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Treatment of childhood T-cell lymphoblastic lymphoma according to the strategy for acute lymphoblastic leukaemia, without radiotherapy: Long term results of the EORTC CLG 58881 trial

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ABSTRACT

From June 1989 through to November 1998, 121 children with newly diagnosed T-cell lymphoblastic lymphoma (T-LBL) were included in the EORTC 58881 trial conducted by the Children's Leukaemia Group. The therapy regimen was based on a Berlin-Frankfurt-Munster protocol, for a total duration of 24 months. Cranial irradiation, prophylactic cranial and local, was omitted, even for patients with central nervous involvement at diagnosis. In total, 119 patients were evaluable. The median follow-up was 6.7 years. The overall event-free survival (EFS) rate at 6 years was 77.5% (standard error (SE) = 4%). Median time of relapse was 1 year after complete remission (range 0.2–5.9 years). Only two (1.8%) patients had an isolated central nervous system relapse. For patients with complete response ($n = 16$) to the 7-day prephase, the EFS rate at 6 years was 100% versus 14% ($P < 0.001$) for patients with no response ($n = 7$). Overall survival rate at 6 years was 86% (SE = 3%). An intensive acute lymphoblastic leukaemia type chemotherapy regimen without irradiation leads to a high cure and survival rate in childhood T-LBL without an

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increased CNS recurrence. This suggests that prophylactic cranial irradiation can safely be omitted. Response to the prephase appeared to be a strong prognostic factor for EFS.

1. Introduction

Childhood T-cell lymphoblastic lymphomas (T-LBL) represent about one third of the non-Hodgkin lymphomas.[1] Morphologically and immunophenotypically, the lymphoblasts in T-LBL and T-cell acute lymphoblastic leukaemia (ALL) share the same features. Compared with precursor B-cell ALL, T-cell malignancies are associated with unfavourable features. The use of more intensive treatment regimens has significantly improved the outcome in children with T-LBL. The reported event-free survival rates are now in the range of 70% to 90%.[2–5] In the Berlin-Frankfurt-Munster (BFM) trials, patients with T-LBL were treated according to the strategy for ALL, including prophylactic central nervous system (CNS) radiotherapy.[6] The value of additional radiotherapy was not yet established although the risk of late toxicity is well known. The European Organisation for Research and Treatment of Cancer (EORTC) Children's Leukaemia Group (CLG) conducted a prospective randomised phase III trial (58881) for ALL and LBL, based on a BFM-like protocol, without prophylactic CNS irradiation or local irradiation. We report here on the results of the T-LBL population.

2. Patients and methods

2.1. Patients

Children and adolescents under 18 years of age with previously untreated ALL or lymphoblastic lymphoma were eligible for the trial 58881 of the EORTC-CLG. Excluded were patients with mature B-cell ALL, mature B-cell lymphoma and T-cell diseases as second malignancies. A total of 28 paediatric centres from France, Belgium and Portugal participated in this trial. T-LBL patients were staged I to IV according to Murphy's classification using clinical and imaging criteria.[7] Bone marrow involvement of more than 25% blasts was considered as ALL. CNS disease was diagnosed when patients had cranial nerve palsy and/or when blasts were identified on cytocentrifuge examination of cerebrospinal fluid with at least 5 leucocytes/μl. Cranial CT scan was not routinely performed. Informed consent from the parents or the legal guardian was provided before entry in the study according to the Declaration of Helsinki. The protocol was approved by the EORTC Protocol Review Committee and by the local institutional ethical committees in each participating centre.

2.2. Definitions

Diagnosis of T-LBL was performed on biopsy material of a lymph node or tumour mass, or on malignant effusion or bone marrow. All cases were studied for specific lymphoblastic characteristics, including histology and immunophenotype. Morphologic classification was made according to the working formulation and the revised European-American Lymphoma Classification.[8] Immunophenotype was determined according to reactivity to a panel of monoclonal antibodies.[9] Complete remission (CR) was defined as disappearance of all clinical, cytological and radiological signs related to the lymphoma. Partial remission (PR) was considered as any response less than CR with at least or more than 50% reduction of the most important lymphomateous tumours. A less favourable response was seen as an induction failure.

