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Full Length Article

Results of treatment of lymphoblastic lymphoma at the children cancer hospital Egypt – A single center experience

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Abstract Introduction

Lymphoblastic lymphoma (LBL) and acute lymphoblastic leukemia (ALL) are neoplasms of immature B or T-cell precursors. They are considered as a unique biological entity in the 2008 World Health Organization Classification of Hematologic Neoplasm. Both entities are arbitrarily separated by a cut-off point of 20–25% of blast cells in the bone marrow. Treatment of LBL has evolved over time from conventional high-grade NHL schedules to ALL-derived protocols.

The aim of this work is to report the clinical characteristics, overall survival (OS), event free survival (EFS), and common chemotherapy toxicities of lymphoblastic lymphoma (LBL) patients during a 5.5 year period.

Patients and methods

A Retrospective review of patient's charts diagnosed and treated as LBL during the period between July 2007 and end of December 2012 was done. Patients were treated according to St. Jude Children Research Hospital ALL Total Therapy XV protocol, standard risk arm.

Results

This study included 77 patients. T-cell LBL patients were 67, while 10 were of B-cell origin. The median age at diagnosis was 9 years (95% CI: 7–10). The majority were males 54/77. Stage III patients were 51, stage IV 13, stage II 11 and stage I 2 patients. Two patients were excluded from analysis as they died before receiving chemotherapy. Complete remission post induction chemother-

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apy was seen in 22 patients considered early responders, and partial remission in 55 considered late responders. With a median follow up duration of 47 months (95% CI: 38–56), the 4 year overall survival and event free survival were 86.45% (95% CI: 73.78–94.09) and 82.18% (95% CI: 69.25–90.61) respectively.

Twelve patients died during the study period; 2 early deaths before starting chemotherapy from disease progression, 2 in CR due to chemotherapy related toxicity and 8 from disease progression. All the relapsed patients were T-cell, had advanced disease at presentation (6 with stage III; 2 with stage IV). Two patients (2.6%) had isolated local, BM, and CNS relapse each, while 1 (1.3%) had both local and CNS relapse. Disease recurrence was local in 3 patients (3.9%), and systemic in 5 (6.4%), while it was early in 6 (7.8%), and late in 2 (2.6%) patients. Median time to disease progression was 20 months (range 5–39 months). All relapsed patients did not survive salvage chemotherapy. The most common chemotherapy toxicities were cerebral venous thrombosis (20%), followed by bone infarcts (10.6%), and avascular necrosis (AVN) of head of femur (9.3%). One patient developed secondary acute myeloid leukemia after 3 years of FU with unfavorable cytogenetic abnormalities.

Conclusion

Results of treatment of LBL on the St Jude's total therapy XV study are comparable to most of the similar reported studies. Outcome of relapsing patients is extremely poor, hence there is a need to identify biologic or clinical prognostic factors including minimal residual tumor to better evaluate chemotherapy response. Steroid induced AVN, and cerebral vascular thrombosis were the main chemotherapeutic adverse events.

Introduction

NHL is a diverse collection of malignant neoplasm derived from mature and immature lymphoid cells of either B-cell or T-cell origin [1]. Lymphoblastic Lymphoma (LBL) has been used to describe predominantly lymph node–based disease. It accounts for 30% of pediatric NHL [2]. The current WHO classification, recognized that this entity represents a spectrum of precursor lymphoid cell disease and developed the diagnostic category of lymphoblastic leukemia/lymphoma [3]. Both diseases share common characteristics, such as immunophenotypic (IPT) features, lymphoblast morphology and clinical characteristics, e.g. the median age at diagnosis, and the favorable outcome after ALL-type chemotherapy [4–6]. For a low stage disease, survival rate is >90%, while for an advanced stage disease survival is >80% [4]. Nevertheless, small molecular profiling studies and genomic studies have demonstrated differential gene expression profiles and loss of heterozygosity at the 6q locus, suggesting the presence of underlying biologic differences [7,8]. T-cell LBL versus T-ALL has less hepatosplenomegaly, central nervous system involvement, better survival and heterogeneity in IPT reflecting various stages of T-cell development [9]. Moreover, the typical sites of relapse differ, with predominantly local in LBL [4,10], and systemic relapse in ALL. The time to relapse tends to be minimally shorter in LBL than in ALL [9].

