FINAL STUDY REPORT

Study Title:
Treatment Protocol for T-Cell and B-Precursor Cell Lymphoblastic Lymphoma of the European Inter-group Co-operation on Childhood Non-Hodgkin-Lymphoma (EURO-LB 02)

Chief Investigator:	Dr Robert Wynn
UK Sponsor:	University of Birmingham
Sponsor's Protocol No:	RG_10-040
REC reference No:	MREC/03/4/055
CTA No:	21275/0254/001
EudraCT No:	2007-005396-34

IMP(s):	Cyclophosphamide, Tioguanine, Methotrexate, Folinic acid, Dexamethasone, Cytarabine, E.coli asparaginase, Vincristine, Prednisolone, Mercaptopurine, Daunorubicin and Doxorubicin.

First Study Approval by MREC:	28th July 2004
First Study Approval by MHRA:	16th June 2004 (DDX)
Substantial Amendments to Date:	Amendment 01: 7th December 2009 Amendment 02: 2nd August 2010 Amendment 03: 28th January 2011 Amendment 04: 31st January 2011

Objective

The first objective of the study was to test the impact of replacing Prednisone by dexamethasone during Induction treatment (Protocol I) on the event free survival of patients with newly diagnosed T-cell Lymphoblastic Lymphoma (T-LBL).

The second objective was to test whether for patients with T-LBL the standard maintenance therapy of 24 months total therapy duration can safely be reduced to 18 months (calculated from the first day of treatment).

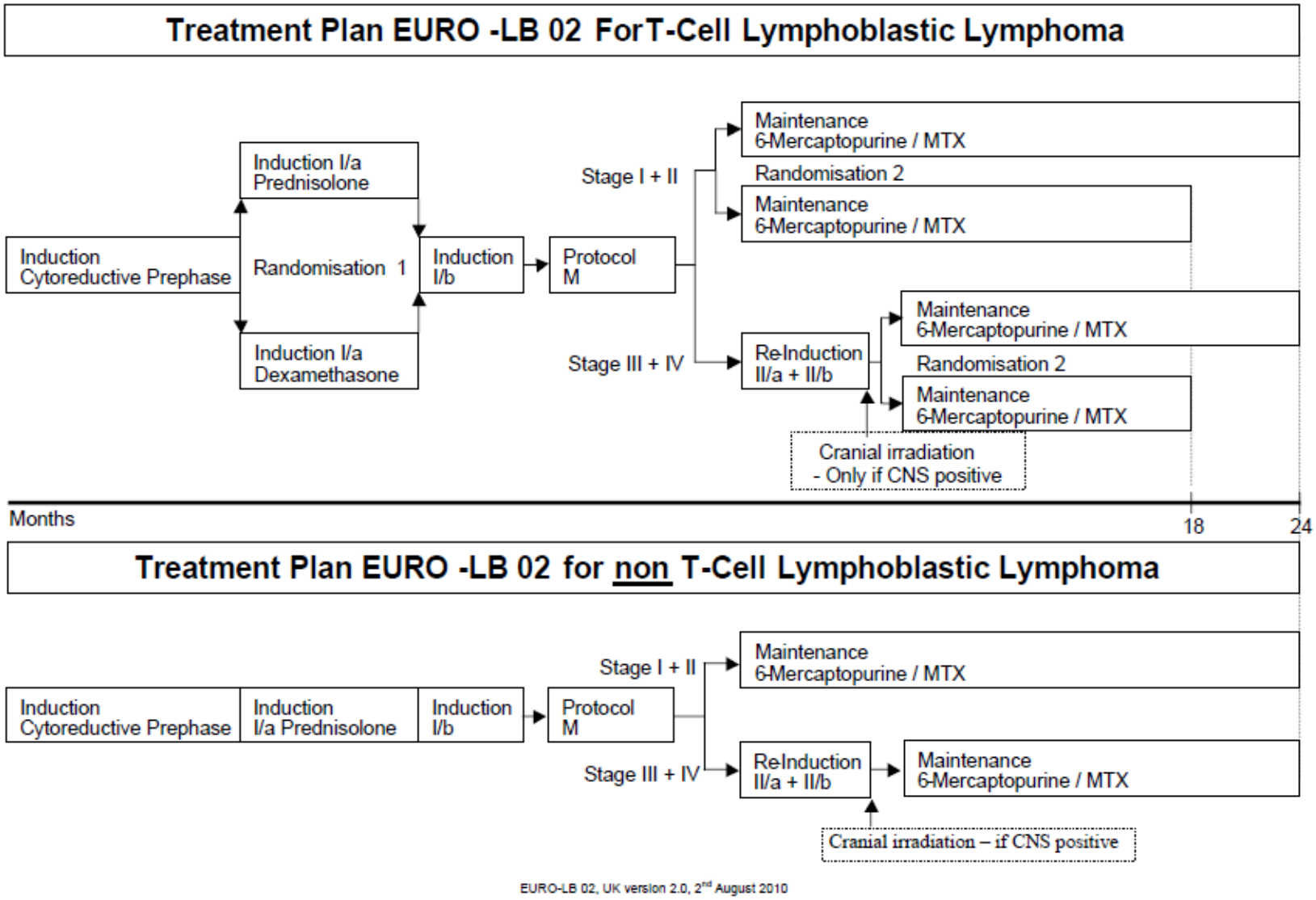
Further aims of the study were:

