Title	Improved outcome of acute lymphoblastic leukaemia treated by delayed intensification in Hong Kong children: HKALL 97 study
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Improved outcome of acute lymphoblastic leukaemia treated by delayed intensification in Hong Kong children: HKALL 97 study

以延緩密集療法醫治香港急性淋巴細胞性白血病兒童所得的改良結果：HKALL 97研究

Key words:
Immunophenotyping;
Leukemia, lymphocytic, acute;
Methotrexate;
Prognosis;
Treatment outcome

關鍵詞：
細胞的分型；
白血病，淋巴細胞的，急性；
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預後；
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Objective. To study the outcome of children with acute lymphoblastic leukaemia who were treated using a protocol including one or two delayed intensifications.
Design. Prospective single-arm multicentre study.
Setting. Five designated children cancer units of the Hospital Authority of Hong Kong.
Patients. Children aged between 1 and 17.9 years with newly diagnosed acute lymphoblastic leukaemia seen from November 1997 to December 2002.
Intervention. Chemotherapy was modified from a German Berlin-Frankfurt-Muenster 95 (BFM95) protocol that included a delayed intensification similar to the induction phase repeated 5 months after diagnosis. High-risk patients were given double delayed intensification.
Main outcome measures. Overall survival and event-free survival of the whole group and the three risk groups (standard-, intermediate-, and high-risk groups), and comparison with historical controls.
Results. A total of 171 patients were recruited with a median age at diagnosis of 5.57 years (range, 1.15-17.85 years). The induction remission rate was 95.3% and non-leukaemia mortality during remission was 2.3%. At 4 years, the relapse rate of this (HKALL97) study was significantly lower than that of the HKALL93 study (15.7 vs 37.3%; P<0.001). The 4-year overall survival of HKALL97 and HKALL93 studies were 86.5% and 81.8%, respectively (P=0.51). The 4-year event-free survival for HKALL 97 and HKALL93 studies were 79% and 65%, respectively (P=0.007). Nonetheless the difference of event-free survival was most remarkable in the intermediate-risk group: 75.6% and 53.1% for HKALL97 and HKALL93 studies, respectively (P=0.06).
Conclusion. A more intensive delayed consolidation phase improved the outcome for children with acute lymphoblastic leukaemia by reducing relapses at 4 years. The early treatment complications were manageable and non-leukaemia mortality during remission remained low.

目的：研究以一或二次延緩密集療法治療急性淋巴細胞性白血病兒童的結果。
設計：前瞻性無對照組的跨中心研究。
安排：香港醫院管理局轄下五間指定兒童癌症治療單位。
患者：由1997年11月至2002年12月期間，首次被診斷患上急性淋巴細胞性白血病的1歲至17.9歲的兒童。
療法：以德國BFM95化學治療方案為藍本，並加以改進。BFM95包括延緩密集治療，與在確診後五個月重覆的引導期治療相似。高危病人則接受雙倍延緩密集治療。
主要結果測量：包括所有病人及三組不同風險度的病人（標準風險、中度風險和高度風險）的總體存活率和無復發存活率，並與過往的文獻紀錄比較。
結果：共有171人被招募參與今次研究。他們在確診時的平均年齡是5.57歲（介乎1.15至17.85歲）。在引導期病情得到緩和的病人佔95.3%，而非因白血病死亡的病人比率為2.3%。病人的四年內復發率為15.7%，與1993年進行相同研究的比率37.3%明顯下降（P<0.001）。1993年和是次（1997年）兩項調查中，四年的總體

存活率分別為 81.8% 和 86.5%（P=0.51）。而四年的無復發存活率，則由 1993 年調查所得的 65% 增至 1997 年的 79%（P=0.007）。然而，最明顯的分別是中度風險病人的無復發存活率，1997年與1993年的研究數字分別為75.6%和53.1%(P=0.06)。**結論：**一個較為密集及延緩的鞏固期，能減少患有急性淋巴細胞性白血病兒童四年內的復發數字，即可改善治療結果。早期治療的併發症屬可處理個案，而在緩和時的非白血病死亡率維持偏低的水平。

