HK J Paediatr (new series) 2013;**18**:89-95

A Small Cohort Review of the Long-term Prognosis for Chinese Older Children and Adolescents with Acute Lymphoblastic Leukaemia Treated on a Paediatric Protocol

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Abstract ***Background.*** Our aim was to examine the biological and clinical characteristics of Chinese older children and adolescents with acute lymphoblastic leukaemia (ALL) and their outcomes. ***Procedure.*** We retrospectively reviewed the treatment and long-term results of 10- to 18- year-old patients with ALL on the Hong Kong paediatric ALL protocol (n=19) and compared with prior literatures. ***Results.*** A total of 10 male and 9 female patients were treated; 4 patients' peripheral white cell counts were more than 100×10^9/L at diagnosis. T-cell lineage was identified in 4 cases and the remaining had B-cell lineage. Ten had abnormal cytogenetic results. Seventh-day post-oral prednisone treatment responses were favorable for 15 patients. On day 33 of treatment, bone marrow results indicated that 2 patients did not achieve remission. Although the rate of complete remission (CR) was 84%, nine patients experienced significant treatment-related side effects and 2 patients died. There were 4 relapses, and the mean time between CR and relapse was 35 months. The mean follow-up time was 88 months. The 7-year overall survival and event-free survival were 89.5% and 72.9%, respectively. ***Conclusion.*** Although apparently with frequent serious therapy related complications, older children and adolescents with ALL had satisfactory prognosis if treated with pediatric oriented protocol.

Key words Acute lymphoblastic leukaemia; Adolescents; Older children; Prognosis

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Received September 9, 2012

Introduction

The chemotherapy regimen and support care for paediatric acute lymphoblastic leukaemia (ALL) has significant improvement over the past 20 years, so does the treatment outcome. Individual risk stratification into specific treatment groups on the basis of biological and clinical characteristics allows 80% of paediatric patients with ALL achieve long-term survival nowadays.[1,2] However, older children and adolescents with ALL seems to have poorer outcome, partly due to the relative increased incidence of Philadelphia chromosome-positive ALL, lower incidence of *ETV6-RUNX1* fusion (formerly known as *TEL-AML1*) and hyperdiploidy, and poor compliance to treatment among this patient group.[3-6] In addition, the fact that some paediatric protocols have yielded significantly better outcomes for older children and adolescents with

ALL than adult protocols suggests the importance of more intensive use of nonmyelosuppressive agents and frequent administration of intrathecal therapy. To verify whether such experience applied to our patients' cohort, we reviewed the treatment and long-term outcome of 19 older children and adolescents patients with ALL who were treated under a paediatric oriented protocol.

Methods

Patients

Between January 1, 1995 and August 31, 2006, nineteen newly diagnosed cases of ALL aged 10 to 18 years were admitted to Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR.

Clinical and Laboratory Data Collection

The clinical data (Table 1) were retrospectively collected from the patients' medical record or the hospital's computer system: sex; age at diagnosis; white blood cell (WBC) count results; the bone marrow (BM) morphology, immunology, cytogenetics and molecular (MICM) results at diagnosis; central nervous system (CNS) status; response to chemotherapy on Day 8 and Day 33; serious side-effect due to chemotherapy; the date of relapse or death; history of haematopoietic stem cell transplantation and irradiation; and follow-up through August 31, 2010.

Risk Stratification Criteria and Therapy

Each patient had received chemotherapy according to the HKPHOSG ALL 1997 protocol which was modified from the BFM-based protocol.[7] According to the risk stratification criteria of the protocol (Table 2), 4 patients were classified as high-risk (HR), another 15 patients as intermediate risk (IR). The protocol for IR has 4 parts: induction, consolidation, re-induction and maintenance. The protocol for HR has 6 phases: induction, intensification, re-induction (2 courses), mid-continuation, and continuation. The total treatment duration for each risk group was 2 years (Table 3).

