A Phase 3 multi-institutional study for treatment of children with newly diagnosed Lymphoblastic Lymphoma using a modified BFM (Berlin-Frankfurt-Munster) Backbone strategy

CCCG-LBL-2016

(A 5-year study program of CCCG lymphoma group)

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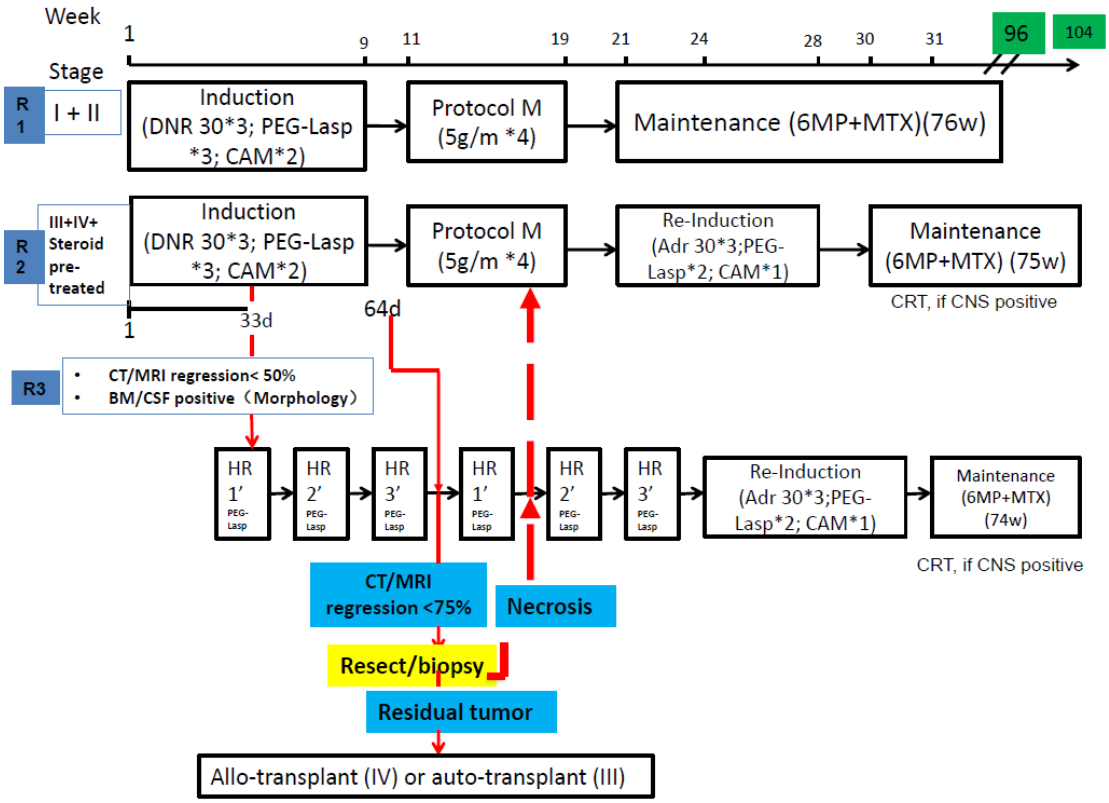
Experimental design schema: CCCG-LBL-2016



1.0 Objectives (Scientific Aims) and Background

Primary aims:

- To determine the 3-year EFS (event free survival) in all evaluable patients with newly diagnosed lymphoblastic lymphoma enrolled in the study compared with the historical study
- To describe the 3-year EFS in high-risk group

Secondary aims:

- To describe the 3-year OS (overall survival) in all evaluable patients with newly diagnosed lymphoblastic lymphoma enrolled in the study

Background

Lymphoblastic lymphoma (LBL) represents about 25%~30% of all non-Hodgkin lymphoma (NHL) cases in children worldwide. In developed countries, LBL therapy is based on acute lymphoblastic leukemia (ALL) protocols that achieve survival rates of >90% for low-stage disease and >80% for advanced-stage disease. The Chinese Children's Cancer Group (CCCG) was set up in 1997 to improve the quality of children with cancer in China. Two prior retrospective multicenter studies for LBL organized by CCCG yielded a 63% 5-year event free survival (EFS) and a 77% 2-year EFS, respectively. These survival rates are 10~20% lower than the rates reported by most medical-developed countries. We are aware of 3 issues through the previous studies: 1) Both 2 previous studies are retrospective studies; 2) Compared with the BFM backbone protocols, many treatment protocols for pediatric LBL used in China have more intensification treatment; 3) Patients who had not achieved complete remission on day 33 of induction (high risk group) had much worse EFS (Less than 30%).