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common childhood malignancy.[1] It is highly responsive to chemotherapy and induction remission rates in most clinical studies are over 95%.[2-4] The major cause of treatment failure is relapse, mainly in the bone marrow and less commonly in extramedullary sites such as the central nervous system (CNS) or testes. With good supportive care, treatment-related mortality can be kept below 5%. The challenge of improving treatment outcome is to maintain continuous remission and prevent relapse. Relapses may occur in the first 2 to 3 years during chemotherapy, but are more common 1 to 2 years after stopping chemotherapy. The current trend of treatment is to increase treatment intensity in the first 6 to 9 months and continue with a milder maintenance phase for up to 2 or 3 years after diagnosis. The mode of intensification in the first 9 months of treatment nonetheless varies among collaborative groups. The HKALL93 study[5] recruited patients from 1993 to 1997 and adopted the United Kingdom ALL XI study approach (UKALL XI[6]). There was a high relapse rate in intermediate- and high-risk patients.[5] The Hong Kong Paediatric Haematology and Oncology Study Group commenced a new clinical study in 1997 that adopted a German Berlin-Frankfurt-Muenster 95 (BFM95) protocol aimed at improving treatment outcome. The main difference between the German and UK protocols is the inclusion of a delayed intensification similar to induction, called re-induction, 5 months after diagnosis. This study aimed to determine the outcome of children with ALL who received a treatment protocol that included either one or two delayed intensifications.

Patients and methods

From November 1997 to December 2002, all children newly diagnosed with ALL in the five paediatric oncology centres under the Hospital Authority (HA) hospitals were included in the study. Patients younger than 1 year were treated under a separate infant ALL study that formed part of an international multicentre study. The age of inclusion was thus 1 year to 17.9 years. All the paediatric ALL patients in Hong Kong were treated in HA hospitals, this was therefore a population-based study. The diagnostic criteria were standardised, and morphology and immunophenotyping were centrally reviewed. Bone marrow smear was examined after Wright's stain and standard cytochemical staining. Acute lymphoblastic leukaemia was diagnosed in the presence of more than 30% blasts in the bone marrow smear. The French-American-British morphological classification was not the essential criteria for diagnosis. Flow cytometry of marrow aspiration was performed using a batch of monoclonal antibodies with 20% as the positivity cut-off: CD10, 20, 19, 22 for B lineage, CD3, 5, 7 for T lineage, cytoplasmic and surface immunoglobulin for pre-B and mature B cell marker, respectively. The subtype was based on the scoring system from the EGIL (European Group for the Immunological Characterization of Acute Leukaemias). All bone marrow samples were also tested for cytogenetics by karyotyping, and molecular study for fusion products of BCR/ABL, TEL/AML1 and MLL/AF4 translocations were also performed.

The chemotherapy protocol was modified from the German BFM95 ALL study. The same stratification cri-

Table 1. Risk stratification criteria of HKALL97 and HKALL93[5] studies

	HKALL97 (present) study	HKALL93 study[5]
Standard risk	Age: 1-5 years + WBC* ≤20 x 10^9 /L + Non-T cell + Absence of t(9;22) or t(4;11) + Prednisolone good response†	Age: 1-9 years + WBC ≤20 x 10^9 /L + Non-T cell + Absence of t(9;22) or t(4;11)
Intermediate risk	Age: ≥6 years or WBC ≥20 x 10^9 /L + Absence of t(9;22) or t(4;11) + Prednisolone good response†	Age: ≥10 years or WBC 20-49 x 10^9 /L + Non-T cell + Absence of t(9;22) or t(4;11)
High risk	Prednisolone poor response or day 33 non-remission or presence of t(9;22) or t(4;11)	WBC ≥50 x 10^9 /L or T-cell or day 29 non-remission or presence of t(9;22) or t(4;11)

* WBC denotes white blood cell count

† Blast <1.0 x 10^9 /L in peripheral blood after 7 days of prednisolone pre-phase treatment