The aim of this work is to report the clinical characteristics, overall survival (OS), event free survival (EFS), and common chemotherapy toxicities of LBL patients treated at the Children Cancer Hospital Egypt during a 5.5 year period.

Patients and methods

This retrospective study was carried out at the Children Cancer Hospital Egypt. Data of treated patients during the period from July 2007 to end of December 2012 were collected from the medical record department.

Patients were included in the study if they were newly diagnosed with LBL by pathology, immunophenotyping (IPT), and cytochemistry, were equal to or less than 18 years of age, and had no other co-morbidities and/or immunodeficiency syndromes. Written informed consent and institutional review board (IRB) approval were obtained before starting the study.

The following data were collected from patient's files:

1. Epidemiologic data regarding age, gender, and clinical presentation.
2. Laboratory and radiological initial work up: blood count, serum electrolytes, bone marrow (BM) aspirate, cerebrospinal fluid analysis (CSF), and imaging studies including computed tomography (CT scan).
3. Staging according to the St Jude staging system [11].
4. Assessment of response at time of evaluation as required by the applied protocol (end of induction, week 7, 17, 48, and end of chemotherapy).
5. Major organ toxicities [12].
6. Causes of death during chemotherapy and FU period.
7. OS and EFS of the studied patients.

Chemotherapy: patients included in this study were treated according to ALL Total Therapy Study XV at St. Jude Children's Research Hospital, standard risk arm. Treatment included the following phases:

Remission induction (6 weeks): prednisone (40 mg/m^2 - × 28 days), vincristine (1.5 mg/m^2 max 2 mg days 1,8,15,22), daunorubicin (30 mg/m^2 days 1, 8), asparginase (25,000 IU/m^{2}days 1,5,9,11,13), and weekly triple intrathecal treatment (age adjusted), cyclophosphamide (1000 mg/m^2 day 2), cytarabine (75 mg/m^2 days 23–26, and 32–35) and 6 mercaptopurine (60 mg/m^2 days 23–36).

Table 1 Characteristics of the 77 studied patients.

	No. of patients	Percentage (95% CI)
Sex		
Male	54	70.13 (58.62–80.03)
Female	23	29.87 (19.97–41.38)
Age (years)		
Range	1–17	
Median	9	(7–10)
Immunophenotyping		
T-LBL	67	87.01 (77.41–93.59)
B-LBL	10	12.99 (6.41–22.59)
Clinical presentation		
Mediastinal mass	40	51.9 (40.26–63.48)
RD	26	33.7 (23.38–45.45)
Generalized lymphadenopathy	22	28.5 (18.85–40)
Cervical lymph node	5	6.4 (2.14–14.51)
Stage		
I	2	
II	11	14.3 (7.35–24.13)
III	51	66.2 (54.55–76.62)
IV	13	16.8 (9.31–27.14)
BM infiltration	11	14.3 (7.35–24.13)
CNS involvement	2	
Response at end of induction (n = 75)		
CR	20	26.67 (17.11–38.14)
PR	55	73.33 (61.86–82.89)

BM: bone marrow, CNS: central nervous system, CR: complete remission, LBL: lymphoblastic lymphoma, PR: partial remission, RD: respiratory distress.

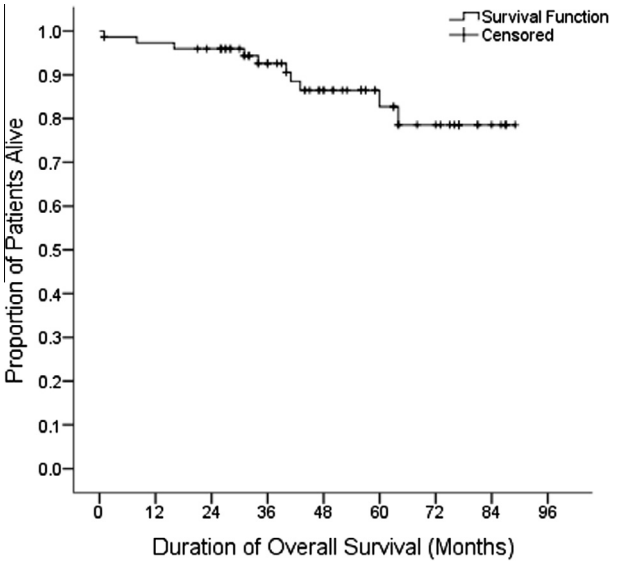

Figure 1 Overall survival of all the studied patients.

