by the absence of TRD in patients with CNS3 status at diagnosis

† Analysis only includes 539 patients with positive results

CR1 or CR2. Further studies are needed to identify optimal treatment adjustments that can improve toxicity profiles among adolescents with ALL who receive paediatric treatment protocols.

Consistent with previous findings,[1,33,34] the present study showed that poor early response to treatment was more common in adolescents, a greater proportion of whom had poor day 8 prednisone response and did not achieve CR. Minimal residual disease response after induction is an important prognostic indicator of treatment failure. In our more recent treatment protocols, MRD was included in the disease monitoring. A greater proportion of adolescents had MRD ≥1% after remission induction, but the relapse rate was not greater in adolescents than in young children. Adolescents received higher intensity consolidation, reinduction, and continuation therapy; some received allogeneic HSCT during CR1. The higher intensity of post-induction treatment led to a lower relapse rate but resulted in greater treatment-related mortality; thus, the OS and EFS rates were worse in adolescents than in young children. To improve survival outcomes among adolescents with ALL, clinical trials have been initiated with a focus on new agents that might achieve better survival without excessive toxicity; these agents include the proteasome inhibitor bortezomib, as well as antibody- or cell-mediated immunotherapy (eg, rituximab, inotuzumab, blinatumomab, or tisagenlecleucel).[35-38]

This study had some limitations. First, it used a retrospective design, which might have allowed incomplete reporting bias and missing data. For example, cytogenetic information at diagnosis was missing for 172 (24.2%) of 711 patients because of culture failure or poor bone marrow blast growth. Individuals with missing data were excluded during overall outcome analyses. However, our estimates might have been biased because of this restricted statistical analysis approach.[39] Second, confounding factors (eg, selection bias and enrolment bias) might have been present. For example, the distributions of high-risk ALL subgroups (eg, Ph-like ALL and early-T-precursor ALL) were not examined in our analysis because of limited data. Therefore, caution is needed when interpreting the results of this study.

In conclusion, our analysis of children with ALL suggested that long-term EFS and OS rates were favourable among adolescents who received intensive paediatric treatment protocols. However, ALL treatment outcomes were worse among adolescents than among young children; further optimisation is needed to reduce treatment-related mortality. Novel targeted agents for patients with poor early response to ALL treatment may overcome treatment resistance, eradicate MRD, and improve clinical outcomes.

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All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

This study was approved by The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CRE2008.007T).

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