高 雄 榮 民 總 醫 院
急性淋巴性白血病診療原則

2019年01月21日第一版

兒童癌症醫療團隊擬訂

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

修訂指引

- 本共識依下列參考資料制定版本
  – 台灣兒童癌症研究群(TPOG)，
  TPOG_ALL_2013 V5_2018_05_25_

會議討論

上次會議：2018/02/22

本共識與上一版的差異

上一版	新版
1.白血病診療指引含括AML和ALL。 2.參考TPOG_ALL_2013_Revised_6.30.2017版本。	1.考量兒童常見白血病種類為ALL，故診療指引方向改成ALL為主。 2.依據TPOG ALL-2013, rev.2018.5.25之版本，同步修訂診療指引之治療內容(以灰底標示)。 3.新增治療流程圖。

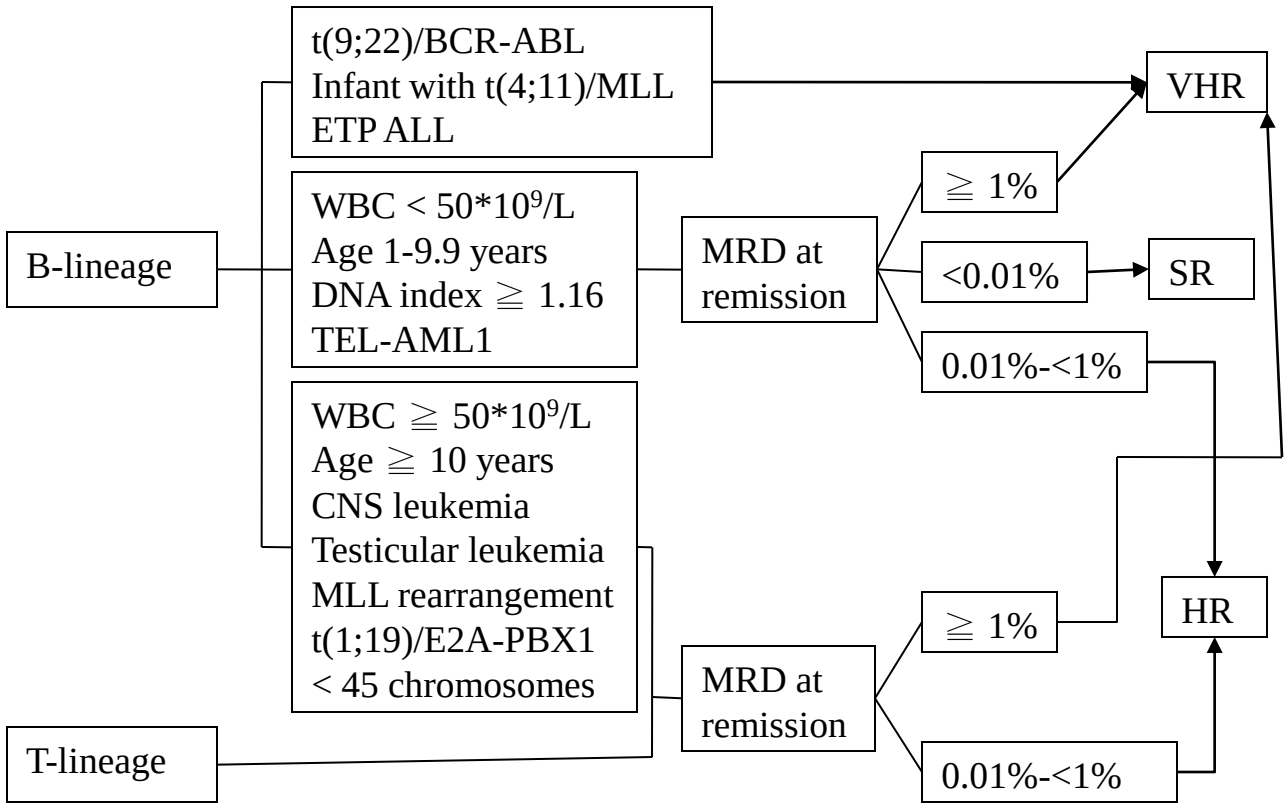
兒癌-急性淋巴性白血病

高雄榮民總醫院
臨床診療指引　2019年第一版

評估	診斷	治療	追蹤

- 病史，理學檢查
- 營養及日常體能狀態
- 身高體重，體表面積計算
- 血液常規
- 電解質及肝腎功能
- 凝血功能
- 腫瘤指標 (LDH)
- 心臟超音波檢查
- 腹部超音波
- 骨髓抹片/切片檢查*
- 脊髓穿刺檢查*
- 骨髓細胞表面標記及染色體檢查*

*與癌症期別相關之主要檢查



※ CBC/DC Q1M*12 then Q3M*4 then Q6M
※ LDH Q6M

Risk Classification

Patients are classified into one of three categories (**standard**-, **high**-, or **very high-risk**) based on

1. Presenting age
2. Leukocyte count
3. Presence or absence of CNS-3 status or testicular leukemia
4. Immunophenotype
5. Cytogenetics and molecular genetics
6. DNA index
7. Early response to therapy.

Hence, definitive risk assignment will be made after completion of remission induction. therapy. The criteria and the estimated proportion of patients in each category are provided below.

Criteria for Standard-risk(SR) ALL

1. B-lymphoblastic ALL with DNA index ≥ 1.16 [or hyperdiploidy (51-68)], *TEL-AML*1 fusion, or age 1 to 9.9 years and presenting WBC < 50,000/mm^3. AND

2. Must ***not*** have:

✓ CNS 3 status (≥ 5 WBC/μL of cerebrospinal fluid with morphologically identifiable blasts or cranial nerve palsy).

✓ Overt testicular leukemia (evidenced by ultrasonogram).

✓ Adverse genetic features: t(9;22) or *BCR-ABL1* fusion; t(1;19) with *E2A-PBX1* fusion; rearranged *MLL* (as measured by FISH and/or PCR)*;* or hypodiploidy (< 44 chromosomes).

✓ Poor early response (≥ 1% lymphoblasts on day 15 of remission induction, ≥ 0.01% lymphoblasts by immunologic or molecular methods on remission date).