- to test if the treatment results of study NHL-BFM 90 can be reproduced in an international study including most European study groups. The omission of prophylactic cranial irradiation for patients with advanced stage disease in study EURO-LB 02 has to be considered in this regard.
- to evaluate prognostic factors highly predictive for treatment failure.
- to evaluate toxicity (early and late) of Dexamethasone compared to Prednisone during Induction.
- to study the epidemiology and biology of the disease.

Methodology

EURO-LB 02 was an international multicentre cooperative study. The study included:

- registration of all patients of participating centres with newly diagnosed lymphoblastic lymphoma
- two consecutive randomisations using a factorial design for patients with T-LBL reference treatment arm for patients with LBL in whom immunophenotype was not available
- Dexamethasone during remission induction therapy in pB-LBL patients (UK recommendation only). This steroid therapy was not randomised and the total duration of therapy in these patients was also not randomised and was set at 24 months.
- program of investigations to identify prognostic factors which might be predictive for failure of current treatment


Treatment Plan EURO -LB 02 ForT-Cell Lymphoblastic Lymphoma
Induction Cytoreductive Prephase
Induction I/a Prednisolone
Randomisation 1
Induction I/a Dexamethasone
Induction I/b
Protocol M
Stage I + II
Stage III + IV
Maintenance 6-Mercaptopurine / MTX
Randomisation 2
Maintenance 6-Mercaptopurine / MTX
Re-Induction II/a + II/b
Maintenance 6-Mercaptopurine / MTX
Randomisation 2
Maintenance 6-Mercaptopurine / MTX
Cranial irradiation - Only if CNS positive
Months
18
24
Treatment Plan EURO -LB 02 for non T-Cell Lymphoblastic Lymphoma
Induction Cytoreductive Prephase
Induction I/a Prednisolone
Induction I/b
Protocol M
Stage I + II
Stage III + IV
Maintenance 6-Mercaptopurine / MTX
Re-Induction II/a + II/b
Maintenance 6-Mercaptopurine / MTX
Cranial irradiation – if CNS positive
EURO-LB 02, UK version 2.0, 2nd August 2010

The first randomisation concerns the glucocorticoid hormone given in Induction phase I/a, namely Prednisolone versus Dexamethasone. The second randomisation concerns the duration of 24 months versus 18 months of maintenance therapy. After this second randomisation, there were four arms:

- Arm 1 (reference arm): strategy NHL-BFM 90 without prophylactic CRT
- Arm 2: NHL-BFM 90 without prophylactic CRT, but Dexamethasone 10 mg/m²/d instead of Prednisolone 60 mg/m²/d in Induction phase I/a
- Arm 3: NHL-BFM 90 without prophylactic CRT, but with a duration of maintenance treatment until 18 months, instead of 24 months, total therapy duration calculated from the first day of prephase

  Arm 4: NHL-BFM 90 without prophylactic CRT, but with Dexamethasone 10 mg/m²/d instead of Prednisolone 60 mg/m²/d in Induction phase I/a and duration of maintenance treatment until 18 months, instead of 24 months, total therapy duration calculated from the first day of prophase.

Endpoints:

Main Endpoint

The main end point is the conditional event free survival (EFSc), defined as minimum time from the date of randomisation to:

- death by any cause
- progressive disease
- non-response at day 33: > 5% blasts in Bone Marrow and/or blasts in Cerebral Spinal Fluid (CNS) or/and <35% regression of primary tumour. In case of non-response, the date of event will be considered the date of the beginning of treatment)
- second malignancy
- late event (malignancy more than 3 years after diagnosis of T-LBL; no differentiation between progression and second malignancy possible)

EFSc will be estimated using the Kaplan-Meier method.

Secondary Endpoints

- overall survival: defined as time of death by any cause, measured from the date of randomisation
- acute and long term toxicity
- non-lymphoma related deaths and early deaths (excluding deaths occurring after second line treatment for failure or relapse)

Statistical Analysis :

According to the factorial design of the study each randomisation is analysed separately. If there is evidence of interaction, this is taken into account in the final analysis.

