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Pediatric mature B-cell non Hodgkin lymphoma treatment with LMB-96 protocol. The Children Cancer Hospital Egypt experience

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Original Article

Abstract

Purpose: Burkitt lymphoma (BL) is a highly aggressive mature B-cell non-Hodgkin lymphoma (NHL) and is the fastest growing human tumor. The outcome of childhood NHL has improved steadily over the past decades through the use of intensive sequential multi-agent chemotherapy regimens. **Methods:** A retrospective study having all patients 18 years old or younger diagnosed with mature B cell NHL and treated at Children Cancer Hospital Egypt (CCHE). All children were treated according to the modified (LMB 96) protocol during the period between July 2007 and December 2012. Patients were followed up till June 2013. **Results:** Three hundred and seventy-seven patients were diagnosed with mature B cell NHL and received the LMB96 treatment protocol. The majorities were males (76.4%) with a median age of 5.3 years, and ranged from 0.1-18.0 years. The median follow-up period was 28.2 months (range 0.9-72 months). Burkitt lymphoma was the most predominant pathologic subtype (79.6%, n = 300), and abdominal mass as a primary site was the most common presentation (71.3%). Twenty seven patients (7.2%) were treated as group A, 268 (71.0%) as group B, and 82 (21.8%) patients as high risk group C. Seventy-one (18.8%) patients suffered adverse events. Major adverse events were early deaths in 17 patients (4.5%), death during induction chemotherapy seen in 18 patients (4.7%), and during maintenance therapy in 7 patients (1.8%), tumor progression in 19 patients (5.0%), and relapse in 10 patients (3.7%). Sixty-three patients (16.7%) died during the study period. The main causes of death were tumor lysis syndrome (TLS) in 25.3%, and severe sepsis during chemotherapy in 41.3% of the patients. The 3 years OS and EFS were 83.3% and 80.4% respectively for the whole groups of patients. OS and EFS were 100% for group A, and 87.5%±3.9% and 85.9±4.3% for group B. For group C BM^{+}/CNS^{-} patients, OS was 55.62%±15.8%, and EFS of 53.8%±15.6%. For BM^{+}/CNS^{+} patients, OS and EFS were 63.2%±21.76% and 57.9%±22.1% respectively. BM^{-}/CNS^{+} patients had OS 72.4%±18.8% and EFS 67.6%±19.7% at 36 months. **Conclusion:** TLS and chemotherapy related toxicity remains a major challenge affecting the outcome of pediatric mature B cell NHL. We identified bone marrow involvement as a risk factor affecting treatment outcome. Aggressive supportive care measures are mandatory to avoid unacceptable high toxicity related mortality.

Keywords: Pediatric NHL; LMB96; Children Cancer Hospital; Mature B cell Lymphoma

Introduction

Burkitt lymphoma (BL) is a highly aggressive mature B-cell non-Hodgkin lymphoma (NHL) and is the fastest growing human tumor. BL represents 40% of all childhood NHL and 3-4% of all childhood malignancies diagnosed each year in the USA.[1, 2] Its annual incidence in Africa has been estimated at 40-50 per million children younger than 18 years compared to 8 cases per million in France, and 7 per million in The Netherlands.[3] The outcome of childhood NHL has improved steadily over the past decades through the use of intensive sequential multi-agent chemotherapy regimens. In high-income countries, 5-year survival rates reaches 90% in patients treated according to the LMB 96 or BFM protocols [4-8], while the therapy offered in oncology units in low-income countries is not as aggressive, and outcome is not as good.[9] The aim of the current study is to report the treatment outcome, overall survival (OS) and event free survival (EFS) of patients who received FAB LMB96 protocol at the Pediatric Oncology Department, Children Cancer Hospital- Egypt (CCHE) during a 5.5 years period. Also to report about incidence of tumor lysis syndrome, relapse rate, treatment related mortality and causes of death in these patients.