Criteria for High-risk(HR) ALL

All cases of T-cell ALL and those of B- lymphoblastic ALL that do not meet the criteria for standard-risk or very high-risk ALL.

Criteria for Very High-risk(VHR) ALL

1. t(9;22) or *BCR-ABL1* fusion (with MRD ≥0.01% after remission induction including dasatinib (60 mg/m^2 per day).
2. Infants with t(4;11) or *MLL* fusion.
3. Induction failure or ≥1% leukemic lymphoblasts in the bone marrow on remission date (with the exception of hyperdiploid (51-68) and *TEL-AML1* cases who should have positive MRD after consolidation therapy).
4. ≥0.1% leukemic lymphoblasts in the bone marrow in week 7 of continuation treatment (i.e. before reinduction I, ~14 weeks post remission induction).
5. Re-emergence of leukemic lymphoblasts by MRD (at any level) in patients previously MRD negative.
6. Persistently detectable MRD at lower levels.
7. Early T-cell precursor (ETP) ALL, defined by lack of expression of CD1a and CD8 and low or absent expression of CD5 together with aberrant expression of myeloid and hematopoietic stem cell markers (such as CD13, CD33, CD34 and CD117).

兒癌-急性淋巴性白血病

高雄榮民總醫院
臨床診療指引　2019年第一版

Criteria for ETP

Classification of ETP-ALL requires the following criteria:
Criteria 1.　Unequivocal diagnosis of T-ALL as defined by:
CD3-positive (surface, or cytoplasmic only)
CD7-positive
Myeloperoxidase (MPO)-negative

Criteria 2.
CD1a-negative AND　CD8-negative

Criteria 3.
Dim CD5.
Definition of "dim": mean fluorescence intensity (MFI) at least 10-fold lower than that of normal T lymphocytes (use residual normal T cells in the sample to calculate) AND/OR <75% CD5-positive blasts

Criteria 4.
Expression of stem-cell associated antigens (CD34, CD133, CD117 and/or HLA-Dr) AND/OR expression of myeloid-associated antigens (CD13, CD33, CD15 and/or CD11b). Positivity with any one of these markers is sufficient.

ALL 4 CRITERIA MUST BE MET TO DEFINE ETP-ALL

[Dr. D-C Liang personal communication with Dr. Campana]

Treatment Plans

◎Induction (6-7weeks)

Induction treatment will begin with prednisone, vincristine, epirubicin, L-asparaginase and triple intrathecal treatment, followed by cyclophosphamide plus cytarabine plus mercaptopurine**. Epirubicin may be delayed in patients with febrile neutropenia, evidence of mucositis or increased hyperbilirubinemia (i.e., total bilirubin 2.0 mg/dl and direct bilirubin > 1.4 mg/dl). Patients with mucositis should be evaluated for herpes simplex infection and treated with acyclovir if work-up is positive.**

[Addendum, 6/2017, Dr. D-C Liang];
It is a good practice to give steroids in patients with large leukemic burden (WBC>100,000;large organs especially mediastinum) to reduce the risk of massive tumor lysis syndrome. Theuse of steroids is limited to 1-3 days.
However, for our MRD-oriented protocol, earlier use of steroids before combination chemotherapy could, on the other hand, not be used..

兒癌-急性淋巴性白血病

高雄榮民總醫院
臨床診療指引　2019年第一版

Treatment Plans

◎Induction (6-7weeks)

Drug	Dosages and Routes	Doses	Schedule (Day)
Prednisolone ‡	40 mg/m^2/d P0 (tid)	84	1-28 (28 days) Tapering in 1 week
Dexamethasone (for ETP immunophenotype)	10 mg/m^2/day PO (divided t.i.d.)	63	Days 1-21
		9	Days 22-24
	4 mg/m^2/day PO (divided t.i.d)		
		12	Days 25-28
	2 mg/m^2/day PO(divided t.i.d)		
Zantac (only for induction; may not be given in infant ALL)			
Vincristine	1.5 mg/m^2 (maximum 2 mg)	4	1, 8, 15, 22
Epirubicin	20 mg/m^2	2	1, 8*
L-asparaginase	6,000 U/m^2 IM **	6	3, 5, 7, 10, 12, 14
TIT	The first TIT is at the disappearance of blast from PB, no later than Day 10. Subsequent TITs depend on CSF finding and risk group.		

兒癌-急性淋巴性白血病

高雄榮民總醫院
臨床診療指引　2019年第一版

Treatment Plans

◎Induction (6-7weeks)

Further treatment is based on the result of MRD on day 15

Part I, For B-precursor ALL

If Day 15, MRD < 1%			
L-asparaginase		3	17, 19, 21
If Day 15, MRD ≥ 1% and < 5%			
L-asparaginase		6	17, 19, 21, 24, 26, 28
Cyclophosphmide	1000mg/m^2 IV 6 hrs	1	22†
Cytarabine	75mg/m^2/dose IV 30 mins	8	Days 23-26, 30-33†
6-mercaptopurine	60mg/m^2/dose	14	Days 22-35†
Dasatinib (*Ph*+)§	60mg/m^2/day	Daily	Starting Day 15 of induction to continue until end of treatment
If Day 15, MRD ≥ 5%			
L-asparaginase		6	17, 19, 21, 24, 26, 28
Cyclophosphamide	300mg/m^2 IV 1 hr	4	q12 hrs on Days 22-23†
Cytarabine	75mg/m^2/dose IV 30 mins	8	Days 23-26, 30-33†
6-mercaptopurine	60mg/m^2/dose	14	Days 22-35†
Dasatinib (*Ph*+)§	60mg/m^2	Daily	Starting Day 15 of induction to continue until end of treatment

兒癌-急性淋巴性白血病

高雄榮民總醫院
臨床診療指引　2019年第一版

Treatment Plans

◎Induction (6-7weeks)

Part II, For T-ALL

II-A. For non-ETP

If Day 15, MRD <1%

L-asparaginase		6	Days 17, 19, 21, 24, 26, 28
Cyclophosphmide	1,000mg/m^2 IV 6 hrs	1	Days 22†
Cytarabine	75mg/m^2/dose IV 30 mins	8	Days 23-26, 30-33†
6-mercaptopurine	60mg/m^2/dose	14	Days 22-35†
TIT, QW		2	Total 4 doses during induction