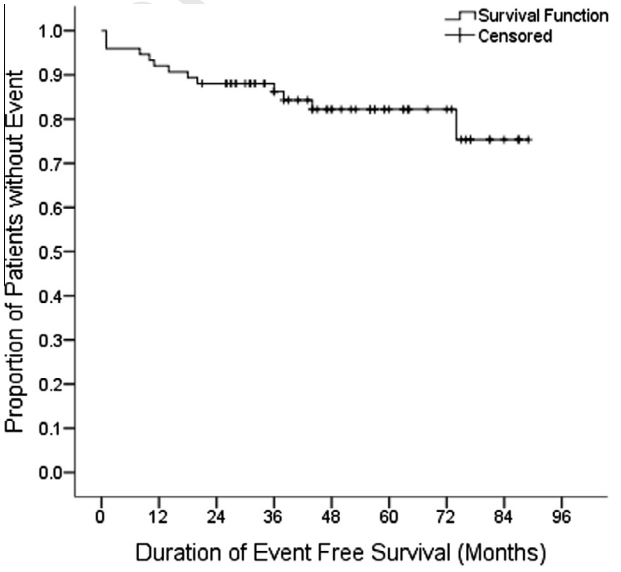

Figure 2 Event free survival of all the studied patients.

Table 2 Causes of death among the studied patients.

Total	12	Percentage (95% CI)
Early	2	
Septicemia (CR)	2	
Relapse/PD	8	66.67 (34.89–90.08)

Consolidation Treatment (8 weeks): high dose methotrexate 5gm/m^2 (every two weeks for 4 doses), associated with triple intrathecal and daily 6 mercaptopurine (50 mg/m^2).

Continuation/maintenance treatment (24 months): started two weeks from the start of the last high does Methotrexate:

- Monthly vincristine 2 mg/m^2 (maximum dose 2 mg) IV push.
- Dexamethasone 12 mg/m^2/day PO divided TID x 5 days, every 28 days.
- 6 mercaptopurine 50 mg/m^2/day till week 20, then 75 mg/m^2/day, PO, once a day.
- Methotrexate 40 mg/m^2/day IM weekly.
- Doxorubicin 30 mg/m^2/day 1 IV over 4 h infusion on week 1, 4, 7, 8, 11, 14.
- Asparginase 25,000 IU/m^2/day 1 IM week 1–19.
- Cyclophosphamide and Ara-C 300 mg/m^2 each, iv monthly for 12 doses.

Patients were given continuous treatment for two years. Assessment of tumor response was done at the scheduled time. In case of inadequate response; patients continued the same line of chemotherapy till documented evidence of disease progression.

Definitions and criteria of response:

Complete Response (CR): complete disappearance of all clinical evidence of disease by physical examination, imaging studies, BM aspirate, and/or CSF evaluation (when indicated).

Early Responders: Those patients achieving CR after induction treatment.

Partial Response (PR): a decrease of 30% or more in the nodal masses, but not satisfying the criteria for CR.

Late Responders: Those patients achieving PR after induction treatment.

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Table 3 Site and timing of relapsed patients.

Patients	Site	Timing	Cause of death
1.	CNS & local	Maintenance week 44	Septicemia during chemotherapy
2.	BM	Maintenance week 48	Chemotherapy toxicity
3.	CNS	During FU	PD on chemotherapy
4.	CNS	Maintenance [week 41]	PD on chemotherapy
5.	Local [Chest]	Consolidation phase	Septicemia during chemotherapy
6.	BM	Maintenance [week 44]	PD post Allogeneic HSCT
7.	BM	Maintenance [week 13]	PD on chemotherapy
8.	Local [nodal]	During FU	PD on chemotherapy

Relapse (RL): appearance or reappearance of tumor in any site.

Progressive Disease (PD): an increase of >25% or the reappearance of tumor in any site of residual disease compared to immediate pre-study volume or best prior response at that site.

Early relapse: recurrence within 36 months from initial diagnosis.

Late relapse: recurrence ⩾36 months from initial diagnosis, or >6 months after the completion of chemotherapy.

Statistical analysis

Q6 The potential follow-up time for each patient was the time from enrollment to the closing date for analyses or the date of last information. For OS, all deaths were counted regardless of cause, and survival times for living patients were censored on the closing date. For EFS, the first progression at any site or death without progression was counted as an event, and times were censored on the date for the patient, who was alive on the date without disease progression.