Statistical Analysis

The event-free survival (EFS) was defined as the time from diagnosis to the date of either last follow-up or the first adverse event. Adverse events were relapse or death from any causes. The overall survival (OS) was defined as the time from diagnosis to either the last follow-up or death from any cause. Survival rates were represented as the mean percent (±s.e.) probability estimates. The Kaplan-Meier method was used to estimate survival rates,[8] which are represented here by mean percent (±s.e.) probability estimates. Chi-square testing was used to compare variables between groups of patients. P values <0.05 were considered statistical significant. All the statistical analyses were performed by using SPSS software version 13.0 (SPSS Inc).

Results

Patient Characteristics

Between 1995 and 2006, a total of 10 males and 9 females with newly diagnosed ALL were identified through our records search. Their mean age at diagnosis was 14.2 years (range, 11-18 years). At diagnosis, 2 patients' disease was identified as CNS status 2 and one's as status 3.

Mean (range) white blood cell (WBC) count at diagnosis was 56.14 $\times 10^9$/L (1.49-254.94$\times 10^9$/L) with 21% of patients having a high WBC count (>100$\times 10^9$/L). Blasts from 4 patients had a T-lineage immunophenotype, and those from the other 15 patients had B-lineage type. One B-lineage patient's blast cells co-expressed myeloid markers (CD13, CD33).

The cytogenetic and RT-PCR results of 15 patients were available. Five patients' results were normal. Cytogenetic aberrations were found in 10 patients (67%) including 5 patients with complex karyotypes. *ETV6-RUNX1* was identified in 2 patients; trisomy 21, *E2X/PBX, inv (9)* and *TCR* gene rearrangement were diagnosed in one patient each.

Outcomes of Treatment

Remissions. All patients received 7 days of oral prednisone treatment, and 4 patients (21%) were classified as poor steroid responder. Among these 4, one eventually complete remission (CR), one experienced partial remission, and the other 2 experienced no remission on day 33 of chemotherapy. All of the 15 good steroid responders achieved CR based on Day 33 bone marrow examination. The total CR rate was 84% (16/19).

Deaths. Two patients died. One died of tumour lysis syndrome leading to acute renal failure and sepsis and had not achieved CR. The other died secondary to relapsed leukaemia combined with serious infection 1 year after initial CR.

Relapses. Four patients (21%) experienced relapse, and the mean duration between CR and relapse was 35 months (10~63 months). One of these patients underwent allogeneic