If Day 15, MRD ≥1%

L-asparaginase		6	Days 17, 19, 21, 24, 26, 28
Cyclophosphmide	1,000mg/m^2 IV 6 hrs	2	Days 22, 49†
Cytarabine	75mg/m^2/dose IV 30 mins	16	Days 23-26, 30-33, 37-40, 44-47†
6-mercaptopurine	60mg/m^2/dose	28	Days 22-49†
TIT, QW		2	Total 4 doses during induction

II-B. For ETP (for all MRD data)

L-asparaginase		6	Days 17, 19, 21, 24, 26, 28
Cyclophosphmide	1,000mg/m^2 IV 6 hrs	2	Days 22, 49†
Cytarabine	75mg/m^2/dose IV 30 mins	16	Days 23-26, 30-33, 37-40, 44-47†
6-mercaptopurine	60mg/m^2/dose	28	Days 22-49†
TIT, QW		2	Total 4 doses during induction

兒癌-急性淋巴性白血病

高雄榮民總醫院
臨床診療指引　2019年第一版

Treatment Plans

◎Induction (6-7weeks)

* Day 8 dose may not be given or be delayed in apparent standard-risk patients with clearance of blasts and leukopenia.

** No special concern of risk of bleeding; IM irrespective of platelet count.

§ May be given to cases with other genetic abnormalities such as *EBF1-PDGFRBor NUP214-ABL1(BCR-ABL1-like ALL)*

‡ Oral prednisone can be substituted with methylprednisolone at 40 mg/m2/day IV (t.i.d.) for patients who cannot tolerate the oral medication

†May be delayed for 3 to 7 days if Day 22 WBC<1000 and Day 22 APC<300and the last few doses of cytarabine and 6-mercaptopurine may be omitted if the patient develops infection with leukopenia and/or neutropenia.

-To avoid dry tap of bone marrow aspiration on day 1 and day 15, No. 16 of BMA needle is recommend.

兒癌-急性淋巴性白血病

高雄榮民總醫院
臨床診療指引　2019年第一版

Treatment Plans

◎Induction (6-7weeks)

For infant with *MLL+*

Agent	Dosage and Route	Doses	Schedule
Clofarabine	25 mg/m^2/day, 2-hour IV infusion	5	Days 22-26
Etoposide	100 mg/m^2/day, 2-hour IV infusion	5	Days 22-26
Cyclophosphamide	300 mg/m^2/day, 1-hour IV infusion	5	Days 22-26

Day 22 Vincristine will be omitted for infants with MLL+

Treatment Plans

◎Induction (6-7weeks)

a. No dose modifications are planned for prednisolone, asparaginase, or epirubicin therapies during induction.Only acute hemorrhagic pancreatitis or severe coagulopathy resulting in stroke syndrome warrants discontinuation of asparaginase.In the case of mild hypersensitivity reactions (e.g., facial flushing or urticaria) to asparaginase, patients will be premedicated with diphenhydramine before the next dose. If the hypersensitivity reactions recur or there is an anaphylactic reaction, patients may switch to the Erwinia preparation(at 20,000 U/m2three times a week). If it is not possible to obtain Erwinia-asparaginase, no further asparaginase treatment will be administered.

b. Dose Adjustment for infants: With the exception of vincristine and prednisolone, all dosages given to infants (< 1 year) will be based on body surface area. 2/3, 3/4, 4/4 dose based on body surface will be given for age <6, 6-12, and >12 months, respectively (As TPOG-ALL-2002 protocol). For infants <1 month of age, or for infants <3 months of age born significantly prematurely (gestational age <32 weeks), a 50% reduction in dosages of clofarabine, epirubicin, asparaginase, etoposide, methotrexate, mercaptopurine, cyclophosphamide, and cytarabine should be made. The vincristine dosage for patients <12 months of age or <10 kg weight is 0.05 mg/kg/dose. Since the dose of prednisolone in TPOG-ALL-2013 is only 40 mg/m2/day, the dose will base on body surface without reduction. [Addendum, 6/2017, Dr. D-C Liang]

Treatment Plans

◎Induction (6-7weeks)

c. Mild vincristine toxicity (jaw pain, constipation, decreased deep tendon reflexes) is anticipated. Only stroke-like syndrome or a motor paralysis warrants discontinuation of this drug. If persistent, severe abdominal cramps or gait impairment develop, the dose will be reduced to 1 mg/m2. The use of azole compound (such as fluconazole, itraconazole, voriconazole), azithromycin or erythromycin may increase the toxicities of vincristine by inhibiting cytochrome P450; these drugs should be stopped one day or more before vincristine treatment.

d. On day 1, epirubicin may be delayed in patients with total bilirubin 2.0 mg/dl and direct bilirubin >1.4 mg/dl. Omit this dose of epirubicin if total bilirubin is still 2 mg/dl and direct bilirubin >1.4 mg/dl on day 8. Epirubicin may be given as soon as hyperbilirubinemia has resolved.The second dose of epirubicin on day 8 may be delayed in standard-risk patient who has cleared circulating blasts and has severe neutropenia, or in any risk group patient who is sick with infection. The second dose of epirubicin may be omitted in standard-risk patient if needed.

Treatment Plans

◎Induction (6-7weeks)

e. Trimethoprim (150 mg/m2/day) plus sulfamethoxazole (750 mg/m2/day) (TMP-SMZ) to prevent Pneumocystis carinii pneumoniawill be given to all patients daily in two divided doses starting on day 15, if prophylactic antibiotics are not given. After CR is achieved, TMP-SMZ will be given on Monday, Wednesday and Friday until 1month after cessation of treatment. Adverse reactions to TMP-SMZ: For patients with rash, neutropenia, fever and other reactions presumed due to TMP-SMZ, withhold drug until reaction resolved.Do not re-challenge patients with severe exfoliative dermatitis (Stevens-Johnson syndrome), anaphylaxis or urticaria. If adverse reactionrecurs, change Pneumocystis carinii pneumonia prophylaxis to pentamidine (preferable), or atovaquone.

f. Bone Marrow Evaluations

A. Day 15 (or between D15 and day 19 if bone marrow procedure cannot be performed on holiday) A bone marrow aspirate will be done on day 15 of remission induction to assess antileukemic response.

