EXCELLENT OUTCOME OF ACUTE LYMPHOBLASTIC LEUKEMIA WITH *TCF3-PBX1* REARRANGEMENT IN HONG KONG

Abstract

Objective The aim of this study was to review clinical outcomes and prognosis of paediatric Acute Lymphoblastic Leukaemia (ALL) patients with TCF3-PBX1 rearrangement. **Patients** All children in Hong Kong diagnosed with ALL with *TCF3-PBX1* rearrangement over the past 2 decades were included. **Methods** Six hundred and twenty-four newly diagnosed ALL patients from 4 consecutive studies were enrolled from 1997 to 2016. Patients carrying *TCF3-PBX1* rearrangement and patients of intermediate risk without the gene expression were compared for the clinical characteristics, overall survival and event-free survival. **Results** The *TCF3-PBX1* rearrangement was detected in 30 of 624 patients (4.8%). Results were consistent across the consecutive clinical trials employed in the past 2 decades. Compared with 239 intermediate risk patients without *TCF3-PBX1* rearrangement, the 5 year OS and EFS for patients with *TCF3-PBX1* rearrangement was superior both at 100% (p=0.12 and p=0.029). **Conclusion** This population based study over the past 20 years demonstrated patients with *TCF3-PBX1* rearrangement had favourable EFS compared to other intermediate risk treated with similar chemotherapy backbone.

Background

Many exciting advances have been made in paediatric acute lymphoblastic leukemia (ALL) research in recent years. Specific genetic abnormalities have been discovered to carry prognostic significance and thereby therapeutic relevance, and some genotypes have been incorporated into treatment stratification.[1] Historically, B-lineage ALL with the *TCF3-PBX1* rearrangement has been associated with poor outcomes and unfavourable presenting features, such as high white blood cell (WBC) count.[2] Intensified chemotherapy regimens have led to reportage of improved outcomes in this cohort of patients but the data from Chinese patients are limited.[3,4] We decided to review the prognostic impact of the *TCF3-PBX1* rearrangement in ~~our~~ ALL patients treated with consecutive clinical trials in the past two decades, and compared the outcome with other ALL patients treated with same chemotherapy in this population based study.

Methods

This is a retrospective study of subjects enrolled on 4 consecutive ALL treatment protocols from 1997 to 2016, namely HKALL 97 (1997 to 2002, n=171), IC-BFM 2002 (2003 to 2008 n=175), CCLG 2008 (2008 to 2015 n=221) and ongoing CCCG 2015 (from 2015 up to Dec 2016, n=57).

HKALL 97 was based on the ALL-BFM 95 protocol with some modifications, and aimed to see if treatment outcomes could be improved with the addition of a delayed intensification block.[1] IC-BFM 2002 was an international randomised control study comparing two delayed intensification approaches.[2] During consolidation phase, B-ALL of standard risk (SR) and intermediate risk (IR) received a lower dose of methotrexate at $2g/m^2$ compared to $5g/m^2$ for IR T-ALL. In CCLG 2008, dexamethasone was employed during therapy. The first three clinical trials utilise BFM-based approach while the CCCG 2015 is St Jude Total XV protocol based which includes a more intensive L-asparaginase treatment approach. Finally, in maintenance therapy, HKALL employed pulse dexamethasone and vincristine as standard treatment, while CCCG 2015 and CCLG 2008 both included a randomisation part testing pulse dexamethasone and vincristine versus no pulse treatment. IC-BFM 2002 only included a short period of 4 pulses in the early phase of maintenance therapy. Risk stratification criteria and chemotherapy outlines are presented in table 1.