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Methods and Materials

A retrospective study having all pediatric patients diagnosed with mature B cell NHL and treated at CCHE. All children were treated according to the modified (LMB 96) protocol during the period between July 2007 and December 2012, and were followed up till June 2013. Approval by our institutional scientific committee and informed written consent were obtained prior to starting chemotherapy.

Eligibility and risk stratification

Newly diagnosed children and adolescents (<18 years) with mature B-cell NHL were included in our study. Diagnosis was done according to the WHO classification and included Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL), Diffuse large B cell lymphoma (DLBCL), mediastinal large B-cell lymphoma (MLBCL), and mature B-cell neoplasm not otherwise specified (NOS).[10] Staging was performed according to Murphy's classification.[11]

Risk classification according to LMB96 protocol was defined as low risk group A with resected stage I and abdominal completely resected stage II; high risk group C with bone marrow disease (25% L3 blasts) or CNS disease defined by one or more of the following: any L3 CSF blast, cranial nerve palsy, clinical spinal cord compression, isolated intracerebral mass, cranial or spinal parameningeal extension; and intermediate risk group B, included all patients not eligible for group A or C. Exclusions to study enrollment included severe immunodeficiency syndromes, HIV positivity, previous malignancy, or prior chemotherapy.

Treatment

Chemotherapy was given according to the FAB LMB96 protocol

Group A

Patients assigned to group A received two courses of cyclophosphamide, vincristine, prednisone, and doxorubicin (COPAD) without intrathecal (IT) chemotherapy.[8]

Group B

Patients received prophase cyclophosphamide, vincristine, and prednisone (COP), followed by induction chemotherapy consisting of two cycles of vincristine, prednisone, adriamycin, methotrexate, cyclophosphamide and intrathecal injection (COPADM), and two courses of cytarabine, methotrexate (CYM) as consolidation if they were in complete remission (CR) post first course of consolidation Patients with less than a 20% response on day 7 of COP and patients with residual disease after CYM-1 were upgraded to group C starting from CYVE1.[12]

Group C

Following prophase COP, patients had induction chemotherapy which consisted of two cycles of COPADM (HD-MTX 8 g/m^2) followed by consolidation with 2 cycles of high-dose continuous infusion ofcytarabine plus etoposide (CYVE). Patients with CNS disease received additional IT therapy as well as an additional HD-MTX course between consolidation courses. At last, 4 maintenance cycles, the first consisted of COPADM, followed by three cycles with low dose cytarabine and etoposide (cycles 2 and 4), with the third cycle being similar to the first but without HDMTX and IT.[13]

Criteria of response

Complete response (CR) was defined as complete disappearance of all tumor masses, partial response (PR; 20% - 99% tumor reduction), no response (NR) or stable disease (SD); <20% tumor reduction. Progressive disease (PD) was > 25% increase in tumor size, while relapse was defined as recurrence of disease at any site after achieving CR. Failure was considered as relapses, deaths and failures to achieve a CR within the time frame.

Unresponsiveness to initial COP in itself was not considered a failure of the treatment strategy. Patients in critical condition (renal failure, sepsis, grade III/IV organ toxicity) were allowed to receive a second course of COP prior to proceeding to induction.[13]

Statistical methods

Data was analyzed using the Statistical Package for Social Sciences (SPSS) for Windows package version 15 (SPSS Inc., Chicago, Illinois, USA). Numerical data was presented as mean ± standard deviation (SD), median and range. Qualitative data was presented as numbers and percentages. Kaplan Meier was used to estimate survival and Log rank test for comparison. Overall survival (OS) was defined as the time from diagnosis till the end of the study period or death, while EFS was defined as the minimum period from diagnosis till the occurrence of an event including induction failure, disease progression, relapse, second malignancy, lost FU or death from any cause. A P-value ≤ 0.05 was considered significant.