Treatment Plans

◎Induction (6-7weeks)

1). For B-precursor ALL

The presence of 1% of leukemic blasts in the bone marrow by morphologic exam or by MRD study is an indication for 3 additional doses of L-asparaginase to be administered between days 24 and 28

Patients with the presence of 1% leukemic blasts in the bone marrow on day 15 receive cyclophosphamide, mercaptupurine, and cytarabine as scheduled if their clinical condition permits, regardless of their ANC. For other patients, the treatment may be delayed for 3 to 7 days to allow some degree of hematopoietic recovery if APC (ANC + monocyte) < 300/mm3.

2). For T-ALL: 依P5之分群方式

B. End of Induction-MRD response

[Addendum, 5/25/2018, Dr. H-C Liu]

1).For all B-precursor ALL; T-ALL treated with 1 course of Cyclo/ara-C: A bone marrow aspirate will be performed on day 35-42 of remission induction, depending on when ANC has recovered to >300/mm3, or APC to ≥500/mm3, WBC to >1,000/mm3, and platelet count to >50,000/ mm3.

Treatment Plans

◎Induction (6-7weeks)

2). For T-ALL treated with 2 curses of Cyclo/ara-C, two MRD levels are required:
a). MRD on D35-D38*: 第1次Cyclo/ara-C結束後†
b). MRD at the end of induction: D51-D56†

†Depending on when the following recommended count recoveries are seen: ANC>300/mm3 or APC to ≥500/mm3, WBC to ≥1,000/mm3.

*Notes: 雖然目前此MRD time points的結果並沒有相對應的調整策略，但仍請進行送檢，以做為日後分析及調整治療的重要依據。

For 1) and 2), if the date falls on a week-end or holiday, the procedure may be performed on closest working day. MRD level will be determined in this bone marrow sample. Poor response will be defined as MRD level 0.01% (one or more lymphoblasts among 104 bone marrow mononuclear cells) by either immunologic or molecular assay. If the result of MRD is positive, provisional standard-risk cases will then be re-classified as high-risk (MRD 0.01% but less than 1%) or very high-risk (MRD 1%), and will receive subsequent 3 doses of HDMTX at a higher dosage (i.e., 5 gm/m2). (These patients would have received the first HDMTX of consolidation therapy at 2.5 gm/m2.)

Treatment Plans

◎Induction (6-7weeks)

g. Transfusion Guidelines

A. Bleeding is generally not a problem during induction treatment (after asparaginase treatment); therefore platelet transfusion is usually not necessary in them even though they may have thrombocytopenia, unless thereis fever or mucositis.

B. There is no need to measure coagulation status during remission induction (after asparaginase treatment) because coagulopathy is expected. Unless there is bleeding complication, fibrinogen preparation or cryoprecipitate should be avoided because they can enhance the risk of thrombosis caused by asparaginase and prednisone.Note that fresh frozen plasma can supply asparagine to leukemic cells and should also be avoided.

Treatment Plans

◎IT ChemotherapyDuring Induction Treatment

As a traumatic lumbar puncture at diagnosis may result in a poorer outcome and the need for extra intrathecal therapy subsequently, all diagnostic lumbar punctures will be performed by experienced personnel, preferably under general anesthesia or deep sedation. Triple intrathecal chemotherapy (MHA) will be administered immediately after cerebrospinal fluid is collected at the disappearance of blast from PB, no later than D10.The dosage is age-dependent as following

TIT is used with dosages based on age as follows:

Age (months)	Methotrexate (mg)	Hydrocortisone (mg)	Ara-C (mg)	Volume (ml)
<12	6	12	18	6
12-23	8	16	24	8
24-35	10	20	30	10
≥ 36	12	24	36	12

Treatment Plans

◎IT ChemotherapyDuring Induction Treatment

Frequency and total number of triple intrathecal treatments for Remission Induction is based on the patient's risk of CNS relapse, as follows:

1.All patients will receive triple intrathecal treatment at the disappearance of blast from PB, no later than D10.It is suggestedto perform the 2ndTIT with bone marrow evaluation on D15.

2.Patients with any of the following features will receive totally 4 weekly TIT during induction therapy:

*Philadelphia chromosome
**MLL rearrangement*
*Hypodiploidy (< 44)
*WBC >100,000/mm3 at presentation
*T-cell ALL
*t (1;19)/*E2A-PBX1*

Treatment Plans

◎IT ChemotherapyDuring Induction Treatment

3.Patients with any of the following features will receive TIT twice a week for 2 weeks followed by weekly TIT for 2 weeks (totally 6 TIT during induction therapy):
*CNS-2 status (<5 WBC/μL of CSF with blasts)
*CNS-3 status (>5 WBC/μL of CSF with blasts or cranial nerve palsy) Traumatic lumbar puncture with blasts

Leucovorin rescue (5 mg/m2/dose, max 5 mg) PO will be given at 24 and 30 hours after each triple intrathecal treatment during induction.
Follow plasma methotrexate levels (starting 24 hours after intrathecal therapy and until level becomes undetectable) in patients with renal dysfunction or extra fluid in third space, and rescue with leucovorin.

It is also important to correct hypertension and to prevent constipation during remission induction because patients with these features are at high risk of seizure (posterior reversible encephalopathy syndrome). Avoid syndrome of inappropriate antidiuretic hormone secretion from vincristine treatment.

Treatment Plans

◎ Consolidation Treatment(8 weeks)

When WBC >1500/mm3, ANC >300/mm3, platelet count >50,000/mm3, and renal function is normal, consolidation treatment will be started.

Drug Dosages

VHR, HR	SR
MTX 5 gm/m^2 IV drip D1, 15, 29, 43	MTX 2.5 gm/m^2 IV drip D1, 15, 29, 43
6-MP 40 mg/m^2/day D1-56	6-MP 40 mg/m^2/day D1-56
TIT D1, 15, 29, 43 (8-12 hrs before HDMTX)	TIT D1, 15, 29, 43 (8-12 hrs before HDMTX)

The subsequent dose of HDMTX, 6-MP and IT will be delayed if WBC <1,000/mm3, ANC < 300/mm3, platelet count <50,000/mm3, SGPT >500U/L, total bilirubin >2 mg/dl and direct bilirubin >1.4 mg/dl, mucositis is present, or renal function is abnormal.