Table 2. Chemotherapy protocol of HKALL97 and HKALL93[5] studies*

	HKALL97 (present) study	HKALL93 study[5]
Induction	Week 1-5 • Prednisolone 60 mg/m^2 D1-29 • Vincristine 1.5 mg/m^2 D8, 15, 22, 29 • L-Asparaginase 5000 IU/m^2 IV from D11 Q3D x 8 doses • Daunorubicin 30 mg/m^2 IV weekly D8, 15, 22, 29 (standard risk: only D8, D15)	Week 1-4 • Prednisolone 40 mg/m^2 D1-28 • Vincristine 1.5 mg/m^2 D1, 8, 15, 22 • L-Asparaginase 6000 U/m^2 SC from D4 Q3D x 9 doses
Early intensification	Week 5-9 • Cyclophosphamide 1 g/m^2 D36, 64 • Ara-C 75 mg/m^2 IV daily on D38-41, 45-48, 52-55, 59-62 • 6-Mercaptopurine 60 mg/m^2 po D36-62	Week 6 • Prednisolone 40 mg/m^2 D1-5 • Etoposide 100 mg/m^2 IV D1-5 • Daunorubicin 45 mg/m^2 IV D1, 2 • Ara-C 100 mg/m^2 IV Q12H D1-5 • Thioguanine 80 mg/m^2 po D1-5
Consolidation	Week 12-20 *Standard risk* • Methotrexate 2 g/m^2 IV Q2W x 4 *Intermediate risk* • Methotrexate 5 g/m^2 IV Q2W x 4 *High risk* • Three 6-day intensive blocks including CNS RT 1200 cGy	Week 8-18 *Standard risk* • 6-Mercaptopurine intrathecal methotrexate *Intermediate risk* • Methotrexate 8 g/m^2 or 6 g/m^2 IV Q2W x 3 *High risk* • 6-Mercaptopurine + CNS RT 1800 cGy
Late intensification	Week 22-29 (re-induction) *Standard and intermediate risks* • Dexamethasone 10 mg/m^2 po D1-21 • Vincristine 1.5 mg/m^2 IV D8, 15, 22, 29 • L-Asparaginase 10 000 units/m^2 IV D11, 2 times/week x 4 doses • Cyclophosphamide 1 g/m^2 D36 • Ara-C 75 mg/m^2 IV daily on D38-41, 45-48 • 6-Thioguanine 40 mg/m^2 po D36-49 *High risk* • Repeat late intensification at week 37-44	Week 20 *All risks* • As early intensification *High risk: week 35-42* • Dexamethasone 10 mg/m^2 po D1-10 • Vincristine 1.5 mg/m^2 IV D1, 8, 15, 22 • L-Asparaginase 6000 unit/m^2 IV 3 times/week from D4 x 9 doses • Cyclophosphamide 600 mg/m^2 IV D1 of week 39 and 41 • Ara-C 75 mg/m^2 IV D1-4 in week 39-42 • Thioguanine 60 mg/m^2 po week 39-42
Maintenance	• 6-Mercaptopurine 50 mg/m^2 po daily • Methotrexate 20 mg/m^2 po weekly • Dexamethasone 6 mg/m^2 po D1-7 and vincristine 1.5 mg/m^2 IV D1, 8 every 10 week • Treatment of up to 2 years from diagnosis	• 6-Mercaptopurine 75 mg/m^2 po daily • Methotrexate 20 mg/m^2 po weekly • Prednisolone 40 mg/m^2 po D1-5 and vincristine 1.5 mg/m^2 IV D1 every 4 week • Treatment of up to 2 years from diagnosis

* D denotes day, IV intravenous, Q3D every 3 days, SC subcutaneous, Ara-C cytarabine arabinoside, po orally, Q12H every 12 hours, Q2W every 2 weeks, CNS RT radiation therapy of the central nervous system