First Randomisation

The test of the null hypothesis (no difference) for first randomisation is carried out, according to the “intention to treat” principle for all randomised patients in order to ensure an unbiased estimation of treatment effect. The EFSc in the two treatment arms is compared with the log-rank test stratified by participating group. A combined estimate of treatment effect and the confidence interval is given, adjusting by participating group, if no significant heterogeneity of the effects will be detected.

Second Randomisation
The test for second randomisation is based on a one-sided confidence interval of the estimated probability of 3-years EFS_c from randomisation ($pEFS_c$). Reduced maintenance is considered equivalent if the lower limit of a one sided confidence interval for the difference of the $pEFS_c$ is below 4% (equivalence range 4%). Primary analysis is a per-Protocol-analysis. All randomised patients, except those who fail before month 18 of treatment, are included in this analysis, but patients who switch the arm are included in the treatment arm actually given. Patients, who fail from month 18 to 24 of therapy, remain in their randomised arm if no switch was intended.

If there are conflicting results for the per-Protocol and the intent-to treat analysis, the Steering Committee and the Data Safety and Monitoring Committee decide about the implication on conclusions from the main analysis for first and second randomisation.

Interim Analysis of Event Free Survival

Two interim analyses are planned for each of the randomisations. The O'Brien and Fleming rules are followed to conclude at each sequential analysis. The boundary proposed in such rules requires very strong evidence of an effect to terminate at the first interim test, whereas the criteria at the final test are rather close to those for a single sample design (i.e. a design with no interim testing). On the discretion of the DMC other time-points and frequencies of interim analysis may be chosen. The p-values will then be based on a Lan-DeMets spending function approach with O´Brien-Fleming type spending function.
If any of the boundaries are reached, patient recruitment is stopped by the DMC, the international study coordinator is informed and a meeting of the Steering Committee is held to discuss further continuation or modification of the trial.
Final analysis is performed three years after the inclusion of the last patient.

First Randomisation
Two interim analyses are planned after observing 33% and 66% of the expected events.

	p value*	**events****	**Approximate time of the analysis**
1st analysis	0.0005	28	2 years after beginning of patient enrolment
2nd analysis	0.014	56	3.5 years after beginning of patient enrolment
final analysis	0.045		3 years after the end of patient enrolment

(p value *) nominal p values for overall type I error of 0.05 O'Brien-Fleming boundaries

(events **) number of events required for the interim analysis

Second Randomisation
For practical reasons (planning of subsequent studies) the first interim analysis is conducted at the end of patient enrolment of this study, the second after the end of patient enrolment of the subsequent study. For safety reasons, the interim analysis is a log-rank test of difference instead of the equivalence test planned for the final analysis (p-values see above).

Recruitment

As an international trial there were both International and UK recruitment targets. The initial aim was to recruit 173 per year internationally for 3.5 years, 20 of which were to be from the UK. The total number actually recruited was 351 internationally; just 8 from the UK.
Recruitment was suspended in Nov 2005 due to toxic-related mortalities, and reopened in July 2006. In July 2008 the trial was again closed to recruitment because of toxic-related mortalities in Europe. In line with the recommendation from the International Steering Committee after review of the twelve toxic deaths in Europe it was decided this trial be closed to patient recruitment in the UK on 19th December 2008.
The UK patients recruited to this point remain on the study and will be followed up until 2019.

To include trial treatment of approximately 5 years and follow up for approximately 10 years, the trial duration is 15 years, making the estimated completion date Sept 2019.

Trial Population

Number of UK patients registered: 8
Number of patients randomised: 8

The trial recruited 351 patients internationally however the University of Birmingham is Sponsor within the UK, for UK patients only.

Breakdown by gender:

Number of Patients Recruited By Sex

Gender	Total Recruitment
Male	4
Female	4
Total	**8**

Sites opened in the UK:

Addenbrooke's Hospital, Cambridge
Bristol Royal Hospital for Sick Children
Children's Hospital for Wales, Cardiff
Leeds General Infirmary
Royal Belfast Hospital for Sick Children
Royal Hospital for Sick Children, Glasgow
Royal Hospital for Sick Children, Edinburgh
Royal Manchester Children's Hospital
Royal Marsden Hospital, Surrey
Royal Marsden Hospital, London
Royal Victoria Infirmary, Newcastle
Sheffield Children's Hospital
Southampton General Hospital, Southampton
St James' Hospital, Leeds

Results

The first aim of the study was to test in a randomised way whether Dexamethasone 10 mg/m²/d in Induction I/a is more efficacious for patients with T-LBL compared to standard treatment with Prednisone 60 mg/m²/d. This was to be evaluated in an "intention to treat" analysis.