2.3. Treatment

The therapy regimen was based on a BFM-like ALL protocol, without prophylactic cranial and local irradiation for a total duration of 24 months. According to the staging and response to treatment, patients were stratified into three groups: low-risk group including stage I and II T-LBL, increased-risk group with stage III and IV T-LBL, and very high-risk group comprising patients with resistant disease or lacking partial remission after completion of induction. The treatment protocol has already been described.[10–13]

The strategy for the low and increased-risk patients is summarised in Table 1. After a prephase of 7 days of prednisolone and one intrathecal injection (IT) of methotrexate (MTX), all patients received induction therapy consisting of daily prednisolone, weekly vincristine and daunorubicine, twice weekly L-asparaginase, and two IT injections of MTX over a period over 4 weeks. Between November 1990 and October 1993 patients were randomised to receive Escherichia Coli asparaginase or Erwinia asparaginase at the same dose. Additionally, five increased-risk patients received, on days 8 and 9, MTX 5 g/m^2 and cyclophosfamide 1 g/m^2 in a pilot study proceeding with the further treatment protocol. Patients who achieved CR at the end of induction received 4 weeks of consolidation therapy with daily 6-mercaptopurine (6-MP), four 4-day courses of ARA-C, two courses of cyclophosfamide and two IT injections of MTX. All patients in CR proceeded to CNS directed regimen (interval therapy) with daily 6-MP and four courses of high-dose (HD) MTX (5 g/m^2) intravenously (IV) and IT injection of MTX every 2 weeks. MTX was given as a 24-h IV infusion. Folinic acid rescue (12 mg/m^2 orally every 6 h) was initiated 36 h after the start of MTX infusion and was continued until the serum MTX concentration decreased below 0.2×10^{-6} mol/l.

From January 1990 until January 1996 increased-risk patients were randomised before the start of the interval therapy to receive HD-MTX alone or HD-MTX in combination with ARA-C, 12 and 24 h after the start of each MTX infusion. After interval therapy, patients continued with the reinduction consisting of 3 weeks of dexamethasone, four weekly doses of vincristine and doxorubicin and four administrations of L-asparaginase, followed by daily 6-thioguanine for 14 days, one dose of cyclophosfamide, two 4-day courses of

Table 1 – EORTC – CLG 58881: treatment protocol for low and increased risk patients

Drug	Dose	Days of administration
Induction: protocol IA		
Prednisolone (PO)	60 mg/m^2	1 – 7 (prephase)
Prednisolone (PO)	60 mg/m^2	8–28, then tapered over 9 days
Vincristine (IV)	1.5 mg/m^2 (max 2,5 mg)	8, 15, 22, 29
Daunorubicin (IV)	30 mg/m^2	8, 15, 22, 29
Methotrexate (IT)	12 mg[a]	1, 8, 22
According to randomisation		
E. coli asparaginase (IV) or	10,000 IU/m^2	12, 15, 18, 22, 25, 29, 32, 35
Erwinia asparaginase (IV)	10,000 IU/m^2	12, 15, 18, 22, 25, 29, 32, 35
Consolidation: protocol IB		
Cyclophosphamide (IV)	1000 mg/m^2	36, 63
Cytarabine (IV)	75 mg/m^2	38–41, 45–48, 52–55, 59–62
Methotrexate (IT)	12 mg[a]	38, 52
6-Mercaptopurine (PO)	60 mg/m^2	36–63
Interval therapy		
6-Mercaptopurine (PO)	25 mg/m^2	1–56
Methotrexate (24 h) with leucovorin rescue at H36	5000 mg/m^2 12 mg/m^2/6 h	8, 22, 36, 50
Methotrexate (IT)	12 mg[a]	9, 23, 37, 51
According to randomisation for increased risk patients		
Cytarabine (IV)	1000 mg/m^2	9, 10, 23, 24, 37, 38, 51, 52
Reinduction: protocol II		
Dexamethasone (PO)	10 mg/m^2	1–21, then tapered over 9 days
Vincristine (IV)	1.5 mg/m^2 (max 2.5 mg)	8, 15, 22, 29
Doxorubicin (IV)	30 mg/m^2	8, 15, 22, 29
Methotrexate (IT)	12 mg[a]	38
Cyclophosphamide (IV)	1000 mg/m^2	36
Cytarabine (IV)	75 mg/m^2	38–41, 45–48
6-Thioguanine (PO)	60 mg/m^2	36–49
According to randomisation		
E. coli asparaginase (IV) or	10,000 IU/m^2	8, 11, 15, 18
Erwinia asparaginase (IV)	10,000 IU/m^2	8, 11, 15, 18
Maintenance (up to 2 years after day 1 of induction)[b]		
6-Mercaptopurine (PO)	50 mg/m^2	daily
Methotrexate (PO)	20 mg/m^2	weekly
According to randomisation		
6- Mercaptopurine (IV)	1 g/m^2	monthly

a Less than 1 year: 6 mg; 1 year: 8 mg; 2 years: 10 mg; 3 years and more: 12 mg.
b For CNS-positive patients: additional five courses of Methotrexate IT and IV 5000 mg/m^2 3-monthly.