CCLG 2008 was in collaboration with the Chinese Children Leukemia Group with another 10 institutions in mainland China. The use of NCI criteria and pilot of MRD monitoring for risk stratification and treatment modification was introduced. CCCG 2015 is a multicentre study under China Children Cancer Group with 20 institutions participating. MRD monitoring for response assessment at the end of induction was adopted as a standard investigation, and a less intensive treatment is employed in Low Risk patients. Total intrathecal chemotherapy numbers amongst the 4 protocols ranged from 15-23. HKALL 97 and IC-BFM 2002 studies employed intrathecal methotrexate, while CCLG 2008 Intermediate Risk (IR) arm and CCCG 2015 studies employed triple intrathecal treatment, i.e. methotrexate, cytarabine and hydrocortisone. None of our t(1;19) positive patients received prophylactic cranial irradiation.

Clinical data, cytogenetic and molecular data of patients were collected. In CCLG 2008 and CCCG 2015, patients with *TCF3-PBX1* rearrangement were directly stratified into IR group, whereas in the earlier

protocols, most patients with the presence of the t(1;19) translocation were also stratified into IR group due to less favourable biological features. Survival outcomes of the first 3 studies was analyzed and compared with that of IR group without t(1;19) translocation, the CCCG 2015 study was not included in the survival analysis due to short follow up duration. Event free survival (EFS) was defined as the time from diagnosis until the date of treatment failure (induction failure, relapse, death or the development of a second malignancy) or until the date of last contact. Overall survival was defined as time from diagnosis to last contact or death. EFS and overall survival (OS) were estimated using the Kaplan-Meier procedure and comparisons were performed with the Mantel Haenszel (log-rank) test. Demographic data comparisons were performed with the Wilcoxon rank sum test. Tests were considered statistically significant at $p<0.05$. All statistical analyses were performed using SPSS 21.0 software (Statistical Product and Service Solutions Inc., Chicago, IL, USA).

Results

The incidence of *TCF3-PBX1* rearrangement was 4.8% (30 out of 624 cases). There were 6, 11, 9 and 4 cases in the 4 consecutive ALL studies respectively. All cases were B lineage and gender distribution was roughly balanced with 16 males and 14 females. Thirteen cases were standard risk and 17 were high risk by NCI criteria (Age 1 to ≤10 years old and WBC <50 as standard risk). One case had CNS leukaemia (CNS 3) and received 18 Gy cranial irradiation. One case had Down syndrome and received a standard dose of methotrexate.

TCF3-PBX1 rearrangement was identified by karyotyping in 27 cases [9 had balanced translocations and 18 had unbalanced translocations with der(19)t(1,19), 19 of which were also detected by PCR. The remaining 3 cases had E2A/PBX1(*TCF3-PBX1)* gene fusion detected by PCR only.

Twenty six subjects were stratified to IR with 5 g/m^2 methotrexate for 4 doses during consolidation and 11 cases recruited in IC-BFM 2002 that 2 g/m^2 were applied. Two subjects were stratified to standard risk group with 1 subject each in the HKALL 97, IC-BFM 2002. One subject was stratified to high risk group in the CCLG 2008 study due to poor prednisolone response. No subjects received stem cell transplant.

These 30 cases with *TCF3-PBX1* rearrangement were compared with 239 other cases in the IR groups of the HKALL 97, IC-BFM 2002 and CCLG 2008 studies. We found that the cohort of patients with *TCF3-PBX1* rearrangement had a younger median age at diagnosis of 4.8 years (range 1.3 to 14.8 years) compared to 7.8 years (range 1.1 to 17.9 years) with $p<0.001$. Median WBC was higher at $26.7x10^9$/L (range $1.3x10^9$/L to $308x10^9$/L) compared to $23.5x10^9$/L (range $0.58x10^9$/L to $999x10^9$/L) with $p<0.001$.