Results

Patients' characteristics: out of the 530 patients diagnosed with NHL between July 2007 and December 2012, 377 (71.2%) patients had mature B cell NHL and received the LMB96 treatment protocol. There was a significant male predominance with 288 male patients (76.4%) and 89 Females (23.6%). The median age was 5.3 years, and ranged from 0.1-18.0 years. Number of patients varied in age group, with the range from 0 to 4 years being the most common (44.0%).

Demographic characteristics of study patients are summarized in **Table 1**, while **Table 2** shows common sites of CNS involvement.

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TABLE 1: Initial characteristics of the 377 studied patients.

	Frequency	Percent
Age		
0-4 years	166	44.0
5-9	127	33.7
10-14	62	16.4
15-19	22	5.8
Sex		
Male	288	76.4
Female	89	23.6
Histology		
Burkitt lymphoma (BL)	300	79.6
B-cell (L3) leukemia	54	14.3
DLBC	18	4.8
MLBCL	3	0.8
Mature B-NHL NOS	2	0.5
Primary site		
Abdomen	269	71.3
Peripheral lymph nodes	121	32.0
Thorax (not primary MDLBC)	87	23.0
Head and neck	62	16.4
Other tumor site	12	3.1
Modified Murphy's staging		
Stage I	18	4.8
Stage II	110	29.2
Stage III	167	44.3
Stage IV	28	7.4
ALL L3	54	14.3
Clinical Group		
Group A	27	7.2
Group B	268	71.0
Group C	82	21.8
BM/CNS involvement		
BM^{+}/CNS^{-}	41	50
BM^{-}/CNS^{+}	22	26.8
BM^{+}/CNS^{+}	19	23.2

BM= Bone marrow; DLBC= Diffuse large B-cell Lymphoma; MLBCL= Mediastinal large B-cell lymphoma; NOS= Non Otherwise specified; CNS= Central nervous system.

TABLE 2: Common sites of CNS involvement.

	Total number	Percentage
CNS involvement	**41**	**10.9**
Parameningeal extension	26	6.9
Blasts in CSF	9	2.4
Clinically manifest spinal cord compression	6	1.6
Cranial nerve palsy	5	1.3
Intra-orbital extension	1	0.3

CSF= Cerebrospinal fluid.

Burkitt lymphoma was the most predominant pathologic subtype (79.6%, n = 300), while abdominal mass as a primary site was the most common presentation (71.3%, n = 269). According to the modified Murphy Staging, stage III was the most common presentation seen in 167 patients (44.8%) **Table 1.**

Tumor Lysis Syndrome (TLS)

Laboratory and/or clinical tumor lysis syndrome was observed in 57 patients (15.1%); of which 30 (11.2%) out of 268 patients were group B, and 27(32.9%) out of 82 in group C. Sixteen patients (4.2%) died out of TLS during the prophase chemotherapy (COP). They represent most of the mortality causes during this period of chemotherapy (16/17 = 94.1%). **Table 3** shows the major adverse events in studied patients.

Chemotherapy outcome

Following the LMB96 protocol risk stratification, 27 patients (7.2%) treated as group A, 268 patients (71.0%) as group B, and 82 patients (21.8%) in high risk group C.

Group A

All 27 patients stratified as group A (7.2%) received chemotherapy successfully, and are alive in CR.

Group B

Two hundred-sixty eight patients were stratified as group B. Following initial COP course of chemotherapy; 218 (81.3%) had >20% radiologic response and continued on same line. Twelve patients (3.18%) died from severe sepsis and/or TLS during prophase. Twenty eight patients (10.4%) didn't receive COP and started COPAM directly as they were considered to have no bulky tumor (stage II unresected tumor and/or incomplete resection anastomosis of primary intestinal mass). Ten patients (3.7%) had mild to no response defined as less than 20% decrease in the initial tumor volume and were upgraded to group C. Eight patients (2.9%) died from sever sepsis during chemotherapy, 12 (4.4%) progression, and 8 (2.9%) relapses (**Table 3**).