teria were used with the stratification criteria of the HKALL93 study[5] shown for comparison (Table 1). A 7-day steroid pre-phase was included as an important stratification factor, patients with peripheral blood blast cells of more than 1.0 x 10^9 /L on day 8 of steroid treatment would be included as high risk. The modification included a lower dose of methotrexate (2 g/m^2 instead of 5 g/m^2 in the standard risk), and use of the double re-induction as the delayed intensification in the high-risk group which was based on the Italian 95 study.[7] The first part of induction comprised four drugs and lasted 5 weeks. The second part comprised 4 weeks of cytarabine arabinoside (Ara-C) and 2 doses of high-dose cyclophosphamide. The consolidation phase included 2 weekly courses of a total of 4 doses of high-dose methotrexate (2 g/m^2 or 5 g/m^2 for standard- and intermediate-risk patients, respectively). The high-risk treatment included three blocks of very intensive treatment courses at 3 weekly intervals as consolidation phase. Each block included 6 days of dexamethasone with a combination of various high-dose chemotherapeutic agents (high-dose Ara-C 2 g/m^2 every 12 hours intravenous for 5 doses, high-dose methotrexate 5 g/m^2, L-asparaginase 25 000 U/m^2, daunorubicin, ifosfamide, etoposide, and vincristine). The delayed intensification was commenced at around week 22 after diagnosis, similar to the induction phase, thus it was also called re-induction. High-dose dexamethasone was nevertheless used instead of prednisolone in the first part of re-induction. High-risk patients received more intensive treatment with double intensification.[7] Prophylactic cranial irradiation at 1200 cGy for CNS leukaemia was only administered to T-cell and high-risk patients. Details of the chemotherapy are shown in Table 2, with HKALL93[5] chemotherapy shown for comparison.

Table 3. Patient characteristics

	HKALL97 (present) study, n=171	HKALL93 study,[5] n=150
Sex		
Male	97 (56.7%)	71 (47.3%)
Female	74 (43.3%)	79 (52.7%)
Age (years)		
Median	5.57	5.01
Range	1.15-17.85	1.00-15.35
Down syndrome	3 (1.8%)	2 (1.3%)
White blood cell count (x 10^9 /L)		
Median	12.6	16.9
Range	0.90-999.00	0.40-680.00
Type		
Early pre-B	6 (3.5%)	5 (3.3%)
Common	96 (56.1%)	96 (64.0%)
Pre-B	38 (22.2%)	33 (22.0%)
T-cell	24 (14.0%)	13 (8.7%)
Biphenotypic	5 (2.9%)	1 (0.7%)
Others	2 (1.2%)	2 (1.3%)
Cytogenetics		
Successful	141	117
Normal	42 (29.8%)	51 (43.6%)
Hyperdiploidy	30 (21.3%)	24 (20.5%)
t(9;22)	5 (3.5%)	6 (5.1%)
t(1;19)	5 (3.5%)	6 (5.1%)
Others	59 (41.8%)	30 (25.6%)

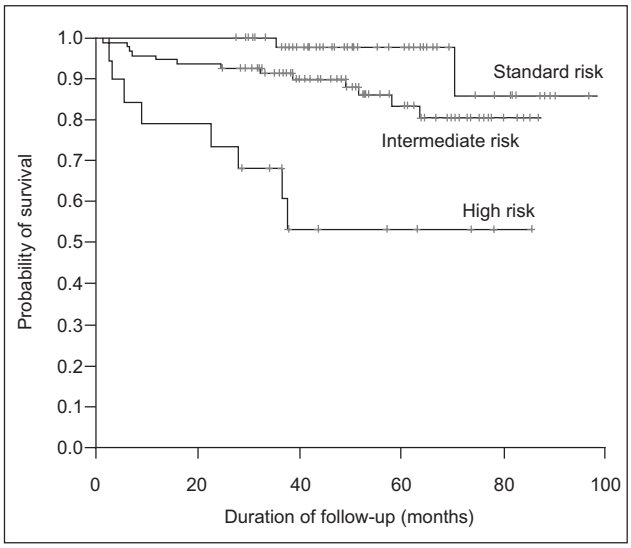

Fig 1. Overall survival of HKALL97 (present) study according to risk groups

Statistical analysis

The overall survival and event-free survival (EFS) were estimated by Kaplan Meier Curve, and the differences in the risk groups were tested by log-rank test. The HKALL93[5] and HKALL 97 (present) studies were compared: categorical variables by Chi squared test and continuous variables by Student's *t* test. The survival outcome of the two groups was compared by log-rank test.