For outcome analyses limited to 26 patients recruited in the HKALL 97, IC-BFM 2002 and CCLG 2008 studies, median follow-up duration was 10 years (range 1.5 to 16.4 years). Four of 26 patients (incidence 15.4%) had poor prednisolone response on day 8 (blast count in peripheral blood $<1.0x10^9$/L), and all achieved complete remission after induction. In the CCLG 2008 protocol which incorporated flow MRD monitoring at regular time points, 5 out of 6 patients with available MRD result on D33 achieved flow MRD <0.01%. There was no bone marrow relapse, CNS relapse or death recorded in all 26 patients with *TCF3-PBX1* rearrangement, yielding EFS and OS of 100%. In contrast, 5-year EFS of 239 IR patients without *TCF3-PBX1* rearrangement in the HKALL 97, IC-BFM 2002 and CCLG 2008 studies were 74.2±4.9%, 80.5±4.4%, 82.8±4.4% and 5-year OS were 77.7±5.7%, 91.5±3.1%, 96.5±2.5% respectively. The major causes of failure were relapses and only 4 ~~people~~ patients died of treatment-related mortality.

Discussion

The incidence of *TCF3-PBX1* rearrangement of 4.8% in this study appears to be slightly higher than the reported incidence of 2-3% in western countries.[7-9] However there are reports from Japan and China showing a higher incidence at around 7%.[10,11] A recent report from Taiwan also reported the incidence of 5.7%.[12] Our study has the strength of being a population based study over two decades, and this is an accurate reflection of genetic incidence in south China. Our data showed that compared to other ALL IR patients, patients with *TCF3-PBX1* rearrangement have younger age and higher median WBC count. There has been conflicting results on the significance of these differences in the biological features.

Historically, *TCF3-PBX1* rearrangement was a poor prognostic factor. Improved outcomes on newer protocols in these patients have been reported when more intensive chemotherapy is given.[4,7] Most studies now stratify *TCF3-PBX1* rearrangement into intermediate or high risk and apply a more intensive treatment. In this

retrospective study we showed outcomes of *TCF3-PBX1* rearrangement compared with other ALL IR patients had significantly better EFS of 100%, p=0.029 and OS of 100%, p=0.12.

St Jude study reported that patients with *TCF3-PBX1* rearrangement have a higher incidence of CNS relapse, 9%.[13] The report from Taiwan Group which adopted the St Jude treatment protocol also reported a higher incidence of CNS relapse, 8.7%.[12] Research has been performed with experimental animal models which demonstrate that those with the *TCF3-PBX1* rearrangement have a particular propensity to enter the CNS.[14] This is postulated to be either via up-regulated survival pathways e.g. PBX1, MER, IL-15, ZAP70, or via up-regulated homing markers e.g. chemokine receptors such as CXCR4 or CCR7, which migrate to the CNS and then activate survival pathways necessary to maintain CNS disease.