Group C

Eighty two patients were treated as group C. They were 41 (10.8%) BM^{+}/CNS^{-}, 22 (5.08%) BM^{-}/CNS^{+}, and 19 patients (5.0%) BM^{+}/CNS^{+}. Twenty two patients (5.8%) had treatment related mortality, while 7 patients (1.8%) had tumor progression, and 2 patients (0.5%) relapsed.

Events, relapses and tumor progression

Seventy-one patients (18.8%) suffered adverse events, 40 (10.6%) in group B, and 31 (8.2%) in group C. There were no events in group A patients. Major adverse events were early deaths in 17 patients (4.5%), death during induction chemotherapy seen in 18 patients (4.7%), death during maintenance therapy in 7 patients (1.8%), tumor progression in 19 patients (5.0%), and relapse in 10 patients (3.7%). **Table 3** describes major events according to risk groups.

Survival

By the end of our study, 291 patients were alive in CR (77.2%) while 63 patients (16.7%) died. Twenty patients (5.3%) lost FU (5 patients; 1.3% in active disease, and 15 patients; 4.0% in CR) as shown in **Table 4**.

TABLE 3: Adverse Events in patients with NHL.

	Death			Progression	Relapse	Total
	Prophase	Induction	Consolidation			
Group B	12	6	2	12	8	40
Group C	5	12	5	7	2	31
BM^+/CNS^-	3	5	2	3	1	14
BM^-/CNS^+	1	2	1	1	1	6
BM^+/CNS^+	1	5	2	3	0	11
Total	17	18	7	19	10	71

TABLE 4: Disease Status in the studied patients.

Disease Status		
	Frequency	Percent
Alive in Active Disease	3	0.8
Alive in CR	291	77.2
Died in Active Disease	57	15.1
Died in CR	6	1.6
Lost Follow Up in Active Disease	5	1.3
Lost Follow Up in CR	15	4.0

The 3 years OS and EFS were 83.3% and 80.4% respectively for the whole group of patients **Figures 1** and **2**.

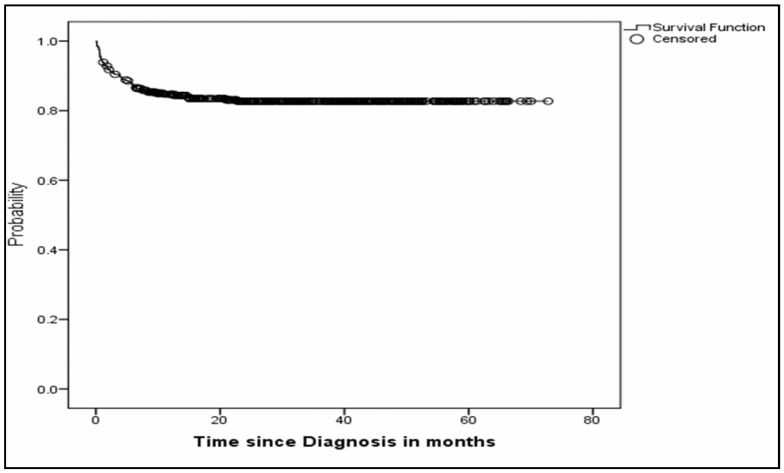

FIG. 1: Overall survival for all Patients (83.3%).