ARA-C and one IT injection of MTX. Following reinduction, maintenance therapy started with daily 6-MP and weekly oral MTX for a total duration of 24 months. From November 1990 to November 1996 patients were randomised to receive additional monthly IV 6-MP during maintenance treatment. Cranial irradiation was omitted even for patients with CNS involvement at diagnosis. Additionally, these patients received IT injections of MTX during induction up till normalisation of the cerebrospinal fluid, and during maintenance on a 3-monthly interval, five courses of HD-MTX infusions with IT injection of MTX at the end of each infusion. Treatment of very high-risk patients was based on rotating chemotherapy courses and allogeneic bone marrow transplantation for patients with a HLA-identical sibling.[10]

2.4. *Statistical analysis*

The primary end point was event-free survival (EFS). Failure to induction was defined as progression during induction IA or no CR at the end of consolidation IB. For patients who failed to reach CR by the end of induction-consolidation, EFS was set to 0 days; for all others who reached CR, EFS was calculated from the evaluation of CR until the date of first relapse or death. Overall survival, secondary endpoint, was computed from date of start of induction until date of death or date last known to be alive (censored observation). Additional secondary endpoints included the rate of CR after the prephase and after induction-consolidation, the rate of different types of relapse in patients who reached CR, and disease-free survival (DFS) for patients randomised for the 6-MP IV and/or for the ARA-C question; DFS was computed from the date of randomisation until date of relapse or date of death, or date last known to be alive (censored observation). The actuarial curves were computed using the Kaplan–Meier technique, and the standard errors (SE) of the estimates were obtained via the Greenwood formula. The differences between curves were tested for statistical significance using the two-tailed log-rank test. To summarise the overall difference, the hazard

ratio of having an event per time in one group versus the one in another group, along with its 95% confidence interval, was estimated via the Cox proportional hazards model.[14] All analyses were performed according to the intent-to-treat principle. The SAS 8.2 software (SAS Institute Inc, Cary, NC, USA) has been used for the statistical analyses.

3. Results

3.1. *Patient characteristics (Table 2)*

From June 1989 through to November 1998, 121 patients (from 19 centres) with T-LBL were enrolled in the EORTC 58881 trial. Two patients, initially misdiagnosed for Burkitt's lymphoma and anaplastic large cell lymphoma and subsequently treated with another protocol, were considered ineligible and excluded for further analysis. Of the 119 evaluable patients, 77 (65%) were boys and 42 (35%) were girls. The median age was 8 years (range 0–16). The distribution according to the Murphy stage was 7 (6%) patients in stage I, 7 (6%) in stage II, 79 (66%) in stage III and 26 (22%) patients in stage IV. Three (2.5%) patients had initial CNS invasion, 96 (81%) patients presented with a mediastinal mass, 5 (6%) boys had testicular involvement and in one girl ovarian involvement was diagnosed.

Less than half of the patient population was randomised for the different treatment steps. For the asparaginase question 19 patients were included in the Medac E. coli asparaginase arm versus 22 in the Erwinia asparaginase arm.[11] Before the period when the randomisation was open, 13 patients received Bayer E. coli asparaginase and two received Erwinia asparaginase, and after the closure of randomisation, 63 patients received E. coli asparaginase. Among 105 Murphy stage III–IV patients, 55 were randomised for the second step: 29 in the arm A with ARA-C and 26 in the arm B without ARA-C.[13] For the third randomisation, 25 patients were allocated to the arm without IV 6-MP and 23 patients to the arm with IV 6-MP.[12] The remaining patients who could start the maintenance received the standard maintenance without 6-MP IV.