Data were analyzed using IBM SPSS advanced statistical version 20 (SPSS Inc., Chicago, IT). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Owing to our small sample size, the 95% confidence intervals for all the results were calculated by binomial exact method [13].

Survival analysis (OS and EFS) was done using Kaplan–Meier method and the comparison between two survival curves was performed using log-rank test. The 95% confidence intervals for the survival analysis were calculated by beta product confidence procedure (BPCP), that is, a non-parametric confidence procedure method designed specifically for small sample size [14]. A p-value <0.05 was considered significant, while a *p*-value of 0.05–0.1 considered borderline statistical significance.

Results

This study included 77 patients who were diagnosed and treated as LBL during the period from July 2007 [date of inauguration of the hospital] to end of December 2012, representing 14.6% of the total number of patient (525) diagnosed with NHL during the same period. The median age at diagnosis was 9 years (range 1–17 years) with 95% confidence interval (95% CI: 7–10). They were 54 males (70.1%) and 23 females (29.8%).

The most common presentation was mediastinal mass seen in 40 patients (51.9%), and respiratory distress in 26 (33.7%), followed by generalized lymph nodes enlargement in 22 (28.5%), and cervical lymphadenopathy in 5 (6.4%) of the patients. T-cell LBL patients were 67 patients (87%), while 10 were B-cell (13%). Stage III was the most common at presentation seen in 51 patients (66.2%), followed by stage II in 11 (14.3%), and IV 13 patients (16.8%). Two patients (2.59%) had stage I disease. BM infiltration (<25%) was detected in 11 (14.3%), while CNS infiltration was detected in 2 of the patients (2.59%). Table 1 describes the clinical characteristics of the studied patients.

Chemotherapy response

Two patients were excluded from analysis as they died before receiving chemotherapy. Following induction chemotherapy, complete remission (CR) was detected in 20/75 patients (early responders, 26.7%), and partial remission in 55/75 patients (late responders, 73.3%). By the end of the consolidation phase (day 100), 66/75 patients were in CR, while 9/75 still had residual tumor. The median of the duration of follow up was 47 months (range 1–89 months) (95% CI: 38–56). The 4 year overall survival (OS) and event free survival (EFS) were 86.45% (95% CI: 73.78–94.09) and 82.18% (95% CI: 69.25–90.61) respectively (Figs. 1 and 2). Other parameters were tested with uni-variant analysis including age, sex, localized (stages I & II) versus advanced disease (stages III & IV) and were statistically insignificant.

Causes of death, relapses, and disease progression

Twelve patients died during the study period; 2 early deaths before starting chemotherapy from disease progression, 2 while in CR due to chemotherapy related toxicity, while 8 from disease progression (Table 2).

Seven patients relapsed, while 1 had PD during consolidation phase. They all had advanced disease at presentation (6 with stage III; 2 with stage IV), and had T-cell IPT. Two patients had isolated local, BM, and CNS relapse each, while 1 had both local and CNS relapse. Disease recurrence was local in 3 patients, and systemic in 5, while it was early in 6, and late in 2 patients. All relapsed patients did not survive salvage chemotherapy. Table 3 describes causes of death, and timing of in relation to chemotherapy.

Chemotherapy toxicities

The most common chemotherapy toxicities were cerebral venous thrombosis (21%), followed by bone infarcts (10.6%), and avascular necrosis of head of femur (9.3%). One patient developed secondary AML after 3 years of FU with unfavorable cytogenetic aberrations (Table 3). Q7

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Q12 **Table 4** Chemotherapy toxicity encountered during chemotherapy.

Organ		Percentage (95% CI)	Grade		
	Total number (n = 59)		Grade 1–2 (mild)	Grade 3–4 (moderate)	Grade 5 (sever; death)
Cardiac	**4**		–	2	2
Chest	**3**		3	–	–
Pancreas	**1**		1	–	–
Cerebrovascular	**21**	**35.59% (23.55–49.13)**			
Thrombosis			1	15	–
PRESS			–	2	–
Infarcts			–	3	–
Bone	**29**	**49.15% (35.89–62.5)**			
AVN			–	11	–
Osteopenia & infarcts			–	14	–
Pathologic fracture			4	–	–
Therapy related AML	**1**				

AML: Acute Myeloid Leukemia, **AVN**: Avascular necrosis, **PRESS**: Posterior Reversible Leukoencephalopathy syndrome.