Table 1 Biological and clinical characteristics of 19 patients

Case	Sex	Age (yrs)	WBC x10^9/L	Immuno-phenotype	Cytogenetics	RT-PCR	CNS Status	D7 Response	D33 BM	Serious side effect	Death from diagnosis	Relapse from CR1	HSCT	Long term Sequels	Duration of follow-up
1	F	16	13.2	B	46;XX	Negative	1	Good	CR	Leukoencephalopathy	No	No	No	No	150
2	F	10	1.49	B	46;XX	Negative	1	Poor	CR	None	No	No	No	No	137
3	M	14	10.34	T	46;XY	Negative	1	Good	CR	None	No	No	No	Yes	130
4	M	16	215.00	B with myeloid marker	No done	No done	1	Poor	CR	Leukoencephalopathy	No	No	No	No	124
5	F	11	31.00	B	46;XX	Negative	1	Good	CR	L-asp induced DM	No	No	No	No	107
6	F	11	5.00	B	46;XX	Negative	1	Good	CR	None	No	No	No	No	105
7	F	17	5.60	B	45-46;XX add(15)(q26)[2], 22 ps+(3)[cp3] / 50;XX, +6,+7,+8,-14, add(15)(q26), +15,+21, 22ps+[3]	Negative	1	Good	CR	Liver damage	No	No	No	No	104
8	F	14	209.00	B	46;XY, t(1,19)(q23,p13)	E2A/PBX	1	Good	CR	None	No	No	No	No	104
9	M	17	117.00	B	46;XY	Clonal TCR gene rearrangement	1	Poor	NR	TLS with ARF, Sepsis and shock	5mo	–	No	No	5
10	M	11	58.00	T	No done	No done	2	Good	CR	TLS with ARF, sepsis	No	No	No	No	98
11	F	15	90.90	T	No done	No done	1	Good	CR	None	No	No	No	No	89
12	M	17	16.26	B	46;XY, t(12,21)	ETV6-RUNX1	1	Good	CR	Venous infarction	No	No	No	No	89
13	M	15	4.90	B	No done	No done	1	Good	CR	DXM induced DM	No	46mo	No	No	89
14	F	12	254.90	B	46;XX, add(1)(p13), add(3)(q29), del(5)(q22q31), add(6)(q15),10, add(12)(p11), del(13)(q12q14), add(14)(q32), add(19)(p11), add(21(q22)	Negative	3	Good	CR	None	No	No	No	No	83
15	M	18	1.80	B	47;XY, tri-21	Negative	1	Good	CR	None	No	19mo	No	No	83
16	M	15	13.20	B	46;XY, t(12,21)	ETV6-RUNX1	1	Good	CR	sepsis	17mo	10mo	No	No	17
17	M	16	4.40	B	46;XY, t(1;3)(p32,q27), del(6)(q21), -13,-16, +mar4[4] / 46;XY[7]	Negative	2	Poor	NR	None	No	No	Yes	No	64
18	F	13	5.50	B	47;XX, del(12)(12.1), +21[1]	Negative	1	Good	CR	None	No	No	No	No	62
19	M	11	9.20	T	46;XY, i(21)(q10)c[13]	Negative	1	Good	CR	None	No	22mo	Yes	No	52

CNS status 1: No identifiable blasts in CSF; CNS status 2: less than 5 WBC in CSF with identifiable blasts or traumatic tap; CNS status 3: more than 5 WBC in CSF with identifiable blasts or cranial nerve palsy. CR: complete remission; NR: no remission; CNS: central nervous system; TLS: tumor lysis syndrome; ARF: acute renal failure; DXM: dexamethasone; DM: diabetes mellitus

Table 2 Risk stratification criteria

Risk	Stratification criteria
Standard risk	Age: 1~5 years; +WBC ≤20x10^9/L; + Non T-ALL + Absence of t(9;22) or t(4;11); + Prednisone good response*
Intermediate risk	Age: ≥6 years or WBC≥20 x 10^9/L; + Absence of t(9;22) or t(4;11); + Prednisone good response
High risk	Prednisone poor response Or Day 33 no remission Or presence of t(9;22) or t(4;11)

*Blast <1.0x10^9/L in peripheral blood after 7 days of prednisolone pre-phase treatment

haematopoietic stem cell transplantation (allo-HSCT). The other 3 were treated according to the HKPHOSG relapsed ALL protocol based on ALL-REZ BFM 1996;[9] one died as previously mentioned, both of the other two patients experienced CR till the last follow-up.

Outcomes of allo-HSCTs. Of the 2 patients who underwent allo-HSCTs, one experienced NR on Day 33 of Chemotherapy, the other relapsed 22 months after CR. Both survived till the last follow-up without serious complications or graft-versus-host disease but one relapsed 8 months after HSCT and has received palliative treatment.

Complication Related to Methotrexate (MTX) Treatment. The use of MTX was withheld for 2 patients because of MTX-induced leukoencephalopathy. Another patient receiving reduced dosage (half) high-dose MTX treatment due to prior MTX-induced significant liver damage.

Other Outcomes. Of the 2 patients who had tumour lysis syndrome with acute renal failure and sepsis, one died. This patient did not receive urate oxidase treatment for it was not available at that time. One patient developed diabetes mellitus after the use of oral dexamethasone. Another patient developed diabetes during the use of L-Asparaginase, both of whom needed insulin treatment with good control of blood glucose and the diabetes resolved after their respective treatment. Superior sagittal sinus thrombosis with intracerebral hemorrhagic infarct developed in another patient receiving L-Asparaginase treatment.