Treatment Plans

◎ Consolidation Treatment(8 weeks)

Pre-hydration

At least two hours before high dose methotrexate, prehydration IV fluid (D5W + 40 mEq NaHCO3/L + 20 mEq KCl/L) will be administered at the rate of 200 ml/m2/hr. At start of prehydration, one IV dose of NaHCO3 (unless otherwise clinically indicated, 12 mEq/m2 for standard-risk patients and 25 mEq/m2 for high-/very high-risk patients) diluted in 50 ml D5W will be given over 15 minutes. Prehydration fluid may also be given overnight at a rate of at least 100 ml/m2/hr, especially in patients who had delayed clearance with prior course. High dose methotrexate treatment will follow, provided that urinary pH is >6.5; exceptions must be cleared with the pharmacokinetics service and the attending physician.

High Dose Methotrexate Infusion

Methotrexate loading dose will be given over 1 hour, followed immediately by maintenance infusion over 23 hours. During the methotrexate infusion, patients should receive hydration fluid with D5W + 40 mEq/L NaHCO3 + 20 mEq KCl/L at 100-150 ml/m2/hr. Urine PH will be monitored with each void during infusion. An IV bolus of 12 mEq/m2 NaHCO3 will be given if urine pH is 6.0; and 25 mEq/m2 will be given if urine pH is <6.0. Acetazolamide 500 mg/m2 orally every 6 to 8 hours may be used if systemic alkalosis limits the administration of bicarbonate for urinary alkalinization. Patients with evidence of renal dysfunction or delayed clearance during the methotrexate infusion may receive less than a 24 hour methotrexate infusion.

Treatment Plans

◎ Consolidation Treatment(8 weeks)

Leucovorin rescue

Leucovorin, 15 mg/m2 (IV or PO) for high-/very high-risk or 10 mg/m2 (PO or IV) for standard-risk cases, will be started at 42 hours after the start of methotrexate and repeated every 6 hours for a total of three doses. The dosage of leucovorin will be increased in patients with high plasma methotrexate concentrations (>1.0μM at 42 hours) and continued until the methotrexate concentration is less than 0.10μM. Additional measures, such as hydration, hemoperfusion, or carboxypeptidase will be considered in patients with 42-hour methotrexate levels > 10μM. Patients with a history of delayed Grade 3 or 4 gastrointestinal toxicity with prior methotrexate or a history of typhlitis with any chemotherapy should have leucovorin continue for 5, rather than 3 doses; those with early toxicity should have leucovorin begin at 36 hours with subsequent methotrexate; if toxicity recurs, the baseline leucovorin dosage should also be increased.

Blood counts should be followed after high-dose methotrexate twice weekly; 6-MP dose should be reduced to half dose (20 mg/m2/day) if WBC is between 1000 to 1500/mm3, and should be held if WBC is less than 1000/mm3.

Avoid the use of concomitant Bactrim or penicillin during high-dose methotrexate treatment because they will delay methotrexate clearance.

*Alternatively, monitoring of MTX levels (starting at 30 hrs) and leucovorin rescue regimen can follow the guidelines of TPOG-ALL-2002 Protocol. Please give adequate prehydration and bolus NaHCO3 before the infusion of high-dose MTX.

Treatment Plans

◎ **REINTENSIFICATION TREATMENT** (for Very High-Risk ALL)

Patients with very high-risk leukemia may receive reintensification therapy and then will be offered the option of transplant. This treatment will attempt to maximize leukemic cell kill before allogeneic hematopoietic stem cell transplantation (HSCT). For patients with Philadelphia chromosome positive ALL and positive MRD at the end of induction, ETP T-ALL, and those with induction failure or 1% leukemic lymphoblasts (determined by MRD study) in bone marrow at the end of remission induction (with the exception of hyperdiploid (51-68) and *TEL-AML1 cases who should have positive MRD after consolidation therapy), treatment will be given after consolidation therapy. However, consolidation therapy may be shortened, depending on patient's response to therapy and on the timing of transplantation.* For patients with 0.1% leukemic lymphoblasts (determined by MRD study) in bone marrow in week 7 of continuation treatment, this treatment will be given after the reinduction I. Upon marrow recovery (i.e., ANC 300/mm3, WBC 1000/mm3 and platelet count 50,000/mm3) after each course of reintensification, bone marrow examination with MRD study will be repeated.

Treatment Plans

◎ **REINTENSIFICATION TREATMENT** (for Very High-Risk ALL)

This treatment course may be repeated only once if the patient still has persistently positive MRD (i.e. ≧ 0.01% blasts). Allogeneic hematopoietic stem cell transplantation may proceed after 1 course of the treatment if MRD becomes negative with the first course of treatment; otherwise, transplant will be performed after two courses of treatment. Patients deemed unsuitable for the transplant or who decline the procedure or whose donor has yet to be identified, will remain on study and receive subsequent chemotherapy as scheduled. The treatment scheme and dosage of chemotherapy are summarized below.

Agent	Dosage and Route	Doses	Schedule
Dexamethasone	20 mg/m^2/day PO or IV (divided t.i.d)	18	Days 1-6
Cytarabine	2 grams/m^2, 3-hour IV infusion every 12 hours	4	Days 1-2
Etoposide	100 mg/m^2, 1-hour IV infusion every 12 hours	5	Days 3-5
TIT		1	Day 5
L-asparaginase	25,000iu/m^2 IM	1	Day 6

Treatment Plans

◎ REINTENSIFICATION TREATMENT (for Very High-Risk ALL)

Patients with suboptimal response to reintensification may receive one to two cycles of clofarabine/cyclophosphamide/etoposide/dexamethasone:

Agent	Dosage and Route	Doses	Schedule
Clofarabine	25 mg/m^2/day, 2-hour IV infusion	5	Days 1-5
Etoposide	100 mg/m^2/day, 2-hour IV infusion	5	Days 1-5
Cyclophosphamide	300 mg/m^2/day, 30-60 minute IV infusion	5	Days 1-5
Dexamethasone	8 mg/m^2/day (divided t.i.d)	15	Days 1-5

Treatment Plans

◎ Continuation Treatment (120 weeks)

Post-remission continuation treatment begins after the completion of consolidation, provided that the ANC≧300/mm3, WBC≧1500/mm3 and platelet count≧ 50,000/mm3 as well as no evidence of mucositis. Continuation treatment (120 weeks) differsaccording to the risk classification, as follows (abbreviations as defined below).