Results

During the 62-month period, 171 patients were recruited, 56.7% of whom were male. The median age at diagnosis was 5.57 years (range, 1.15-17.85 years). There were three (1.8%) patients with Down syndrome. The initial median white blood cell count (WBC) at diagnosis was 12.6 x 10^9 /L (range, 0.9-999 x 10^9 /L). Common ALL was the most common (56.1%) immunophenotype, and the T cell type comprised 14.0%. Karyotyping was successful in 141 (82.5%) patients. Among those with successful karyotyping, chromosome number of higher than 50 (hyperdiploidy) occurred in 21.3%; both Philadelphia chromosome and t(1;19) were present in 3.5% of the patients. The risk stratification according to HKALL97 criteria was standard risk, 33%; intermediate risk, 55%; and high risk, 11%. Patient characteristics are shown in Table 3, with the similar characteristics of HKALL93[5] patients included for comparison.

Response to treatment

On day 33 of induction treatment, 163 (95.3%) of 171 patients achieved remission, three patients achieved remission after further treatment. One of 171 patients died during induction because of intracranial bleeding and four did not achieve remission.

At the end of 2004, with a median follow-up period of 48 months (range, 24-86 months from diagnosis), 26 (15.7%) of 166 patients had experienced a relapse, a significantly lower proportion than that (37.3%) in the HKALL93 study[5] (P<0.001). Among the relapsers, 13 came from the intermediate-risk group, eight from the standard-risk group, and five from the high-risk group. Eleven of 26 relapses occurred within 24 months of diagnosis, ie before completion of chemotherapy. Of those patients who relapsed after completion of chemotherapy, the latest occurred 53 months after diagnosis. The sites of relapse were bone marrow (n=18), CNS (n=3), combined bone marrow and CNS (n=2), combined bone marrow and testes (n=1), testes (n=1), and combined CNS and testes (n=1). Bone marrow was the main site of relapse in both studies and was the sole affected site in 60% of relapse cases. Relapse of CNS, alone or combined with another site, occurred in six (3.6%) of 166 patients in the HKALL97 study, and 12 (8.2%) of 146 patients in the HKALL93 study. Allogeneic haematopoietic stem cell transplantation was performed in 11 patients, four in first remission and seven in second remission. Five of them survived in remission. The five patients with Philadelphia chromosome had a poor outcome: one had refractory leukaemia and died, three relapsed and two died, and one is in first remission after transplantation.

Survival outcome according to HKALL97 stratification criteria

Four patients failed to achieve remission after further chemotherapy and died from infection or bleeding 1.6 to 5.7 months after diagnosis. Four patients died from a non-leukaemic cause after achieving remission. Three deaths occurred during the re-induction phase and one following