3.2. *Response to prephase and to induction-consolidation*

On day eight, after 7 days of corticosteroids and one intrathecal injection of methotrexate, 16 patients had a complete tumour response, 87 had PR, seven had no response and nine were not evaluable. Among 119 patients, one patient died

Table 2 – Patient characteristics and outcome

Characteristics	Total (N = 119)	Ouctome		
		EFS rate at 6 yrs % (SE%)	HR (95% CI)	P-value
Sex (*n*)				
Female	42	70 (7.3)	1	0.19
Male	77	81 (4.5)	1.66 (0.77,3.60)	
Age (yrs) at diagnosis				
<1	2	0	–1	
1 – 9	68	82 (4.6)	1.38 (0.62,3.07)	0.43
10 – 16	49	74 (6.7)		
Stage				
I	7	86 (13.2)	1	0.96
II	7	64 (21.0)	1.84 (0.17,20.3)	
III	79	78 (4.7)	1.51 (0.20, 11.3)	
IV	26	77 (8.2)	1.65 (0.20,13.7)	
Initial involvement				
CNS	3	67 (27.2)	–	–
Mediastinum	96	77 (4.4)		
Testes[a]	5	60 (21.9)		
Response to prephase				
CR	16	100 (0)		
PR	87	78 (4.5)		<0.001
resistance	7	14 (13.2)		
not evaluated	9	89 (10.5)		
Randomisation 1				
Medac E. coli asparaginase	19	79 (9.4)	1	0.48
Erwinia asparaginase	22	68 (9.9)	1.54 (0.45,5.27)	
Not randomised	78	–		
Randomisation 2				
No ARA-C	26	85 (7.1)	1	0.38
ARA-C	29	75 (8.2)	1.72 (0.50,5.87)	
Not randomised	64	–		
Randomisation 3				
No IV 6-MP	25	87 (7.0)	1	0.21
IV 6-MP	23	74 (9.2)	2.35 (0.59,9.41)	
Not randomised	71	–		

a In addition, one girl had a gonadal involvement; she is in CCR.

early during induction due to an encephalitis and five (4%) did not reach CR after induction-consolidation. Four patients demonstrated resistant disease at the end of induction and one patient at the end of consolidation. These four patients resistant at IA were switched to the very high risk protocol. Two of them achieved a persistent CR after the intensified consolidation IB', the other two died of progressive disease as did the patient with resistance at end IB. After completion of IB, in eleven patients with a minimal residual mass, the local physicians decided to perform a biopsy. In seven patients, pathology of the biopsy showed necrotic material. Out of these seven patients, three patients later developed a relapse. In the remaining four patients, vital lymphoma was found in pathology specimens. These four patients received an intensified treatment and developed no relapse.

3.3. *Type of first event after complete remission*

Among 113 (95%) patients who reached CR after induction-consolidation, 18 (15.9%) patients relapsed. Two patients had isolated CNS relapse (1.8%), two patients had isolated bone marrow relapse (1.8%), one had combined CNS and bone marrow relapse (0.8%) and another one combined testicular and bone marrow relapse (0.8%). Eleven patients (9.2%) suffered from local mediastinal relapse and/or other lymph node involvement. One patient (0.8%) showed a late skin relapse. Median time of relapse was 1 year after diagnosis with a range of 2 months to 5.9 years. Two patients died in first CR: one due to a fungal CNS infection that occurred during the reinduction therapy. The other patient developed a secondary acute myeloid leukaemia 4.3 years after diagnosis.

3.4. *Event-free survival (Table 2)*

The median follow-up was 6.7 years (range 1.3 – 11.3). The overall EFS rate at 6 years was 77.5% (SE = 4%) (Fig. 1). The 6-years EFS rate was 70% (SE = 7.3%) for female and 81% (SE = 4.5%) for male patients (logrank test $P = 0.19$). According to age the 6-years EFS in the 1- to 9-year old patients was 82% (SE = 4.6) versus 74% (6.7) in the 10- to 16-year old patients. The two infants in the study population died of disease progression. The 6-year EFS rate according to the Murphy stage

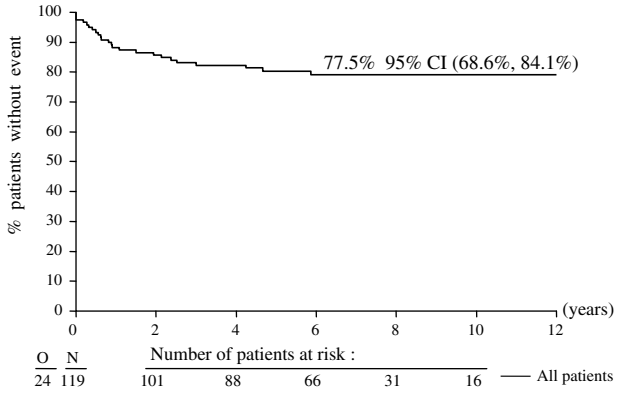

Fig. 1 – Overall event-free survival. O = observed number of events (lack of CR, relapse or death in CR), N = number of patients.