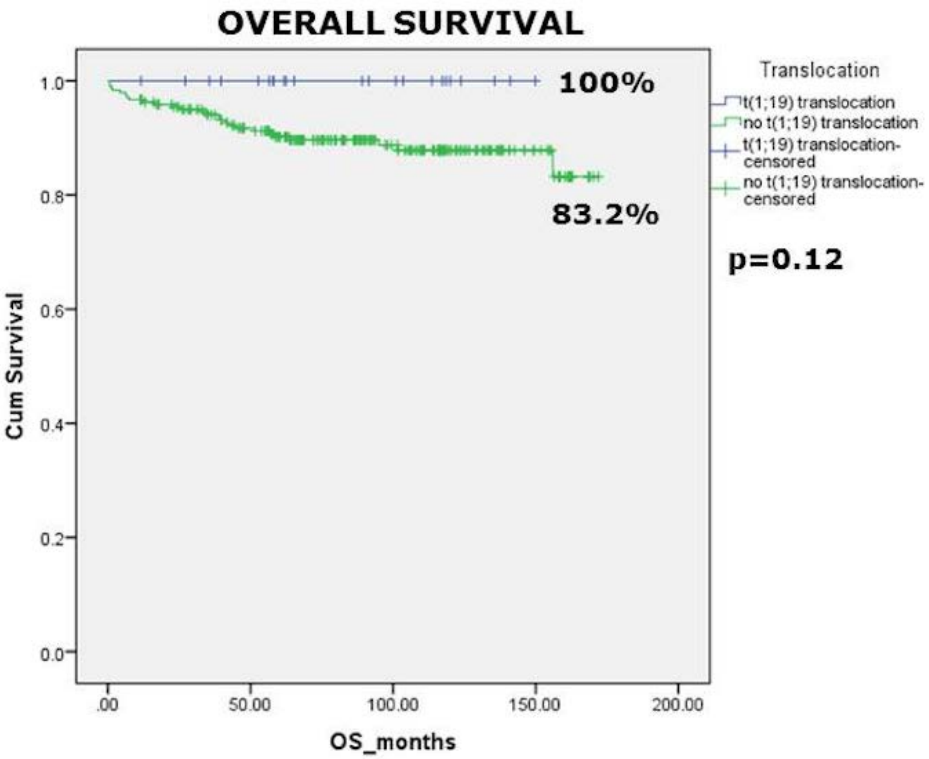
Prevention of CNS relapse in patients with *TCF3-PBX1* rearrangement would be important in the survival outcome. In our study only one of 30 patients had CNS disease at presentation, and there was no CNS relapse. Though the number of patients with *TCF3-PBX1* rearrangement is small, it appears that chemotherapy without cranial irradiation may be effective to prevent CNS relapse. Of interest, the more recent BFM protocols (BFM 90, 95 and 2000) as reported by Austrian group showed excellent outcome. Only one of 26 patients had bone marrow relapse and no patient developed CNS relapse.[4] In a large Chinese ALL study adopting BFM approach, CCLG 2008 Study, similar good outcome was also observe, and none of the 121 *TCF3-PBX1*positive patients developed CNS relapse.[15] The dose of methotrexate given in the IC-BFM 2002 study was only 2 g/m^2 and the intrathecal chemotherapy was methotrexate alone, whereas the other two studies adopted methotrexate at 5 g/m^2, and CCLG 2008 adopted triple therapy in the intrathecal chemotherapy, it seems either approach of BFM based protocol provide good CNS control for the *TCF3-PBX1* patients. We are unable to draw any conclusions on what may be the optimal dose of methotrexate or type of intrathecal chemotherapy for the prevention of CNS and bone marrow relapse. The number of intrathecal chemotherapy may be another important factor, a total 15 to 19 intrathecal chemotherapy was given in our first 3 clinical trials. Other factors such as inclusion of dexamethasone in the whole chemotherapy course, or escalation of treatment intensity could also have contributed to the better outcome. Additional genetic mutation such as *IKZF1* may also have prognostic significance in this genetic group.[10]

The strength of this study is that it is a population-based study which includes all children diagnosed with leukaemia in Hong Kong over the past 20 years. There was no loss to follow up of these patients. Karyotyping or molecular genetic studies was performed in all of these patients with a high success rate, thus the calculated incidence should be representative of the true incidence. The limitation of this study is the small sample size and the patients having been treated by 4 different protocols. However, the backbone of the chemotherapy these patients received is similar in the 3 studies included for survival analysis, and the excellent result actually persisted across the 3 protocols.

Conclusion

TCF3-PBX1 rearrangement occurs in approximately 5% of paediatric ALL in Hong Kong. The prognosis of this subgroup is excellent with BFM based chemotherapy including high dose methotrexate and repeated intrathecal chemotherapy. CNS disease or relapse is not increased in the contemporary chemotherapy protocols.

Figure 1


OVERALL SURVIVAL
100%
83.2%
p=0.12
Translocation
t(1;19) translocation
no t(1;19) translocation
t(1;19) translocation-censored
no t(1;19) translocation-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
50.00
100.00
150.00
200.00
OS_months