The CCCG-LBL-2016 trial is a planned 5-year study. A total of 8 tertiary referral centers for childhood cancers in CCCG will participate. The BFM backbone was chosen for the following reasons: 1) The favorable results for BFM trials were achieved; 2) BFM trials for pediatric LBL are well-known in China; 3) A 55% 5-year EFS was achieved in the high-risk group in the intercontinental trial ALL IC-BFM 2002.

Besides the scientific aims, we are also willing to test the feasibility of developing prospective multicenter studies for childhood LBL in China.

2.0 Patient eligibility

2.1 General

Each center was responsible for its own data collection. A predefined set of data was collected for each patient using protocol-specific forms (EXCEL table) and sent to a coordinating center where the findings were reviewed for consistency and completeness. The data were transferred every 12 months. All 12-month reports were reviewed by each local investigator. The protocol was approved by the primary institutional ethnics committee located in Shanghai Children's Medical Center (SCMC), and written informed consent was obtained for all patients or their legal guardian in the treating hospital. All cases were reviewed by two individual pathologists based on morphological features and immunophenotypic studies. Any discordant diagnoses were reviewed by the third pathologists from the National Pathology Experts Group to reach a final consensus diagnosis.

2.2 Patient Eligibility Criteria

- Patient must be >1 year and ≤ 18 years of age with newly diagnosed biopsy-proven lymphoblastic lymphoma (LBL).
- Patients shall have had no prior cytotoxic chemotherapy with the exception of 1-week steroids (<420mg/m^2)
- Exclusion Criteria: Patients with congenital disease or primary/secondary immune compromised disease.

Risk stratification for LBL patients

Low risk group (R1)	Stage* I or II
Intermediate risk group (R2)	Stage III or IV or receiving steroids within one week prior to the diagnosis (<420mg/m^2)
High-risk group (R3)	Failure to qualify a PR, or >5% BM blasts, or with CNS disease on d33 of induction

*International Pediatric Non-Hodgkin Lymphoma Staging System

3.0 Treatment plan

3.1 CCCG-LBL-2016 Treatment protocols

Drug	Dose	Days of administration
Induction I		
Prednisone (orally)	60 mg/m^2 per day	1-28, then taper over 9 days
Vincristine (iv)	1.5 mg/m^2 per day (max 2 mg)	1，8, 15, 22
Daunorubincin (iv over 1h)	25 mg/m^2 per dose	1，8, 15, 22
PEG-LASP (im)	2000 IU/m^2 per dose	4,29,57
Cyclophosphamide (iv over 1 h)	1000 mg/m^2 per dose	36, 57
Cytarabine (iv over 30min 或皮下)	75 mg/m^2 /d	36-42, 57-63
6-Mercaptopurine (orally)	60 mg/m^2 per day	36-42, 57-63
Triple it[a]		8,15,22,29,36,57 (43[b],50[b])
Protocol M		
6-Mercaptopurine (orally)	25 mg/m^2 per day	1-56
Methotrexate[c]	5 g/m^2 per dose	1, 15, 29, 43
Triple it[a]		1, 15, 29, 43
Reinduction II		
Dexamethasone (orally)	10 mg/m^2 per day	1-7, 15-21
Vincristine (iv)	1.5 mg/m^2 per day (max 2 mg)	8, 15, 22, 29
Doxorubincin (iv over 1 h)	25 mg/m^2 per dose	8, 15, 22
PEG-LASP (im)	2,000 IU/m^2 per dose	4, 25
Cyclophosphamide (iv over 1 h)	1000 mg/m^2 per dose	36
Cytarabine (iv)	75 mg/m^2 /d	36-42,
6-Mercaptopurine (orally)	60 mg/m^2 per day	36-42
Triple it[a]		1, 36
HR 1’		
Dexamethasone(orally or iv)	20mg/m^2/d, in 3 fractions	1-5
Vincristine (iv)	1.5 mg/m^2 per day (max 2 mg)	1, 6
Methotrexate[c]	5000mg/m^2, 24hr	1
Cyclophosphamide (iv over 1 h)[d]	200mg/m^2/per dose, q12h×5, MESNA 70mg/m^2，IV，×3，0h，+4h，+8h	2-4
Cytarabine (iv over 3 hr)	2000mg/m^2/per dose，q12h×2	5
PEG-Lasp (im)	2,000 IU/m^2 per dose	6
Triple it[a]		1
HR 2’		
Dexamethasone (orally or iv)	20mg/m^2/d, PO/IV, in 3 fractions	1-5
Vindesine (iv)	3mg/m^2（MAX 5mg）	1, 6
Methotrexate[c]	5000mg/m^2, 24hr	1