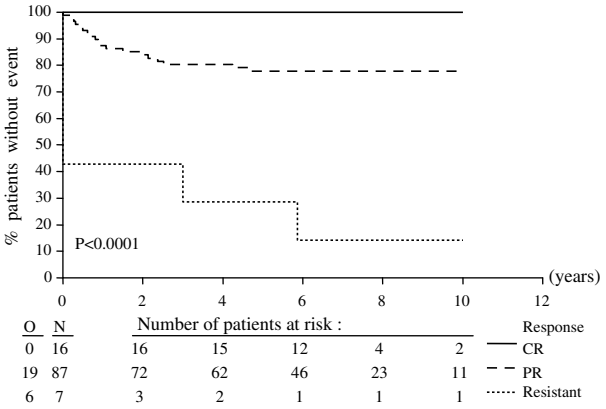

Fig. 2 – Event-free survival according to the response to prephase. O = observed number of events; N = number of patients. P-value was given by the logrank test.

was 86% (SE = 13%) for stage I, 64% (SE = 21%) for stage II, 78% (SE = 5%) for stage III and 77% (SE = 8%) for stage IV. The EFS at 6 years according to the response to prephase was 100% for those patients who reached CR, 78% for PR group and 14% in patients with no response after corticosteroids (Fig. 2). For the asparaginase question, the EFS rate at 6 years was 79% in the E. coli arm and 68% in the Erwinia arm (logrank test $P = 0.48$).[11] The EFS rate at 6 years was 75% and 85% according to whether patients were assigned to receive ARA-C or not (logrank: $P = 0.38$).[13] For the third randomisation, the EFS rate at 6 years was 87% for the arm without 6-MP IV and 74% for the group with 6-MP IV (logrank: $P = 0.21$).[12]

3.5. *Overall survival*

Of the relapsed patients, 10 never achieved a second CR. They died due to progressive disease or due to toxicity during reinduction or post stem cell transplantation. However, eight patients reached a second CR after intensive chemotherapy followed by stem cell transplantation.

The overall survival rate at 6 years was 86% (SE = 3%) (Fig. 3) and according to Murphy stage: 86% (SE = 13%) for stage I, 100% for stage II, 84% (SE = 4%) for stage III and 88% (SE = 6%) for stage IV.

4. Discussion

The results of the EORTC 58881 trial showed an overall EFS rate at 6 years of 77.5% in T-LBL, with an intensive chemotherapy regimen without local or cranial irradiation. These data are comparable with published data.[2,5,6,15] The larger EORTC 58881 study, incorporating precursor B-cell ALL and LBL patients as well as T-cell ALL patients, demonstrated significantly worse outcome in those allocated to Erwinia asparaginase versus those allocated to Medac E. coli asparaginase arm, and a significantly disadvantage to the administration of IV 6-Mercaptopurine during maintenance therapy.[11,12] In the T-LBL subgroup the same trends were observed, as indicated by hazard ratios greater than 1 (1.54 and 2.35 for the Erwinia versus E-Coli asparaginase and for 6-MP IV versus no 6-MP IV comparison, respectively). The differences did

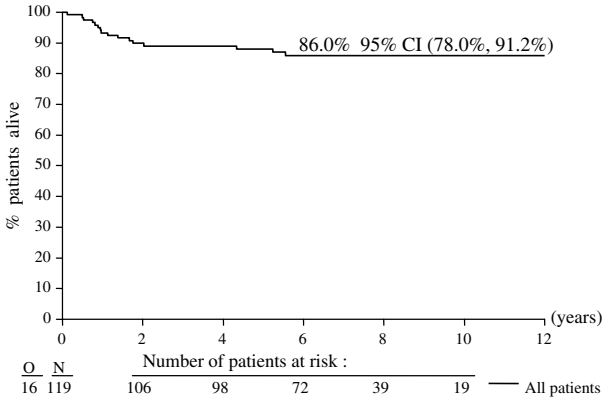

Fig. 3 – Overall survival. O = observed number of deaths; N = number of patients.

not appear to be significant, but this was most probably due to the very limited number of patients who were randomised, and the total number of events which were reported. Since in previous studies of the Paediatric Oncology Group early intensive asparaginase contributed to improved outcome, we might expect a disadvantage towards Erwinia asparaginase comparable to that found in the ALL population.[5] In the main EORTC 58881 study, the outcome of those randomised to receive high-dose ARA-C during the interval therapy was very similar to those randomised not to receive the high-dose ARA-C.[13] In the T-LBL patients, the apparent worse results were in the HD-ARA-C arm (estimated hazard ratio was 1.72), but the 95% CI largely contained 1, i.e. the results were compatible with no treatment difference.