兒癌-急性淋巴性白血病

高雄榮民總醫院
臨床診療指引　2019年第一版

Treatment Plans

◎ Continuation Treatment (120 weeks)

Treatment (Weeks 1 to 20)

Week	VHR/HR	SR
1	DEX + EPI + VCR + 6MP + ASP§	6MP + DEX + VCR
2	6MP + ASP	6MP + MTX
3	#6MP + ASP	*6MP + MTX
4	DEX + EPI + VCR + 6MP + ASP	6MP + DEX + VCR
5	6MP + ASP	6MP + MTX
6	6MP + ASP	6MP + MTX
7	*†(Reind I)DEXx8d+VCR+EPI+ ASPx3	*(Reind)DEXx8d+VCR+EPI+ ASPx3
8	(Reind I) VCR+EPI+ASPx3	(Reind) VCR+ASPx3
9	(Reind I)DEXx7d+VCR+ASPx3	(Reind)DEXx7d+VCR+ASPx3
10	6MP + ASP	6MP + MTX
11	EPI + VCR + 6MP + ASP	6MP + MTX
12	*6MP + ASP	* 6MP + MTX
13	6MP + ASP	6MP + MTX
14	DEX + EPI + VCR + 6MP + ASP	6MP + DEX + VCR
15	6MP + ASP	6MP + MTX
16	6MP + ASP	6MP+ MTX
17	*†(Reind II)DEXx8d+VCR+ASPx3	*6MP + DEX + VCR
18	(Reind II) VCR+ ASPx3	6MP + MTX
19	(Reind II)DEXx7d+VCR+ASPx3	6MP + MTX
20	6MP + MTX	6MP + DEX + VCR

Treatment Plans

◎ Continuation Treatment (120 weeks)

§First dose of ASP given at day 3 (after 2 days of DEX) to reduce the risk of ASP allergy.

#Triple intrathecal treatment will be given to other standard/high-risk cases with WBC ≥100,000/mm3, T-cell ALL, presence of Philadelphia chromosome, *MLL rearrangement, t (1;19)/E2A-PBX1, hypodiploidy <44, or CNS-3 status, with CNS-2 or traumatic lumbar puncture with blasts at diagnosis..*

*IT MHA (methotrexate + hydrocortisone + cytarabine)

† MRD study before each reinduction therapy will be done in patients with positive MRD at end of remission induction. Bone marrow sample will be used in B-lineage All and blood sample can be used for T-lineage ALL.

Patients with MRD ≥0.1% at week 7 receive reintensification treatment after Reinduction I Dexamethasone, vincristine and L-asparaginase can be given regardless of blood counts, provided that the patient is not sick. Methotrexate, mercaptopurine and epirubicin will be held if ANC <300/mm3, APC<500/mm3, WBC <1,000/mm3, or platelet count <50,000/mm3.

(‡) Continue Dasatinib in cases with Ph, EBF1-PDGFRB or NUP214-ABL1

Treatment Plans

◎ Continuation Treatment (120 weeks)

Drug dosages, schedules and routes for continuation therapy weeks 1 to 6 and 10 to 16

DEX (dexamethasone)	12 mg/m2(VHR/HR) or 8 mg/m2(SR) POdaily (tid) x 5 days, Days 1-5
EPI (epirubicin)	30 mg/m2IV, Day 1
VCR (vincristine)	2.0 mg/m2IV push (max. 2 mg), Day 1 (0.05 mg/kg for patients < 1 year of age or < 10kg in weight)
6MP (6-mercaptopurine)	40 mg/m2PO h.s.daily x 7 days (VHR/ HR), Days 1-7 50 mg/m2PO h.s. daily x 7 days (SR), Days 1-7
ASP (L-asparaginase)	10,000 U/m2 IM, Day 1
MTX (methotrexate)	40 mg/m2IV or IM, Day 1

Treatment Plans

◎ **Continuation Treatment (120 weeks)**

REINDUCTION TREATMENT

This phase of treatment will be started at weeks 7 and/or 17 if patients have ANC 500/mm3, WBC 1500/mm3, and platelet count 50,000/mm3.

Intrathecal treatment will be followed by leucovorin rescue (5 mg/m2/dose PO, max 5 mg) at 24 and 30 hours **only in patients with prior CNS toxicities or in patients with WBC < 1500/mm3, or ANC < 500/mm3**

Reinduction I for VHR/HR ALL excluding infant with *MLL*+(3 weeks)

Agents	Dosages and routes	# Doses	Schedules
Dexamethasone	12 mg/m^2/day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m^2/week IV (max 2 mg)	3	Days 1, 8, 15
Epirubicin	30 mg/m^2	2	Days 1,8
L-asparaginase	6,000 U/m^2/thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14,17,19,21
Methotrexate + hydrocortisone + ara-C	Age-dependent, IT	1	Day 1

Treatment Plans

◎ Continuation Treatment (120 weeks)

Reinduction II for VHR/HR ALL including infant with *MLL*+ (3 weeks)

Agents	Dosages and routes	# Doses	Schedules
Dexamethasone	12 mg/m^2/day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m^2/week IV (max 2 mg)	3	Days 1, 8, 15
L-asparaginase	6,000 U/m^2/thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14,17,19,21
Methotrexate + hydrocortisone + ara-C	Age-dependent, IT	1	Day 1

Reinduction for SR ALL (3 weeks)

Agents	Dosages and routes	Doses	Schedules
Dexamethasone	10 mg/m^2/day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m^2/week IV (max 2 mg)	3	Days 1, 8, 15
L-asparaginase	6,000 U/m^2 thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14,17,19,21
Epirubicin	30 mg/m^2/week IV	1	Day 1
Methotrexate + hydrocortisone + ara-C	Age-dependent, IT	1	Day 1