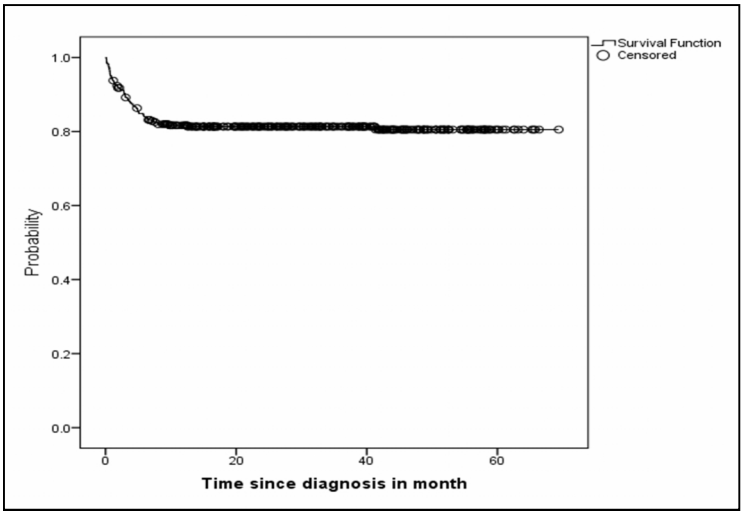

FIG. 2: Event-free survival for all patients (80.4%).

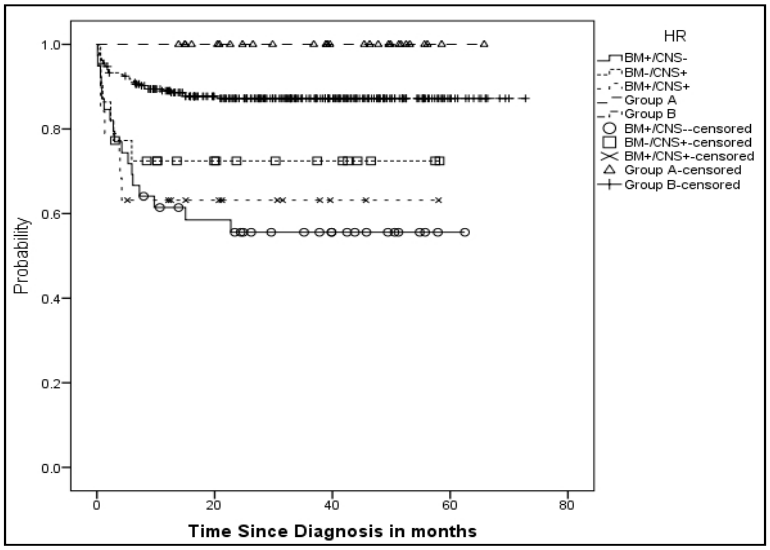

FIG. 3: Overall survival in different group categories.

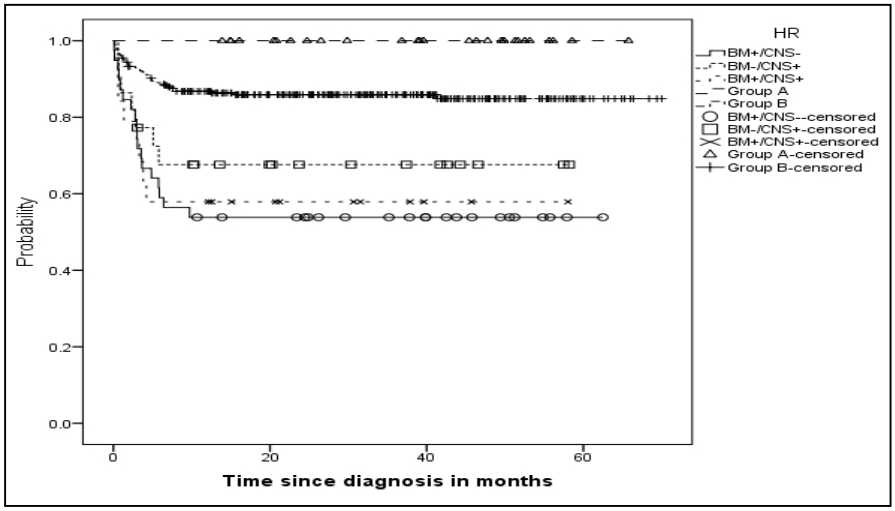

FIG. 4: Event free survival in different group categories.

OS and EFS were 100% for group A, and 87.5%±3.9% and 85.9±4.3% for group B. For group C BM^+/CNS^- patients, OS was 55.62%±15.8%, and EFS of 53.8%±15.6%. For BM^+/CNS^+ patients, OS and EFS were 63.2%±21.76% and 57.9%±22.1% respectively. BM^-/CNS^+ patients had OS 72.4%±18.8% and EFS 67.6% ±19.7% at 36 months (**Figure 3** and **4**).