Discussion

This report presents the results of a retrospective study including LBL patients treated according to ALL Total Therapy Study XV at St. Jude Children's Research Hospital during 5.5 years. The mean age at diagnosis was 9 years which is similar to other reports [4,15,17,18], while other reports showed a younger mean age ranging from 7 to 8 years [10,18–20]. The male predominance present in the current study is well documented in most similar studies [4,16,19,21] (see Table 4).

In our study, mediastinal mass, T-cell LBL, and stage III Murphy's classification were the most common modes of presentation. This observation was made as well by many authors [10,15,17,18]. B-cell LBL in our study represented 10% of the cohort, similar to other studies; 14.8% [18], 12.2% [21], 23% [17]. In B-cell LBL, bone, skin and SC nodules were a common mode of presentation, and early stages represented 75% of the patients [20].

In the current study, BM infiltration was detected in 14.3%, similar to other study groups as 10.8% [15], 14.2% [4], rising up to 22% [16], 27% [17], and as high as 42.6% [18], 44% in adult patients [22]. Central nervous system (CNS) infiltration was detected in 2.6% of our patients. Data in the literature are heterogeneous with a rate of infiltration ranging from 0.7% up to 15% in adults [15,17,18,21,22]. In most of the studies, including the present one, BM and/or CNS infiltration were not recognized as an independent prognostic factor for OS and EFS [23,24]. In contrast, Jabbour et al. (2006) defined BM infiltration as a strong prognostic factor in adults [22].

Following induction chemotherapy, CR was detected in 26.7% of the patients, PR in 73.3%, while at day 100, 88% where in CR and 12% still had residual tumor. Similar CR rate was reported by many other groups as 70% [15], 77.8% [18], 95% [21], 63% [4], 57% [17], and 75%, 67% [19,22]. Higher CR rates were reported in EORTC trials 58881 as 92.3%, 95% [16,20], with different definitions of time of response [16,17,19–21] making data comparison more difficult.

Evaluation of residual mass was one of the major difficulties during the treatment [25]. The lack of reliable biological and/or radiological prognostic factors rendered the decision making in continuing treatment despite the presence of residual tumor a controversial one. Moreover, pathologic documentation especially in high risk organs poses many problems, and holds unnecessary risks. In the current study, patients continued treatment despite the presence of radiologically documented residual mass till the evidence proof of progressive disease. The prognostic relevance of residual mediastinal infiltration in patients with bulky disease at presentation didn't seem to influence a long term outcome in childhood LBL [26].

OS for early versus late responders was statistically significant as 100% and 81.7% respectively (p-value = 0.04). Other parameters including age, sex, T versus B cell, stage I/II versus III/IV were tested in univariate analysis and had no statistical significance. Data concerning the presence of prognostic factors are controversial. Uytterbroeck et al. (2008) reported 100% OS for 13% of patients with T-cell LBL in CR after 7 days of steroids and IT Methotrexate, and concluded that CR at day 7 of steroid therapy carries a good prognosis [16], while Ducassou et al. (2010) concluded that disease stage (stage I-III, versus stage IV) has a major prognostic factor with better OS and EFS [16]. In the NHL-BFM-95 protocol, treatment was adjusted according to initial stage, and response at day 33 induction chemotherapy [4]. Pillon et al. reported in 2015 that there was no statistically significant difference in DFS observed between patients who obtained early or late CR. Moreover, no subgroup or prognostic factors could be identified [17].

The median of the duration of follow up 47 months (range 1–89 months). The 4 years OS, EFS were 86.45% and 82.18% respectively. Our results are similar to most of those reported in the literature as OS 86.5% [15], lower than results reported by Sandlund (2009) as 5 years OS 90.2% and EFS 82.9% [21]. Reiter et al. for the BFM group reported 5 years EFS as 90% [4], and much better than the Chinese result reported by Gao et el (2014) as EFS 63.9% [18], and 63% [22]. Pillon et al. reported a 7 year OS 82%, EFS 74% [17].