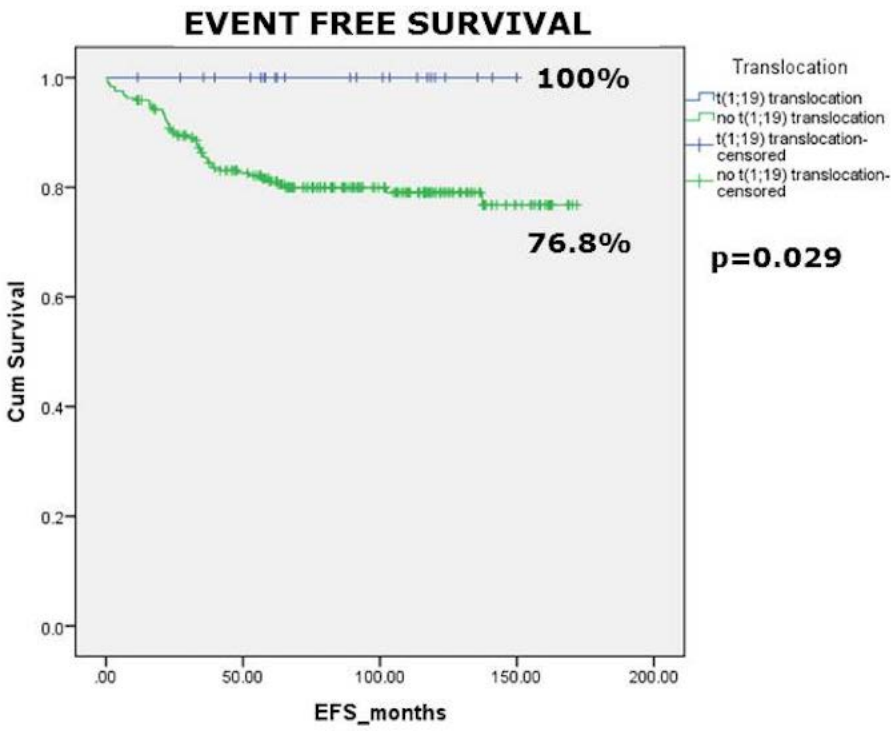

EVENT FREE SURVIVAL
100%
76.8%
p=0.029
Translocation
t(1;19) translocation
no t(1;19) translocation
t(1;19) translocation-censored
no t(1;19) translocation-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
50.00
100.00
150.00
200.00
EFS_months

Table 1 Patient characteristics and treatment outcome

Demographics	HKALL97	IC-BFM 2002	CCLG 2008	CCCG 2015	Overall
Total number of patients	171	175	221	57	624
Total number of IR patients	96 (56.1%)	92 (52.6%)	76(34.4%)	27(47.4%)	291 (46.7%)
Incidence of t(1;19) translocation	6 (3.5%)	11 (5.8%)	9 (4.1%)	4 (7%)	30 (4.8%)
Male	4	6	4	2	16
Female	2	5	5	2	14
Median Age (range)	8 (3.7-13.3)	4.7 (2.3-14.8)	6.8 (1.4-13.9)	3.4 (1.3-10.3)	4.8 (1.3-14.8)
Median presenting WBC (range)	33.2 (1.3-209)	20.4 (4.4-307)	26.8 (2.1-308.2)	93.6 (5.4-317.7)	26.7 (1.3-308)
CNS 3	-	-	1	-	1
Cytogenetics					
Balanced translocation	2	2	4	1	9
Unbalanced translocation	3	9	5	1	18
Gene fusion detected by RT-PCR only	1	-	-	2	3
Hyperdiploidy	-	-	1	-	1
Hypodiploidy	-	-	-	-	0
Down Syndrome	-	1	-	-	1
Standard risk	1	1	-	0	2 (6.6%)
Intermediate risk	5	10	8	4	27 (90%)
High risk	-	-	1	-	1 (3.3%)
NCI standard risk	2	6	4	1	13
NCI high risk	4	5	5	3	17
Survival Analysis					
5 year EFS for other IR groups (%)	74.2±4.9	80.5±4.4	82.8±5.4	NA	76.8±3.5
5 year OS for other IR groups (%)	77.7±5.7	91.5±3.1	96.5±2.5	NA	83.2±5
5 year OS and EFS *TCF3-PBX1* rearrangement (%)	100	100	100	NA	100

Table 2: Stratification criteria

1. HK ALL 97 study

Standard risk

Patients with **all** the following characteristics will be entered in this group:

- WBC <20,000/mm3
- Age ≥ 1 year and <6 years
- Non-T immunophenotype
- Good PRD response (absolute peripheral blast count <1,000/μL on day 8)
- M1 bone marrow on day 33
- No t(9;22), t(1;19) and t(4;11) or equivalent molecular abnormalities,
- No CNS or testicular involvement

Intermediate risk

All patients not eligible for standard or high risk will be entered in this group.