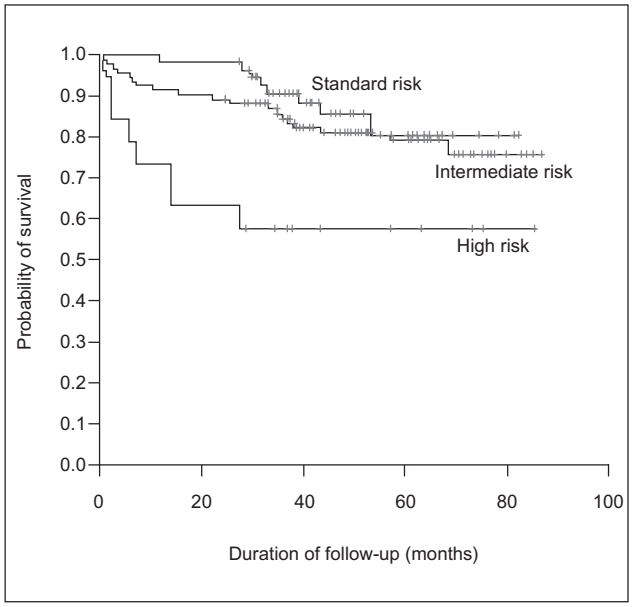

Fig 2. Event-free survival of HKALL97 (present) study according to risk groups

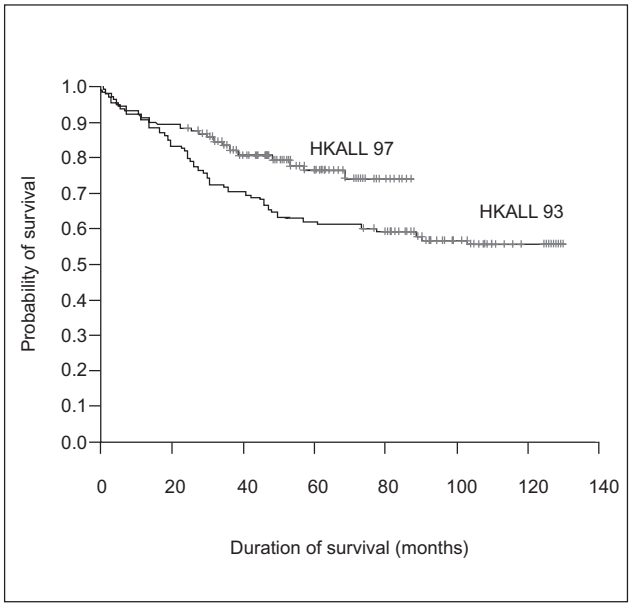

Fig 3. Comparison of event-free survival of the HKALL93[5] and HKALL97 studies

bone marrow transplantation in the first remission. The causes of non-leukaemic death were gram-negative bacteria septicaemia and systemic fungal infection. The other deaths were due to relapsed or refractory leukaemia. At the last analysis at 2 years after completion of study, 23 patients had died and 148 patients were surviving. The remission status of the survivors was first remission (n=137), second remission (n=10), and third remission (n=1). The 4-year overall survival for the whole group was 86.5% (standard deviation [SD], 2.7%). According to the risk groups, the 4-year overall survival for standard risk, intermediate risk, and high risk were 97.9%, 89.1%, and 58.2%, respectively (Fig 1). The 4-year EFS for the whole group was 79% (SD, 3.3%). According to risk groups, the EFS was 88.5%, 77.9%, and 57.1% for standard risk, intermediate risk, and high risk, respectively (Fig 2).

Survival outcome according to HKALL93 stratification criteria and comparison of two studies

To enable more accurate comparisons to be made, HKALL97 patients were reclassified according to HKALL93 criteria. The HKALL93 study[5] adopted less strict stratification criteria, thus more patients in the HKALL97 study were classified as standard and high risks. Comparison of HKALL93 criteria versus HKALL97 criteria for HKALL97 patients revealed there were 47% versus 33% in standard-risk group, 23.5% versus 55% in intermediate-risk group, 29.5% versus 11% in high-risk group, respectively. There were 24% and 36% in the HKALL97 intermediate-risk group reclassified as standard-risk and high-risk respectively according to HKALL93 criteria. All the HKALL97 standard-risk patients were also of HKALL93 standard risk, whereas 16% and 84% of HKALL97 high-risk patients fell into HKALL93 intermediate-risk and high-risk groups, respectively. There was no difference in the overall survival (81.8% for HKALL93 vs 86.5% for HKALL97, P=0.51) but there was significantly better EFS for HKALL97 group (65% for HKALL93 vs 79% for HKALL97, P=0.007) [Fig 3]. According to HKALL93 criteria, the overall survival and EFS for standard risk of the two studies were not significantly different (P=0.66 and P=0.48). There was a trend of better EFS for HKALL97 study in the intermediate-risk group, 75.6% against 53.1% for HKALL97 and HKALL93, respectively (P=0.06). The EFS in high-risk patients of the HKALL97 study appeared to be better although results did not reach statistical significance (P=0.14), probably due to the small sample size.

Discussion

This was a multicentre trial that included all five hospitals that treat childhood cancer in Hong Kong. It can therefore be considered a population-based study. All data and events were recorded prospectively. Randomisation was not possible because of insufficient patients, thus the findings of this study were compared with those of a previous one. The cytogenetic and molecular data were also incomplete. Nonetheless patient characteristics of the two studies were similar and both studies were population-based and included all newly diagnosed ALL children in Hong Kong. The duration of the two studies was similar—around 5 years—so was the number of patients recruited. Isolation facilities have improved over the time of these two studies and Hong Kong now has dedicated children cancer centre/ward/cubicles in the five public hospitals. Supportive care is also much improved, with more potent anti-microbials

and cytokines (eg granulocyte colony-stimulating factor) available.