Ifosfamide (iv over 1 hr) [d]	800mg/m^2/per dose, q12h×5	2-4
Daunorubicin (iv over 1 hr)	30mg/m^2/day	5
PEG-Lasp (im)	2,000 IU/m^2 per dose	6
Triple it[a]		1, 5[b]
HR 3’		
Dexamethasone (orally or iv)	20mg/m^2/d, PO/IV, in 3 fractions	1-5
Cytarabine (iv over 3 hr)	2000mg/m^2/per dose，q12h× 4	1, 2
Etoposide (iv over 2 hr)	100mg/m^2/per dose，q12h×5	3-5
PEG-Lasp	2,000 IU/m^2 per dose	6
Triple it[a]		5

iv, intravenously; im, intramuscularly; it, intrathecally; max, maximum.

[a] Doses were adjusted for children younger than 3 years.

[b] Patients with CNS disease received additional IT.

[c] A loading dose of 10% was infused over 30 minutes, the remaining 90% over 23.5 hours. Leucovorin rescue was given 15 mg/m^2 at hour 42, 48 and 54. If the MTX level at hour 42 （44） was >1.0 μmol/L, rescue was continued at 6-hour intervals until MTX levels were ≤0.3μmol/L.

[d]From Day 2 night

3.2 Dose of CCCG-LBL-2016

	Total (maintenance) wks	Systemic chemotherapy							IT N.O. *
		HDMTX (g/ m^2)	HDAra-C (g/ m^2)	DOX+DNR (mg/ m^2)	PEG-LSP (U/ m^2)	ETO (mg/ m^2)	CPM (g/ m^2)	IFOS (g/ m^2)	
R1	96 (76)	20	--	90	2000 *3	--	2	--	20
R2	104 (75)	20	--	180	2000 *5	--	3	--	22 +(3#)
R3	104 (74)	20	24	230	2000 *11	1000	5	8	22 + (5#)

i.t., intrathecally; CPM, cyclophosphamide; IFOS, ifosfamide; DOX, doxorubincin; DNR, Daunorubicin; MTX, methotrexate; Ara-C, cytarabine; ETO, etoposide; PEG-LSP, Pegaspargase; * Doses were adjusted for children by age.; # For patients with central nervous system disease;

4.0 Evaluation, End of therapy and Follow-up

4.1 Disease Evaluation at diagnosis or during therapy (See 5.0)

- CBC with differentiation
- Liver/Kidney function
- Bone marrow Cytomorphology
- C.S.F cell count and cytospin: with each intrathecal therapy
- Primary or Metastatic tumor site imaging: Either CT or MRI can be performed; Contrast CT is preferred; Ultrasound may be performed at diagnosis or each imaging time point as part of the work-up, however, it can not be tumor response assessment.