High risk

All patients with **one or more** of the following characteristics will be entered in this group.

- Resistance to PRD (absolute peripheral blast count ≥ 1,000/μL on day 8)
- Bone marrow not M1 on day 33
- t(9;22) or BCR/ABL,
- Age <1 **year : with** t(4;11) or MLL/AF4, or B lineage with CD10 negative immunophenotype

2. **IC-BFM 2002 study**

Intermediate risk group:

Peripheral blood day 8: < 1,000 blasts/μL
+ Age<1yr or ≥6yr and/or WBC≥20,000/μL
+ M1 or M2 marrow on day 15
+ M1 marrow on day 33
or: Standard-risk criteria but M3 marrow on day 15 and M1 marrow on day 33

3. CCLG 2008 study

Intermediate risk group:

Prednisone good response and day 15 BM M1/M2, and any one of:

1. Age > 10 years or WBC > 50, or age < 1year without MLL gene rearrangement, or
2. T-cell (except Early T-ALL) or
3. t(1;19) or E2A/PBX1, or
4. SR with day 15 BM M3, or
5. If MRD available, day 33 MRD $<10^{-2}$

Table 3: Chemotherapy Treatment Summary for Intermediate Risk Groups

	CCCG 2015	CCLG 2008	IC-BFM 2002	HKALL 97
Induction	Week 1-5 - Dexamethasone 6mg/m^2 D1-7 - Prednisolone 45-60mg/ m^2 D8-28 - Vincristine 1.5mg/ m^2 D5, 12, 19, 26 - L-Asparaginase 6000 IU/ m^2 IV from D6, 3 days/week x 12 doses - Daunorubicin 25mg/ m^2 D5, 12	Week 1-5 - Prednisolone 60mg/ m^2 D1-7 - Dexamethasone 6mg/m2 D8-28 - Vincristine 1.5mg/ m^2 D8, 15, 22, 29 - L-Asparaginase 5000 IU/ m^2 IV from D11 Q3D x 8 doses - Daunorubicin 30mg/ m^2 IV weekly D8, 15, 22, 29 IT MTX on D1 and triple D15, 33	Week 1-5 - Prednisolone 60mg/ m^2 D1-29 - Vincristine 1.5mg/ m^2 D8, 15, 22, 29 - L-Asparaginase 5000 IU/ m^2 IV from D11 Q3D x 8 doses - Daunorubicin 30mg/ m^2 IV weekly D8, 15, 22, 29	Week 1-5 - Prednisolone 60mg/ m^2 D1-29 - Vincristine 1.5mg/ m^2 D8, 15, 22, 29 - L-Asparaginase 5000 IU/ m^2 IV from D11 Q3D x 8 doses - Daunorubicin 30mg/ m^2 IV weekly D8, 15, 22, 29
Early intensification	Week 5-8 - Cyclophosphamide 1mg/ m^2 D29 - Ara-C 50mg/ m^2 IV daily D29-35 - 6-Mercaptopurine 60mg m^2 po D29-35	Week 5-9 - Cyclophosphamide 1g/ m^2 D36 - Ara-C 75mg/ m^2 IV daily on D38-41, 45-48 - 6-Mercaptopurine 60mg/ m^2 po D36-49 Repeat above 2 weeks course after marow recovery	Week 5-9 - Cyclophosphamide 1g/ m^2 D36, 64 - Ara-C 75mg/ m^2 IV daily on D38-41, 45-48, 52-55, 59-62 - 6-Mercaptopurine 60mg/ m^2 po D36-62	Week 5-9 - Cyclophosphamide 1g/ m^2 D36, 64 - Ara-C 75mg/ m^2 IV daily on D38-41, 45-48, 52-55, 59-62 - 6-Mercaptopurine 60mg/ m^2 po D36-62