The mean FU period was 29.2 months (range 0.9 - 72 months), with an SD 19.2 months. Median FU period of all patients was 28.2 months for all patients.

Discussion

This retrospective study describes the treatment outcome of pediatric patients treated on the LMB-96 in our institute during 5.5 years period. To the best of our knowledge, it's one of the largest single center patient's series in the Middle East region. Mean age of the patients is slightly lower than many previous studies [5, 12, 14], but similar to our previous report [15]. Age category below 4 years was the most common in the studied group in contrast to other study groups [13, 16], were ages between 5-9 years being the most common, although age is not considered as risk factor [17]. Cairo *et al.* in 2012 identified advanced stage, increased LDH level $\geq$ 2 X normal value, mediastinal disease and combined BM^+/CNS^+ as the main risk factors for treatment response.[17] In our study, analysis of prognostic factors including age, gender, upfront tumor resection and CNS status were all statistically insignificance. Nevertheless, BM involvement was found to be associated with lower OS and EFS, but this difference was statistically insignificant probably due to small sample size.

The obvious male predominance observed in the current study is a common finding in pediatric mature B cell NH [5, 12, 13, 15-20]. BL and B-ALL were the predominant pathologic subtype followed by DLBC of the studied patients, but in different ratio, as they represented 5% of the patients compared to 14% [12], 10% [13], 11.7% [15], 14.9% [14] and 31.4% [16] of

the patients in different studies. Other rare subtypes observed were PMLBCL and mature B-NHL NOS.

In most studies reporting pediatric mature B cell NHL -including the present one- abdominal mass, stage III, group B were the most common presentation, followed by peripheral lymph enlargement including head and neck regions, mediastinal mass, CNS involvement but with different incidences according to the studies.[5, 12, 14, 15-17, 20]

In the current study, 15.1% of the patients had laboratory and/or clinical TLS, representing 11.1% of group B and 32.9% of group C patients reflecting its increased incidence in close association with tumor aggressiveness. Management of TLS was done using the administration aggressive hydration and allopurinol as non-recombinant urate oxidase is not available routinely in our country. In previous, studies laboratory TLS incidence ranged from 27% to 42% of the patients [21-24], although clinical TLS incidence is much lower ranging from 4.4% to 8.4% [21-23].

Stage I disease represented 4.8%, stage II 29.1%, stage III 44.8%, stage IV 21.7%, while L3 ALL were 14.3%. Similarly, few authors reported the same incidence in stage I [5, 15, 20], and stage III disease [5, 14, 17, 20]. Our results are higher in stage II compared to few reports.[5, 15, 17] On the other hand, we report lower incidence in stage IV disease [5, 15-17, 20]and L3 ALL than some studies[5, 16].

Low risk group A patients represented 7.2% compared to 71.0% group B and 21.8% for high risk group C patients. In group A patients, incidence is in concordance with Patte *et al.*[5], and higher than our previous report [15], this is probably be due to accumulation of experience and better risk stratification. In group B and C patients, similar incidence was reported in the literature.[5, 15, 17] Reiter *et al.* reported different incidence: 17% in R1, 40% in R2 and 43% in R3 group of patients but with a risk stratification based on tumor resection, LDH level, and localization of the primary tumor.[14] In our study, LDH was not considered as it was not part of the risk stratification.

Following initial cytoreductive chemotherapy, 90.8% of the patients were good responders and continued as group B, while 3.7% were upgraded to group C. Patte *et al.* reported 95% response to prophase treatment [5, 12] and 4.9% [12], 4.5% [5] as non-responders. We previously reported a similar response rate.[15] Ten percent of the patients underwent incomplete resection of their abdominal mass, or had small initial tumor size, hence we estimated no need for cytoreductive course of chemotherapy and they received COPADM1 directly.