Three patients experienced prolonged myelosuppression with sepsis causing their chemotherapy to be delayed; 2 of these patients died partly because of serious infection. After chemotherapy was completed, one patient experienced poor interpersonal relationship.

The surviving patients have no signs of secondary cancer, cardiologic damage, or growth retardation at last follow-up.

Survival Rates. The mean follow-up time after the diagnosis was 88 months (5-150 months). The 7-year OS (Figure 1) and EFS (Figure 2) rates were 89.5%±7% and 72.9%±10.4%, respectively.

Discussion

Although paediatric ALL has been the one of the most successful treatment models in modern clinical oncology, the long-term survival rate for older children and adolescents with ALL was lagging behind in many countries at around 40~50%. One possible contributing factor for the discrepancy is that these patients were treated under the adult haematologists with different regimens. In fact, some prospective studies showed that older children and adolescents with ALL who were treated in the adult haematology/oncology department with adult regimens had much poorer outcomes (i.e., 5-6 years EFS: 35-50%) than those treated in paediatric department with paediatric protocols (i.e., 5-6 years EFS: 65-70%), despite consistent biological characteristics.[2,4,5,10]

Boissel et al[10] first reported the difference in the effect of paediatric and adult protocols on 15- to 20- year-old patients with ALL. After treating a total of 177 patients on either the FRALLE-93 protocol for children or the LALA-94 protocol for adults, the CR rates were 94% and 83%, respectively, and 5-year EFS rates were 67% and 41%, respectively. The difference between the protocols was that the children's protocol includes 5 times more prednisone, 3 times more plant alkaloids, and 20 times more Asparaginase than the adult's protocol dosages.

A retrospective analysis of 321 older children and adolescents patients who were similarly stratified to either a children's or adults' treatment protocol showed that the 7-year EFS and OS rates were higher for those treated with the children's protocol even though the CR rates of both

Table 3 HKPHOS ALL protocol for patients with intermediate risk (IR) or high risk (HR)