Treatment Plans

◎ Continuation Treatment (120 weeks)

Reinduction I for infant with *MLL*+

Agent	Dosage and Route	Doses	Schedule
Dexamethasone	8 mg/m^2/day (divided t.i.d)	45	Days 1-8; Days 15-21
Clofarabine	25 mg/m^2/day, 2-hour IV infusion	5	Days 1-5
Etoposide	100 mg/m^2/day, 2-hour IV infusion	5	Days 1-5
Cyclophosphamide	300 mg/m^2/day, 1-hour IV infusion	5	Days 1-5
L-asparaginase	6,000 U/m^2 thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
Methotrexate + hydrocortisone + ara-C	Age-dependent, IT	1	Day 1

Treatment Plans

◎ Continuation Treatment (120 weeks)

Dose Adjustment for infants: With the exception of vincristine and prednisolone, all dosages given to infants (< 1 year) will be based on body surface area. 2/3, 3/4, 4/4 dose based on body surface will be given for age <6, 6-12, and >12 months, respectively (As TPOG-ALL-2002 protocol). For infants <1 month of age, or for infants <3 months of age born significantly prematurely (gestational age <32 weeks), a 50% reduction in dosages of clofarabine, epirubicin, asparaginase, etoposide, methotrexate, mercaptopurine, cyclophosphamide, and cytarabine should be made. The vincristine dosage for patients <12 months of age or <10 kg weight is 0.05 mg/kg/dose. Since the dose of prednisolone in TPOG-ALL-2013 is only 40 mg/m2/day, the dose will base on body surface without reduction. [Addendum, 6/2017, Dr. D-C Liang]

Treatment Plans

◎ Continuation Treatment (120 weeks)

Treatment (weeks 21 to end of therapy)

Week	HR	SR
21	6MP + MTX	6MP + MTX
22	6MP + MTX	6MP + MTX
23	Cyclo + Ara-C	6MP + MTX
24	*DEX + VCR	*6MP + DEX + VCR
25	6MP + MTX	6MP + MTX
26	6MP + MTX	6MP + MTX
27	Cyclo + Ara-C	6MP + MTX
28	*DEX + VCR	(*)6MP + DEX + VCR

*TIT

(*)IT MHA for standard-risk cases, *TEL-AML1 fusion and hyperdiploidy (51-68) with WBC > 100,000/mm3, CNS-2 or traumatic lumbar puncture with blast.*

Treatment Plans

◎ Continuation Treatment (120 weeks)

Drug Dosages, Schedules and Routes for Continuation Therapy from Week 21 to End of Therapy

6MP (6-mercaptopurine)	60 mg/m2PO h.s. daily x 7 days, Days 1-7
MTX (methotrexate)	40 mg/m2IV or IM(or PO, if parenteral route is not feasible), Day 1
Cyclo (Cyclophosphamide)	300 mg/m2IV, Day 1 (VHR/HR)
Ara-C (Cytarabine)	300 mg/m2IV, Day 1 (VHR/HR)
DEX (dexamethasone)	12 mg/m2(VHR/HR) or 8 mg/m2(SR) PO daily (tid) x 5, Day 1-5
VCR (vincristine)	2.0 mg/m2IV push (max. 2 mg), Day 1

Treatment Plans

◎ Continuation Treatment (120 weeks)

The same treatment (weeks 21-28) will be repeated for a total of 6 times (until week 68). After week 68, cyclophosphamide and cytarabine will be replaced by daily 6MP and methotrexate; all patients will then receive daily 6MP and weekly MTX with pulses of dexamethasone and vincristine every 4 weeks until week 100, after which only 6MP and methotrexate will be given.

Cyclophosphamide and cytarabine dosages may need to be reduced by 33% to 50% in patients who repeatedly have very low counts (WBC < 1000/mm3 or ANC < 300/mm3 or platelets < 50,000/mm3) one to two weeks later.

Dexamethasone dose decreases to 6 mg/m2 beginning week 68.

Continuation therapy will be discontinued after 120 weeks.

Treatment Plans

◎ IT Chemotherapy During Continuation Treatment

-Triple intrathecal treatment will be given toSR cases with CNS-1 status (no identifiable blasts in CSF)on weeks 3, 7, 12, 17, 24, 32, 40, and 48. (14 times)
-Triple intrathecal treatment will be given to SR cases with CNS-2 or traumatic CSF with blasts statuson weeks 3, 7, 12, 17, 24, 28, 32, 36, 40, 44 and 48. (19 times)
-Triple intrathecal treatment will be given to HR caseswith CNS-1 status on weeks 7, 12, 17, 24, 28, 32, 36, 40, 44 and 48. (16Times)
-Triple intrathecal treatment will be given to other high/very high-risk cases with WBC ≧100,000/mm3 at presentation, , T-cell ALL, t (1;19)/E2A-PBX1,presence of Philadelphia chromosome, MLL rearrangement, hypodiploidy <44, CNS-2 or CNS-3 status, or traumatic lumbar puncture with blasts on weeks 3, 7, 12, 17, 24, 28, 32,36, 40, 44, 48, 56, 64, 72, 80, 88 and 96. (25Times)

Treatment Plans

◎ IT Chemotherapy During Continuation Treatment

Leucovorin will not be given after intrathecal treatment during continuation treatment unless the patient has an adverse reaction with previous intrathecal or methotrexate treatment, e.g., seizure or encephalopathy, has renal dysfunction resulting in high plasma methotrexate concentration, or has Down syndrome. Leucovorin may be given when patient is neutropenic, at treating physician's discretion; however, it is generally preferable to delay intrathecal therapy if patient has neutropenia. Down syndrome patients will receive leucovorin with every LPIT.

Note that WBC and ANC counts should be double a week following dexamethasone pulse therapy. If WBC or ANC counts fail to double (indicating low bone marrow reserve), 6-MP and MTX dosages should be reduced to half. If WBC or ANC remains the same or is lower, 6-MP and MTX should be held because the patient is at high risk of infection, and blood counts should be repeated in 3 to 4 days to decide if 6-MP can be resumed. Patients 10 years of age or old are at especially high risk of sepsis. If patient has abdominal pain, typhlitis must be excluded and antibiotics may be started even if the patient has no fever.