According to the calculation of required numbers of randomised patients about 270 patients per arm had to be randomised. Due to the premature stop of patient accrual the required number of randomised patients to answer the question of randomisation 1 could not be recruited.

The second aim of the study was to prove in a randomised way for patients with T-LBL the equivalence of reduced duration of maintenance (18 months) vs. standard (24 months) total therapy duration, calculated from the first day of cyto-reductive therapy. Therefore, for answering the question of randomisation 2, it would have

been necessary to continue the second randomisation in a subsequent inter-group study on lymphoblastic lymphoma. Due to the premature stop of patient accrual into the study EURO-LB 02 the required number of patients to answer this question could not be recruited.

Toxicity

The trial had 2 randomisations and, in the first randomisation, toxicities were sub-divided into Treatment Related Mortalities (TRM) which formed the basis of the stopping rule, and non-fatal SAEs.

Treatment Related Mortalities (Fatal SAEs) in R1
The stopping rule boundary for TRMs was crossed on 2 occasions. On the first occasion, and in agreement with the DMC, the stopping rule was modified. However, this modified boundary (12 TRM in 319 patients) was itself subsequently crossed and recruitment consequently stopped. Six of the 12 cases of TRM occurred in the 186 patients randomised in R1; 2 in the Prednisolone arm and 4 patients in the Dexamethasone arm.

Treatment Related Mortalities (Fatal SAEs) in R2
There were no TRMs during R2

Non-fatal SAEs
A total of 65 non-fatal SAE were reported in 51 of 319 protocol patients. Only 3 of the non-fatal SAEs occurred during R2.

10 patients suffered from 2 SAE, 2 patients had suffered from 3 SAE. 59 of 65 SAE (91%) recovered without late effects.

The rate of grade 3 or 4 toxicities was significantly higher for patients in the Dexamethasone arm with regards to haematological toxicity (haemoglobin, leukocytes, platelets), infections, and peripheral neurotoxicity.

Abstracts

None yet written

Publications

The primary analysis has not been performed as follow-up is on-going. No data is yet published.

Other papers

Oschlies I, Burkhardt B, Chassagne-Clement C, et al.
Diagnosis and immunophenotype of 188 pediatric lymphoblastic lymphomas treated within a randomised prospective trial: experiences and preliminary recommendations from the European childhood lymphoma pathology panel. *Am J Surg Pathol*. 2011 Jun;35(6):836-44.

Conclusion

The primary objectives of the study were not achieved due to the premature closure of patient accrual.

The feasibility and the compliance to the protocol proved acceptable. With the exception of L-Asparaginase, generally more than 90% of the patients received at least 90% of the scheduled doses of drugs.

The only difference between the reference arm of study EURO-LB 02 and the treatment strategy of study NHL-BFM 90 was the omission of prophylactic cranial irradiation for patients with advanced stage disease in study EURO-LB 02. Seven of the 38 progressive diseases among 319 protocol patients of study EURO-LB occurred isolated in the CNS plus 2 combined CNS progressive diseases. Of note, all progressive diseases in the CNS occurred in patients receiving Prednisone in Induction I/a.

Although there was no statistically significant difference of the TRM rate between patients receiving Prednisone or Dexamethasone, respectively, during Induction I/a, non-fatal acute toxicity was significantly higher in the group of patients receiving Dexamethasone regarding haematotoxicity, infections, stomatitis, arrhythmia, thromboses, and peripheral neurotoxicity. Moreover, the higher toxicity in the Dexamethasone arm resulted in significant delay of treatment realization.

The study enrolled the highest ever reported number of children and adolescents diagnosed with lymphoblastic lymphoma, uniformly characterized and treated with a fairly complete follow-up. Moreover, diagnosis of lymphoblastic lymphoma was based on a common catalogue of diagnostic criteria and in the majority of patients, tumour probes were subject to central and international panel review. Thus, the study cohort provides an ideal basis for further studies on prognostic factors and biology of the disease.

Follow-up of these patients continues.

Declaration

This report was prepared by the Chief Investigator and the Cancer Research UK Clinical Trials Unit (CRCTU) on behalf of the Sponsor.

Contact Details

Cancer Research UK Clinical Trials Unit
School of Cancer Sciences
University of Birmingham
Edgbaston
Birmingham. B15 2TT

☎0121 415 8572 🖷 0121 414 3700 ✉ m.j.gibson@bham.ac.uk

Signature of Chief Investigator:	
Print name:	Dr Robert Wynn
Date:	26 August 2014