In the current study, 10.4% of patient relapsed or had disease progression. They were all T-cell, and had an advanced stage. Our relapse rate is similar to what is reported in the literature as 13.5% [15],7.3% [21], 11% for T cell and 8% for B cell LBL [27], 16% [16], and much lower than Gao et al. (2014)

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as 23.1% [18], 22% [17]. Temuhlen et al. (2012) reported 8.9% relapse rate in localized LBL treated on COG trial A5971 [19], while Jabbour et al. reported 52% relapse rate in T cell LBL in adults [22]. As we can see from previous data, relapse rate is constant irrespective of disease stage [19], B [20,27], or T cell [22,27], with very few identifiable prognostic factors [18,19].

All relapsed patients in the current study died either from toxicity of salvage chemotherapy, or tumor progression, including one patient following allogeneic HSCT. Survival in relapsed patients is dismal. Burkhardt et al reported about the extremely poor outcome of patients who fail 1st line chemotherapy [27]. Following salvage chemotherapy and allogeneic HSCT transplant, OS for relapsed patients ranged from 7.4% [4] to 14% [27]. Ducassou et al. (2011) had 15.1% relapse rate in B-cell LBL, and they all died [20]. Moreover, difficulty in salvage therapy of relapsed patients has been mentioned by many study groups [20,27]. Duration of chemotherapy for LBL patients remains controversial. Patients in our study received induction, consolidation followed by a 24 months maintenance chemotherapy. Many centers treat low stage for a shorter duration [28], or lower dose of chemotherapy [4,28], but the average duration of therapy remains 24 months.

One patient developed secondary AML after 3 years of FU, refusing salvage chemotherapy, and is under palliative treatment. Similarly, secondary malignancy was reported in many studies with various rates of incidence, mainly AML [4,17,19,21]. Other reported secondary malignancy included cancer thyroid [17], pelvic Ewing's sarcoma [19], melanoma and stage IV glioblastoma [20].

In the current study, osteopenia, bony infarcts and avascular necrosis (ANV) of head of femur were the most common long term side effects of chemotherapy. Relling et al. (2004) reported that 26% of the patients had asymptomatic MRI changes at week 10 of maintenance chemotherapy, with minority of them requiring surgical intervention [29]. Risk factors for developing osteonecrosis were age between 16 and 20, females, obesity [30], and the association of dexamethasone and asparginase commonly used in the total XV protocol [31]. In the ALL BFM 95, the 5-year cumulative incidence of symptomatic osteonecrosis was 1.8% with more predominance in those above 10 years of age and particularly adolescents >15 years [32]. In a recent study about the impact of Dexamethasone versus prednisolone, on the incidence of osteonecrosis, it proved that it was similar in both arms. On the other hand, vincristine steroid pulses during maintenance treatment were responsible of more osteonecrosis 4.4% versus 2% [33].

Steroid therapy was reduced to 6 mg/m^2 or stopped once the radiologic bony changes were detected.

Other commonly detected toxicity was cerebrovascular thrombosis, seen in 27.2% of the patients, a common toxicity of the association of dexamethasone and asparginase, managed symptomatically with no serious complications. The toxic effect of pegylated asparginase in the form of adverse events, infections and hospitalization was lesser or similar to the native *E. Coli* form with sometimes a higher rate of pancreatitis [34]. In an experience on compassionate basis, using pegylated asparginase in multi relapsed and refractory ALL, the toxicity was severe allergic manifestations, however rapidly responding to treatment with no CNS thrombotic event or acute pancreatitis [34]. In a recent 5 year prospective multicenter cohort study the Nordic Society of Paediatric Haematology and Oncology ALL 2008 protocol, 20 children out of 1038, presented with cerebral sinus venous thrombosis with a cumulative incidence of 2%. Sixteen of the thromboses were related to asparginase, and 16 to steroids. Most accidents occurred in the consolidation phase [36]. In our center, pegylated asparginase is not available.

Conclusion

Results of treatment of LBL on the St Jude's total therapy XV study are comparable to most of the reported studies. Outcome of relapsing patients is extremely poor, hence the need to identify biologic or clinical prognostic factors including minimal residual tumor to better evaluate chemotherapy response. Steroids induced AVN, and cerebral vascular thrombosis was the main chemotherapeutic adverse events.

Conflict of interest

The author declared that there is no conflict of interest.

Uncited reference

[35].