The number of non-leukaemia deaths was low in both studies, 1.3% and 2.3% for HKALL93 and HKALL97, respectively. Thus the improved outcome currently seen cannot be explained by a decrease in such deaths, but is more likely due to the decreased relapse rate (15.7%) in the HKALL97 study against 37.3% in the HKALL93 study. This decrease was a result of the increased intensity of chemotherapy in the HKALL97 study. Number of deaths due to other causes was not affected.

Overall survival in the HKALL93 and HKALL97 studies was similar (86.5% vs 81.8%), although the EFS in the HKALL97 study was superior to that of the HKALL93 study (79% vs 65%). As in our previous report,[5] we observed a satisfactory overall survival but were dissatisfied with the poor EFS. The relatively good overall survival was achieved through further chemotherapy for another 2 to 3 years or bone marrow transplantation for relapsed patients. In such patients, we anticipated more late complications such as growth retardation, endocrine complications, and avascular necrosis. Secondary brain tumour is the most disastrous late complication.[8] In the new HKALL97 study, the relapse rate was very much reduced and a second course of treatment was avoided in a large proportion of patients. The reduced relapse rate in our study is due to a more effective chemotherapy protocol. No new chemotherapeutic agents were administered: the reduced relapse rate was mainly due to the inclusion of a re-induction phase at around 5 months after diagnosis. The induction treatment and high-dose methotrexate during consolidation are quite similar whereas the early intensification of the HKALL93 study was toxic with pancytopenia and febrile neutropenia as common occurrences.[5]

Re-induction, sometimes called delayed intensification, is now recognised as an important component of treatment for ALL in children. The German BFM studies in the 1980s and 1990s demonstrated improved outcome after introduction of a more intensive delayed intensification.[9] The American Children's Cancer Group also demonstrated such an improvement for both standard- and high-risk patients after inclusion of the BFM-delayed intensification.[10,11] High-dose dexamethasone may confer better CNS and systemic anti-leukaemic effects than prednisone.[12] Together with other cytotoxic drugs used in this phase, the minimal residual leukaemia cells may be further cleared up. In the current study, we observed better EFS for the whole group, especially those at intermediate risk. The main difference in the chemotherapy protocols of the two studies was the use of dexamethasone and delayed intensification. Nonetheless this intensive phase is very toxic and associated with a high infection rate. The three non-leukaemia deaths in this study all occurred during this delayed intensification phase, the other patient died following transplantation.

The present (HKALL97) study included the in-vivo response to steroid as the stratification criteria. Patients who exhibited a poor response to 7 days of steroid treatment were stratified as high risk. This is a simple laboratory test that can be performed in all laboratories. Its prognostic significance has been demonstrated in many studies: it is an independent predictor for response to treatment and survival in addition to age and immunophenotyping. White blood cell count is no longer a distinguishing feature between intermediate- and high-risk patients. Thus more patients with high WBC counts were then classified as intermediate risk. The high-risk group was confined to a small subset of 'very' high-risk patients—only 11%. The advantage of further defining the high-risk group is the reduced number of patients subjected to cranial irradiation. The chance of second malignancy and intellectual impairment is thus further decreased.[13] Whether the reduced dose of cranial radiotherapy from 1800 cGy to 1200 cGy is less damaging remains uncertain. The CNS relapse rate remained very low, 1% in standard-risk and 2.2% in intermediate-risk patients, despite a more restricted cranial irradiation approach.

Despite some modification of this study from the original BFM95 study, our preliminary results are comparable. The BFM95 study had 6-year EFS of 79% for the whole group; and 89%, 79%, and 49% for the standard-, intermediate-, and high-risk groups, respectively (unpublished data). The reduction of methotrexate dosage in the current study for standard-risk patients appeared to be safe.

Conclusion

We observed significant improvement in the survival and EFS for ALL in Hong Kong children. Cranial irradiation was avoided in most patients with consequent prevention of some late complications and improved long-term quality of life. We are now participating in a multi-national randomised study aimed at further improving EFS in intermediate-risk and high-risk patients, and also defining better methods to improve their quality of life.

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