IR	HR
Prednisone (7d)	
d1, 20 mg/m^2; d2, 40 mg/m^2; d3~7, 60 mg/m^2/d, total cumulative dose between 210~240 mg/m^2 in the first 7 days Intrathecal MTX: d1	
Induction Remission	
Ia Prednisone: 60 mg/m^2/d Oral d8~d28, then tapered over two weeks; VC: 1.5 mg/m^2/d, d8, d15, d22, d29; DNR: 30 mg/m^2/d, d8, d15, d22, d29; L-ASP: 5000 IU mg/m^2/d, d12, d15, d18, d21, d24, d27, d30, d33.	
Ib CTX: 1000 mg/m^2/d, d36, d64; 6-MP: 60 mg/m^2/d, d36~63 (total 28 days); Ara-C: 75 mg/m^2/d, d38~41, d45~48, d52~55, d59~62, four cycles of 4 days each. Triple intrathecal therapy: d45, d59	
IR: Consolidation	**HR: Intensification (starts at around week 12)**
MTX: 5 g/m^2/d, d8, d22, d36, d50, 6-MP 25 mg/m^2/d, d1~56; Triple intrathecal therapy: d8, d22, d36, d50; 2 hours after the start of MTX infusion.	(1) DXM: 20 mg/m^2/d, d1~5; VCR: 1.5 mg/m^2/d, d1, d6; MTX: 5 g/m^2/d, d1; Ara-C: 2 g/m^2/12h, d5; L-ASP 25000 IU/m^2, administered 3 hours after the end of the second Ara-C infusion; 6-MP: 100 mg/m^2/d, d1~5; Triple intrathecal therapy: d1. (2) *DXM: 20 mg/m^2/d, d1~5; VCR: 1.5 mg/m^2/d, d1, d6; MTX: 5 g/m^2/d, d1; CTX: 150 mg/m^2/d, d1~5; L-ASP: 25000 IU/m^2, d5; 6-TG: 100 mg/m^2/d, d1~5; DNR: 50 mg/m^2/d, d5; Triple intrathecal therapy: d1. (3) DXM: 20 mg/m^2/d, d1~5; Ara-C: 2 g/m^2/12h, d1~2; VP-16: 150 mg/m^2/d, d3~5; L-ASP: 25000 IU/m^2, d5 Triple intrathecal therapy: d5
Re- Induction (starts at week 22)*	
IIa DXM: 10 mg/m^2/d, PO, d1~21, then tapered over in 10 days; VCR: 1.5mg/m^2/d, d8, d15, d22, d29; Adriamycin: 30 mg/m^2/d, d8, d15, d22, d29; L-ASP: 10000 IU/m^2/d, d8, d11, d15, d18; Triple intrathecal therapy: d1, d8; only for CNS leukaemia.	
IIb CTX: 1000 mg/m^2/d, d36; 6-TG: 60 mg/m^2/d, d36~49, total 14 days; Ara-C: 75 mg/m^2/d, d38~41, d45~48; Triple intrathecal therapy: d38, d45.	
Cranial RT	**Interim maintenance + cranial RT**
Scheduled for patients aged ≥2 year with T-ALL or WBC >100x10^9/L at diagnosis, or CNS disease, d36~50, daily fractions of 1.5Gy per time, total 18Gy	6-MP: 50 mg/m^2/d, d1~28; MTX: 20 mg/m^2/d, d7, 14, 21, 28; Triple intrathecal therapy: d4, d14; RT: for patients ≥2 year at the time of RT with T-ALL or WBC >100x10^9/L at diagnosis, or CNS disease, d8~22, 1.5Gy per time, total 18Gy
	Second re-induction
	The same as the first re-induction except that intrathecal is no need for the patient has recently undergone RT.
Maintenance	
Maintenance starts 2 weeks after the end if re-induction and is continued until the total duration of therapy is 24 months from diagnosis. 6-MP: 50 mg/m^2/d, po daily; MTX: 20 mg/m^2/d, po weekly; VCR: 1.5 mg/m^2/d, every 10 weeks; DXM: 6 mg/m^2/d, d57~63, every 10 weeks; Triple intrathecal therapy: every 10 weeks at week 9 during cyclic pulse for a total of six administrations.	

Abbreviation: VCR, Vincristine; DNR, Daunrubicin; Ara-C, Cytosine arabinoside; CTX, Cyclophosphamide; MTX, Methotrexate; DXM, Dexamethasone; 6-MP, 6-Mercaptopurine; 6-TG, 6-Thioguanine; CNS, central nervous system; RT, Cranial radiotherapy

*For high-risk, haematopoietic stem cell transplantation (HSCT) should be arranged after (2) and preferably before Protocol II if a compatible donor is available.

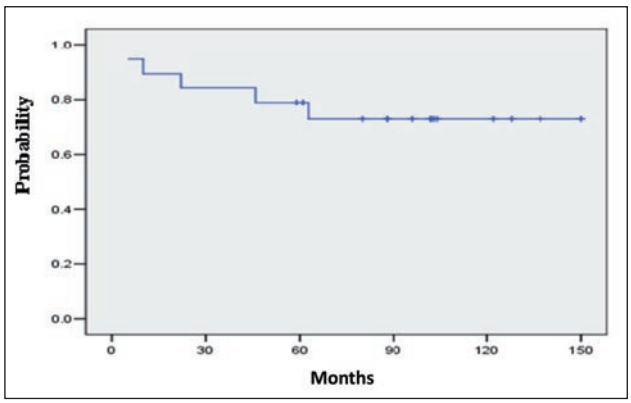

Figure 1 7-year event-free survival rates of 19 patients with ALL.