Prophylaxis of the central nervous system was accomplished with administration of HD-MTX IV (4×5 g/m^2 with folinic acid rescue starting at 36H) and 10 IT injections of MTX. Omission of cranial radiotherapy did not influence the rate of isolated CNS relapses. Only 1.8% of the patients showed isolated CNS recurrence. This rate is within the range of CNS event-free survival greater than 90% accepted in previous studies and by comparison with the expected risk of secondary malignancies following radiotherapy and the complexity of salvage therapy in irradiated patients.[16,17] No patient with initial CNS involvement presented with a CNS relapse: two are in continuous CR and one showed a combined bone marrow and testicular relapse. None of them demonstrated increased neurotoxicity due to the larger cumulative dose of HD MTX and IT MTX.

The overall relapse rate was 16% with a median time from CR to relapse of 1 year (range 2 months–5.9 years). The majority were early relapses. However, we also reported six late relapses occurring after the end of treatment, even up to 5.9 years from CR. This is in contrast with the NHL-BFM 90 study where no recurrences occurred later than 1 year from diagnosis.[6] Previous studies also reported late recurrences.[4,18] The BFM studies reported an extremely poor survival rate for children who failed to respond to the front-line therapy.[6] However, we demonstrated that intensified chemotherapy regimen followed by stem cell transplantation resulted in a second continuous remission in 44% of the relapsed patients, particularly for the late relapses. The overall survival rate at 6 years was 86%.

In a recent study by Burkhardt, adolescent females with T-LBL had a worse outcome.[19] Regarding age and gender there was no statistical difference in our cohort. We observed the same trends: a higher 6-year EFS rate for male patients and for the 1- to 9-year age group. The outcome for the infants was disastrous, although there were only two infants in our population. Recent BFM data showed also a dismal prognosis for infant non Hodgkin lymphoma.[20] Other previous studies could not identify a subgroup of patients with significant increased risk of failure of therapy.[15] According to our findings, evaluation of the response at the prephase, after 7 days of prednisolone and one intrathecal injection of MTX, seemed to be an important prognostic factor. EFS for patients with complete clinical and radiological response at day 8 was 100%, compared to an EFS of 14% for the resistant group ($P < 0.001$). Therefore, the speed of tumour response at day 8 could possibly be a marker for risk of tumour failure and might be used for therapy stratification. Those corticosteroid-resistant patients should have benefit from an intensified induction regimen. Of note there was no centralised review of the radiological data. Prospective studies with standardised measurements of tumour volumes are necessary to confirm our data in a larger group of patients. At day 35 four patients with persistent resistant disease were switched to an intensive chemotherapy regimen. Early intensification with a high risk ALL-regimen led to complete remission in two out of four patients. Among the patients who had a biopsy of a residual tumour at the end of the induction-consolidation IB, three relapses were observed. These three relapses occurred in patients in whom pathology confirmed a CR. We did not observe relapses among the other patients with a pathological biopsy who received an early intensified treatment. Positron emission tomography (PET) might play a role in monitoring response to therapy. However, given the small numbers of patients, larger prospective trials are needed to investigate possible therapy-stratification factors which could be used to optimise treatment for T-LBL in childhood.

In conclusion: The overall results of our trial are comparable with previous reported data. It is important to use Medac E. coli asparaginase and the standard maintenance, without 6-MP IV. In this case, most probably, the results would be better than the present overall results. Prophylactic cranial irradiation can safely be omitted. Response to the prephase with corticosteroids appeared to be a strong prognostic factor. Additional criteria and valuable parameters to measure response rate are needed for identification of the small group of high risk patients who will have benefit from early exposure to an intensive therapy regimen. Some late relapses were observed, but the feasibility of obtaining a second CR was quite promising.

Conflict of interest statement

None declared.

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