兒癌-急性淋巴性白血病

高雄榮民總醫院
臨床診療指引　2019年第一版

癌症藥物停藥準則

骨髓及血液檢查，腫瘤有復發或變大情況，應停止或改變治療方式。

Reference

*TPOG-ALL2013, rev.2018.5.25 47 PROTOCOLS FOR CHILDHOODACUTE LYMPHOBLASTIC LEUKEMIA FOR CHILDHOOD CANCER FOUNDATION OF TAIWAN BY TAIWAN PEDIATRIC ONCOLOGY GROUP, 2018.5.25

1. Nachman JB, Sather HN, Sensel MG et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. N.Engl.J.Med. 1998;338:1663-1671.
2. Silverman LB, Gelber RD, Dalton VK et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood 2001;97:1211-1218.
3. Vora A, Mitchell CD, Lennard L et al. Toxicity and efficacy of 6-thioguanine versus 6- mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. Lancet 2006;368:1339-1348.
4. Mitchell CD, Richards SM, Kinsey SE et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. Br.J.Haematol. 2005;129:734-745.
5. Bostrom BC, Sensel MR, Sather HN et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. Blood 2003;101:3809-3817.
6. Matloub Y, Lindemulder S, Gaynon PS et al. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with intrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. Blood 2006;108:1165-1173.
7. Pinheiro JP, Boos J. The best way to use asparaginase in childhood acute lymphatic leukaemia--still to be defined? Br.J.Haematol. 2004;125:117-127.
8. Wetzler M, Sanford BL, Kurtzberg J et al. Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: Cancer and Leukemia Group B Study 9511. Blood 2007;109:4164-4167.
9. Hijiya N, Franklin J, Rytting M et al. A phase I study of clofarabine in combination with cyclophosphamide and etoposide: A new regimen in pediatric patients with refractory or relapsed acute leukemia. ASCO Meeting Abstracts 2007;25:9529.
10. Flotho C, Coustan-Smith E, Pei D et al. Genes contributing to minimal residual disease in childhood acute lymphoblastic leukemia: prognostic significance of CASP8AP2. Blood 2006;108:1050-1057.
11. Flotho C, Coustan-Smith E, Pei D et al. A set of genes that regulate cell proliferation predicts treatment outcome in childhood acute lymphoblastic leukemia. Blood 2007;110:1271-1277.
12. Flotho C, Coustan-Smith E, Pei D et al. Genes contributing to minimal residual disease in childhood acute lymphoblastic leukemia: prognostic significance of CASP8AP2. Blood 2006;108:1050-1057.
13. Holleman A, Cheok MH, den Boer ML et al. Gene-expression patterns in drug-resistant acute lymphoblastic leukemia cells and response to treatment. N.Engl.J.Med. 2004;351:533-542.
14. Lugthart S, Cheok MH, den Boer ML et al. Identification of genes associated with chemotherapy crossresistance and treatment response in childhood acute lymphoblastic leukemia. Cancer Cell 2005;7:375-386.

Reference

*TPOG-ALL2013, rev.2018.5.25 47 PROTOCOLS FOR CHILDHOODACUTE LYMPHOBLASTIC LEUKEMIA FOR CHILDHOOD CANCER FOUNDATION OF TAIWAN BY TAIWAN PEDIATRIC ONCOLOGY GROUP, 2018.5.25

15. Cheng Q, Yang W, Raimondi SC et al. Karyotypic abnormalities create discordance of germline genotype and cancer cell phenotypes. Nat.Genet. 2005;37:878-882.

16. Cheng C, Pounds SB, Boyett JM et al. Statistical significance threshold criteria for analysis of microarray gene expression data. Stat Appl.Genet.Mol.Biol. 2004;3:Article36.

17. Pounds S, Cheng C. Robust estimation of the false discovery rate. Bioinformatics. 2006;22:1979-1987.

18. Benjamini Y, Krieger AM, Yekutieli D. Adaptive linear step-up procedures that control the false discovery rate. Biometrika 2006;93:491-507.

19. Pounds S, Cheng C. Robust estimation of the false discovery rate. Bioinformatics 2006;22:1979-1987.

20. Pounds S, Cheng C. Sample size determination for the false discovery rate. Bioinformatics 2005;21:4263-4271.

21. Holleman A, Cheok MH, den Boer ML et al. Gene-expression patterns in drug-resistant acute lymphoblastic leukemia cells and response to treatment. N.Engl.J.Med. 2004;351:533-542.

22. Cheng C. Microarray gene co-expression analysis and validation by a sequential clustering algorithm [abstract]. Joint Statistical Meetings of the American Statistical Association 2007;Salt Lake City, UT:

23. De Pauw B, Walsh T, Donnelly J et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clinical Infectious Diseases 2008;46:1813-1821.

24.Manabe A, Ohara A, Hasegawa D et al. Significance of the complete clearance of peripheral blasts after 7 days of prednisolone treatment in children with acute lymphoblastic leukemia: the Tokyo Children's Cancer Study Group Study L99-15. Haematologica 2008; 93:1155-1160.

25.Kishi S, Yang W, Boureau B et al. Effects of prednisone and genetic polymorphisms on etoposide disposition in children with acute lymphoblastic leukemia. Blood 2004;103:67-72.

26. Kishi S, Griener J, Cheng C et al. Homocysteine, Pharmacogenetics, and Neurotoxicity in Children With Leukemia. J Clin Oncol 2003;21:3084-3091.

27. Blanco JG, Edick MJ, Hancock ML et al. Genetic polymorphisms in CYP3A5, CYP3A4 and NQO1 in children who developed therapy-related myeloid malignancies. Pharmacogenetics 2002;12:605-611.

28. Relling MV, Yang W, Das S et al. Pharmacogenetic Risk Factors for Osteonecrosis of the Hip Among Children With Leukemia. J Clin Oncol 2004;22:3930-3936.

29. Mullighan CG, Goorha S, Radtke I et al. Genome-wide analysis of genetic alterations in TPOG-ALL2013, rev.2018.5.25 60 acute lymphoblastic leukaemia. Nature 2007;446:758-764.