4.2 Response Criteria

4.1.1 *Complete Remission (CR):* Disappearance of all evidence of disease from all sites for at least 4 weeks. This will be determined by physical exam and appropriate imaging studies. Bone marrow aspirate/biopsy must be morphologically normal and any macroscopic nodules in any organs detectable on CT should no longer be present. ***OR*** A residual lymph node mass > 1.5 cm in greatest transverse diameter that has regressed by > 75% in sum of the products of the greatest perpendicular diameters (SPD), or any residual lesions in organs that have decreased by > 75%.

4.1.2 *Partial Remission (PR):* > 50% decrease in the SPD of the lesions for at least 4 weeks. No new lesions.

4.1.3 No Response (NR): Failure to qualify for a PR. No new lesions.

4.1.4 Progressive Disease: Greater than 25% increase in the size of any lesions or appearance of new lesion(s).

4.3 End of Therapy & Follow-up

End of Therapy	Year 1 (Month 2,4,6,8,10,12)	Year 2 (Month 3,6,9,12)	Year 3 (Month 4, 8,12)	Year 4 (Month 6, 12)	Year 5 (yearly)
Physical Exam	√	√	√	√	√
CBC with differential	√	√	√	√	√
Liver/Renal function	√	√	√	√	√
Primary Tumor Evaluation*	√	√	√	√	√

*Mainly based on x-ray or Ultrasound. CT/MRI: Optional.

4.4 Criteria for removal from protocol therapy

- Progressive disease or relapse
- Found to be Ph+ LBL
- Unacceptable toxicity
- Refusal of further protocol therapy by patient/parent/guardian
- Completion of all protocol-specified chemotherapy.
- Physician determines it is in patient's best interest.
- Development of a second malignancy
- D64, CT/MRI regression <50% or BM/CSF positive (Morphology)

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken off study

4.5 Off study criteria

- Death
- Lost to follow-up
- Patient enrollment onto another therapeutic study (e.g., at recurrence).
- Withdrawal of consent for any further data submission

5.0 Therapy Delivery Map

Date	Risk group	Regimen	i.t. (N.O.)	Note
Induction				At diagnosis evaluation (D-7~D0)
	R1,R2,R3	PVDL	2 (if CNS+,4)	D33 evaluation
	R1,R2	CAM	1	
	R1,R2	CAM	1	D64 evaluation
Consolidation				
	R1,R2	HDMTX + 6-MP/CF	1	
	R1,R2	HDMTX + 6-MP/CF	1	
	R1,R2	HDMTX + 6-MP/CF	1	
	R1,R2	HDMTX + 6-MP/CF	1	
	R3	HR1’	1	
	R3	HR2’	1 (if CNS+,2)	
	R3	HR3’	1	D64 evaluation
	R3	HR1’	1	
	R3	HR2’	1 (if CNS+,2)	
	R3	HR3’	1	
Re-induction				
	R2,R3	VDLD	1 (if CNS+,2)	Evaluation，if indicated
	R2,R3	CAM	1	
Maintenance				
W1		（6-MP+MTX）x4 wks	1	Radiation，if indicated
W5		（6-MP+MTX）x4 wks	1	
W9		（6-MP+MTX）x4 wks	1	
W13		（6-MP+MTX）x4 wks	1	
W17		（6-MP+MTX）x4 wks	1	Evaluation，if indicated
W21		（6-MP+MTX）x4 wks	1	
W25		（6-MP+MTX）x4 wks	1	
W29		（6-MP+MTX）x4 wks	1	
W33		（6-MP+MTX）x4 wks	1	
W37		（6-MP+MTX）x4 wks	1	
W41		（6-MP+MTX）x4 wks	1	
W45		（6-MP+MTX）x4 wks	1	
W49		（6-MP+MTX）x4 wks		
W53		（6-MP+MTX）x4 wks		
W57		（6-MP+MTX）x4 wks		
W61		（6-MP+MTX）x4 wks		Evaluation，if indicated
W65		（6-MP+MTX）x4 wks		
W69		（6-MP+MTX）x4 wks		
W73		6-MP+MTX		
W74		6-MP+MTX	R3, 104 wks (END)	End of therapy
W75		6-MP+MTX	R2, 104 wks (END)	evaluation
W76		6-MP+MTX	R1, 96 wks (END)	