Consolidation	Week 11-15 - Methotrexate 5g/ m^2 IV Q2W x4	Week 12-20 - Methotrexate 5g/ m^2 IV Q2W x4	Week 12-20 B-ALL - Methotrexate 2g/ m^2 IV Q2W x4 T-ALL - Methotrexate 5g/ m^2 IV Q2W x4	Week 12-20 - Methotrexate 5g/ m^2 IV Q2W x4
Late intensification	Week 16-31: 3 weekly cycle x 5 - Dexamethasone 12mg/m^2 po D1-5 - Daunorubicin 25mg/m^2 D1 - Vincristine 1.5mg/m^2IV D1 - L-Asparaginase 2000 units/ m^2 D3 weekly x 15 doses Week 32-34 - Dexamethasone 8mg/ m^2 po D1-7, D15-21 - Vincristine 1.5mg/ m^2 D1, 8, 15 - Ara-C 2g/ m^2 IV Q12H x 4 doses - L-Asparaginase 20 000 units/ m^2 IV on D3, 10, 17	Week 22-29 - Dexamethasone 10mg/ m^2 po D1-7, D15-21 - Doxorubicin 25mg/ m^2 D1, 8, 15 - Vincristine 1.5mg/ m^2 IV D1, 8, 15 - L-Asparaginase 10 000 units/m2 IV D8, 2 times/week x 4 doses - Cyclophosphamide 1g/ m^2 D29 - Ara-C 75mg/m2 D31-34, D38-41 - 6-Thioguanine 60mg/ m^2D29-42 Repeat second intensification 8 weeks later.	Week 22-29 - Dexamethasone 10mg/ m^2 po D1-21 - Vincristine 1.5mg/ m^2 IV and doxorubicin 30mg/ m^2 IV on D8, 15, 22, 29 - L-Asparaginase 10 000 units/ m^2 IV D8, 2 times/week x 4 doses - Cyclophosphamide 1g/ m^2 D36 - Ara-C 75mg/ m^2 IV daily on D38-41, 45-48 - 6-Thioguanine 40mg/ m^2 po D36-49	Week 22-29 (re-induction) - Dexamethasone 10mg/ m^2 po D1-21 - Vincristine 1.5mg/ m^2 IV D8, 15, 22, 29 - L-Asparaginase 10 000 units/ m^2 IV D11, 2 times/week x 4 doses - Cyclophosphamide 1g/ m^2 D36 - Ara-C 75mg/ m^2 IV daily on D38-41, 45-48 - 6-Thioguanine 40mg/ m^2 po D36-49
Maintenance (up to total treatment 2 to 2.5 years)	8 weekly cycle: Week 1-6 - 6-Mercaptopurine 50mg/m2 po daily - Methotrexate 25mg/m2 po weekly - Dexamethasone 8mg/m2 po D1-7 - Vincristine 1.5mg/m2 D1 Week 7: - Cyclophosphamide 300mg/m2 D1 - Ara-C 300mg/m2 IV D1	- 6-Mercaptopurine 50mg/m2 po daily - Methotrexate 20mg/m2 po weekly - Dexamethasone 6mg/m2 po D1-7 every 8 weeks - Vincristine 1.5mg/m2 D1 every 8 weeks	- 6-Mercaptopurine 50mg/m2 po daily - Methotrexate 20mg/m2 po weekly - Treatment of up to 2 years from diagnosis	- 6-Mercaptopurine 50mg/m2 po daily - Methotrexate 20mg/m2 po weekly - Dexamethasone 6mg/m2 po D1-7 and vincristine 1.5mg/m2 IV D1, 8 every 10 weeks - Treatment of up to 2 years from diagnosis

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