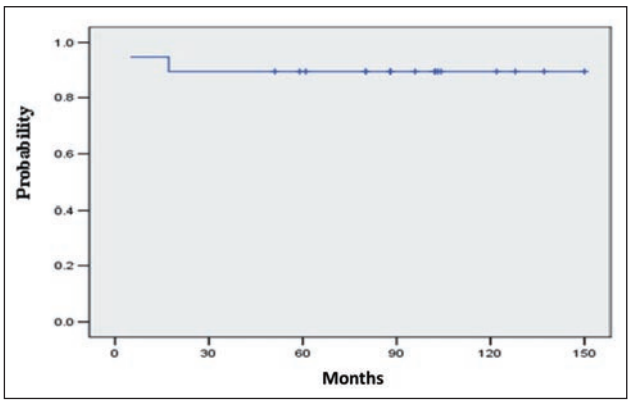

Figure 2 7-year overall survival rates of 19 patients with ALL.

groups were similar.[5] The difference between these protocols was that patients on the children's protocol received earlier and more intensive CNS prophylactic treatment, and with more cumulative doses of nonmyelosuppressive agents. Similar to that study, the St. Jude Total XV[11] and the DFCI protocols[12] have also yielded excellent results for older children and adolescents, likely because of the early intensification therapy with vincristine and Asparaginase.

In our hospital, each older child and adolescent with ALL is treated using a paediatric protocol based on the German Berlin-Frankfurt-Muenster 95 (BFM95) protocol, including intensive chemotherapy, more than one year of maintenance treatment, and more intensive use of the nonmyelosuppressive agents as glucocorticoids, L-asparaginase, and vincristine. Our patients also received earlier and more intensive CNS-directed therapy than that used in the adults' protocol.

In addition to the therapeutic agents given, a patient's response to chemotherapy is also a factor in determining his or her prognosis. Metabolic clearance and response of chemotherapy may be different in older patients and thus they appear to have more serious complications. More than half of the patients in this study developed serious chemotherapy-related side effects. In particular, the rate of high-dose MTX treatment-induced leukoencephalopathy was higher in our study than it is in the reports of younger children.[13] However, the reported CR rates (95.3%, 163/171), relapse rate (15.7%, 26/166), and death rate (13.5%, 23/171) of 1- to 17.9-year-old patients using the same protocol,[7] were no significant statistical difference from those of our patients ($P>0.05$). Additionally, despite the higher rate of serious therapy-related side effects, the 7-year OS and EFS rates in our study indicated that more intensive chemotherapy could eventually help to improve the long-term survival of older children and adolescents with ALL.

In this study, one patient experienced poor interpersonal relationship after cranial irradiation; however, we do not know whether it is related to the radiation or will be a long-term effect. Two recent studies have shown that cranial irradiation could be safely substituted for intensive triple intrathecal therapy with effective chemotherapy in the treatment of childhood ALL.[14,15]

Although it has been suggested that adult high-risk ALL can undergo allo-HSCT after the first CR,[16] HSCT was confined to a very high-risk group in our protocol. The criteria were:1) those experiencing a poor response to prednisone and having either T-cell ALL, a peripheral WBC count $>100\times10^9$/L, or t (4; 11) – *MLL/AF4* positive at diagnosis; 2) those had t (9; 22) or *BCR /ABL* positive; 3) those whose bone marrow biopsy results at day 33 failed to enter into remission. In the 2 patients with HSCT, one had no CR on his Day 33 marrow and another experienced early relapse soon after treatment was discontinued. Minimal residual disease (MRD) has been suggested as a measure to accurately screen whether the patients with high-risk ALL need HSCT[17] and it has been adapted to our current treatment protocol.

In summary, the long-term prognosis for older children and adolescents with ALL treated with paediatric ALL risk-stratification protocol is comparable to younger children. However, approximately half of the patients experience serious chemotherapy-related side effects and therefore patients have to be carefully monitored. Further research should be focused on optimising chemotherapy and reducing therapy-related side effects so as to improve the quality of life and long-term prognosis of this special group of patients.

Conflict of Interest

We declare that we have no conflict of interest.

Acknowledgements

We thank Dr. Cheng Yu Tung Fellowships for supporting of Dr. Xiong Hao's clinical training in the Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong.

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