References

[1] Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. N Engl J Med 1996;334:1238–48.
[2] Bollard CM, Lim MS, Gross TG, on behalf of the COG Non-Hodgkin Lymphoma Committee. Children's Oncology Group's 2013 blueprint for research: Non-Hodgkin lymphoma. Pediatr Blood Cancer 2013;60:979–84.
[3] Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood 2011;117(19):5019–32.
[4] Reiter A, Schrappe M, Ludwig WD, Tiemann M, Parwaresch R, Zimmermann M, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM group report. Blood 2000;95:416–21.
[5] Patte C, Kalifa C, Flamant F, Hartmann O, Brugieres L, Valteau-Couanet D, et al. Results of the LMT81 protocol, a modified LSA2L2 protocol with high dose methotrexate, on 84 children with non-B-cell (lymphoblastic) lymphoma. Med Pediatr Oncol 1992;20:105–13.
[6] Goldberg JM, Silverman LB, Levy DE, Dalton VK, Gelber RD, Lehmann L, et al. Childhood T-cell acute lymphoblastic leukemia: the Dana-Farber Cancer Institute acute lymphoblastic leukemia consortium experience. J Clin Oncol 2003;21:3616–22.
[7] Raetz EA, Perkins SL, Bhojwani D, Smock K, Philip M, Carroll WL, et al. Gene expression profiling reveals intrinsic differences between T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. Pediatr Blood Cancer 2006;47:130–40.
[8] Burkhardt B, Moericke A, Klapper W, Greene F, Salzburg J, Damm-Welk C, et al. Pediatric precursor T lymphoblastic leukemia and lymphoblastic lymphoma: differences in the common regions with loss of heterozygosity at chromosome 6q and their prognostic impact. Leuk Lymphoma 2008;49:451–61.
[9] Uyttebroeck A, Vanhentenrijk V, Hagemeijer A, Boeckx N, Renard M, Wlodarska I, et al. Is there a difference in childhood

T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma? Leuk Lymphoma 2007;48(9):1745–54.
[10] Burkhardt B, Reiter A, Landmann E, Lang P, Lassay L, Dickerhoff R, et al. Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: a report from the berlin-frankfurt-muenster group. J Clin Oncol 2009;27:3363–9.
[11] Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. Semin Oncol 1980;7:332–9.
[12] Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).
[13] Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26 (4):404–13.
[14] Fay MP, Brittain EH, Proschan MA. Pointwise confidence intervals for a survival distribution with small samples or heavy censoring. Biostatistics 2013;14(4):723–36.
[15] Katz OB, Ben Barak A, Abrahami G, Arad N, Burstein Y, Dvir R, et al. Treatment of T cell lymphoblastic lymphoma in children and adolescents: Israel Society of Pediatric Hematology Oncology retrospective study. Isr Med Assoc J 2011;13:161–5.
[16] Uyttebroecka A, Suciub S, Laureysc G, Robertd A, Pacquemente H, Alina Fersterf A, on behalf of the Children's Leukaemia Group (CLG) of the European Organization for Research and Treatment of Cancer, et al. 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 (EORTC). Eur J Cancer 2008;44(6):840–6.
[17] Pillon M, Aricò M, Mussolin L, Carraro E, Conter V, Sala A, et al. Long-term results of the AIEOP LNH-97 protocol for childhood lymphoblastic lymphoma. Pediatr Blood Cancer 2015;62:1388–94.
[18] Gao Y, Pan C, Tang JY, Lu FJ, Chen J, Xue HL, et al. Clinical Outcome of Childhood Lymphoblastic Lymphoma in Shanghai China 2001–2010. Pediatr Blood Cancer 2014;61:659–63.
[19] Termuhlen AM, Smith LM, Perkins SL, Lones M, Finlay JL, Weinstein H, et al. Outcome of newly diagnosed children and adolescents with localized lymphoblastic lymphoma treated on children's oncology group trial A5971: a report from the children's oncology group. Pediatr Blood Cancer 2012;59:1229–33.
[20] Ducassou A, Ferlay C, Bergeron C, Girard S, Laureys G, Pacquement H, et al. Clinical presentation, evolution, and prognosis of precursor B-cell lymphoblastic lymphoma in trials LMT96, EORTC58881, and EORTC 58951. Br J Heamotol. 152, 441–51.
[21] Sandlund JT, Pui CH, Zhou Y, Behm FG, Onciu M, Razzouk BI, et al. Effective treatment of advanced-stage childhood lymphoblastic lymphoma without prophylactic cranial irradiation: results of St Jude NHL13 study. Leukemia 2009;23:1127–30.
[22] Jabbour E, Koscielny S, Sebban C, Peslin N, Patte C, Gargi T, et al. High survival rate with the LMT-89 regimen in lymphoblastic lymphoma (LL), but not in T-cell acute lymphoblastic leukemia (T-ALL). Leukemia 2006;20:814–9.
[23] Colgan JP, Andersen J, Habermann TM, Earle JD, O'Connell MJ, Neiman RS, et al. Long-term follow-up of a CHOP-based regimen with maintenance therapy and central nervous system prophylaxis in lymphoblastic non-Hodgkin's lymphoma. Leuk Lymphoma 1994;15:291–6.
[24] Hoelzer D, Gokbuget N, Digel W, Faak T, Kneba T, Reutzel R, et al. Leukemia GMAIL: outcome of adult patients with T lymphoblastic lymphoma treated according to protocols for acute lymphoblastic leukemia. Blood 2002;99:4379–85.
[25] Patte C, Auperin A, Gerrard M, Michon J, Pinkerton R, Sposto R, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: It is possible to reduce treatment for the early responding patients. Blood 2007;109:2773–80.
[26] Attarbaschi A, Mann G, Dworzak M, Wiesbauer P, Schrappe M, Gadner H. Mediastinal mass in childhood T-cell acute lymphoblastic leukemia: significance and therapy response. Med Pediatr Oncol 2002;39:558–65.
[27] Burkhardt B, Reiter A, Landmann E, Lang P, Lassay L, Dickerhoff R, et al. Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: a report from the Berlin-Frankfurt-Muenster group. J Clin Oncol 2009;20:3363–9.
[28] Fortune A, O'Leary H, Gilomre R, Chadwick N, Brennan L, NíChonghaile M, et al. T-lymphoblastic leukemia/lymphoma: a single center retrospective study of outcome. Leuk Lymphoma 2010;51(6):1035–9.
[29] Relling MV, Yang W, Das S, Cook EH, Rosner GL, Neel M, et al. Pharmacogenetic risk factors for osteonecrosis of the hip among children with leukemia. J Clin Oncol 2004;22:3930–6.
[30] Kadan-Lottick NS, Dinu I, Wasilewski-Masker K, Kaste S, Meacham LR, Mahajan A, et al. Osteonecrosis in adult survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2008;26:3038–45.
[31] Teuffel O, Kuster SP, Hunger SP, Conter V, Hitzler J, Ethier M-C, et al. Dexamethasone versus prednisone for induction therapy in childhood acute lymphoblastic leukemia: a systematic review and meta-analysis. Leukemia 2011;25:1232–8.
[32] Bürger B, Beier R, Zimmermann M, Beck JD, Reiter A, Schrappe M. Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL)–experiences from trial ALL-BFM 95. Pediatr Blood Cancer 2005;44:220–5.
[33] De Moerloose B, Suciu S, Bertrand Y, Mazingue F, Robert A, Uyttebroeck A, et al. Children's Leukemia Group of the European Organisation for Research and Treatment of Cancer (EORTC). (2010). Improved outcome with pulses of vincristine and corticosteroids in continuation therapy of children with average risk acute lymphoblastic leukemia (ALL) and lymphoblastic non-Hodgkin lymphoma (NHL): report of the EORTC randomized phase 3 trial 58951. Blood 2010; 8;116:36–44. Bürger B, Beier R.
[34] Alvarez OA, Zimmerman G. Peg-asparginase-induced pancreatitis. Med Pediatr Oncol 2000;34:200–5.
[35] Sedki M, Vannier JP, Leverger G, Yakouben K, Adjaoud D, Vilmer E, et al. Liposomal daunorubicin (Daunoxome) and polyethylated glycol conjugated asparaginase (PEG-ASPA) in children with relapsed and refractory acute lymphoblastic leukemia treated on compassionate basis. J Egypt Natl Canc Inst 2008;20:55–62.
[36] Ranta S, Tuckuviene R, Mäkipernaa A, Albertsen BK, Frisk T, Tedgård U, et al. Cerebral sinus venous thromboses in children with acute lymphoblastic leukaemia – a multicentre study from the Nordic Society of Paediatric Haematology and Oncology. Br J Haematol 2015;168:547–52.

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