We report a high mortality rate (16.7%) in our study when compared to 7.3% reported in FAB LMB 89 study [5], 3.3% in NHL-BFM 90 study [15], 4.6 % in LMB 96 high risk patients [13]. Another large-scale study resulted in a cure rate above 90% with a 7.7% mortality rate, and <1% toxic death in childhood B-NHL.[16]

Analyzing this high mortality rate, out of 16.7% died during therapy; 4.2% died directly or indirectly due to TLS, 6.9% out septicemia during chemotherapy, and 5.3% due to tumor progression. Again, this very high induction mortality rate was due to sepsis following grade IV neutropenia. Reiter *et al.* reported 3.3% deaths from different causes including acute TLS, toxic death or infection, but none during the course of chemotherapy[14], while Patte *et al.* reported 7.3% [12].

Deaths during induction period (28%) were mostly following COPADM1 course, probably due to accumulated hematologic toxicity of the two courses given in short duration, while high dose Ara-C and related toxicity was the main cause of death during consolidation (11%) in group C patients. Similarly, life threatening infections were reported during COPADM1 and CYVE [5, 25]. Other causes of death were tumor progression in 10% of the patients.

Our 3-years OS and EFS were 83.3% and 80.4% respectively. The current results are similar to what we have reported previously [15], but are worse than most of the studies using similar protocols or multi-drug combination. Patte *et al.* reported 5 years OS 92.5% and EFS 91% in 2001.[5] Six years EFS 89% $\pm$ 2% was reported by Reiter *et al.* [14], while 3 years EFS was 88% $\pm$ 1% was reported by Cairo *et al.*[17] A recent Japanese study reported 4 years OS and EFS were 92.7% and 87.4% respectively[16]. For group A patients, we confirm our excellent results obtained previously.[15] The same is reported by most of the study groups that resected stage I and abdominal stage II have excellent prognosis regardless of the chemotherapy regimen given[5, 12, 14, 16.] Four years EFS reported by Gerrad *et al.* was 98.3%, while OS was 99.2%.[8] OS and EFS for low risk patients were between 98% to 100% in most of the studies.[5, 14-17]

For group B patients, OS and EFS were 87.5%±4.1% and 85.9%±4.3% respectively, lower than most studies performed as 92% [5, 12], 96% [14], 89% [17], and 93.6% [16]. This could be explained by high rate of chemotherapy related mortality (11.1%), as relapse rate and disease progression in our study (8.7%) were not higher than any study group report.[12, 14, 16]

Fifty percent of group C patients in our study were BM^+, while 26% had CNS involvement and 24% were both BM^+ and CNS^+. Similar incidence rate was reported.[5, 13-16]

Our worst results are in high risk group C BM^+/CNS^-, and BM^+/CNS^+ patients. OS was 55.62%±15.8% and 63.2%±21.76 % respectively, while EFS was 53.8%±15.6% and 57.9%± 22.1% respectively. The sub-group of patients with BM involvement at diagnosis was associated with poor outcome, compared to CNS involvement. To the contrary of most of

the studies, combined BM^+ and CNS^+, or those with CNS^+ disease had the worst outcome [5, 13, 16, 17, 26-29] and B-ALL had excellent overall survival; 88% [5, 13, 14, 27, 28], and 86.2%±4.0% [16]. This might be due to the fact that patients with BM involvement express more hematologic toxicity and therapy related mortality.

Patte *et al.* identified CNS involvement as the only prognostic factor in group C patients.[5] Similar conclusion was reported by most of the study groups.[13, 14, 16, 17, 25]

Conclusion

In conclusion, chemotherapy related toxicity remains a major challenge affecting the outcome of pediatric mature B cell NHL. We identified BM involvement, and treatment related toxicity during prophase/induction period of treatment as risk factors affecting outcome. Aggressive supportive care measures are mandatory to avoid unacceptable high toxicity related mortality.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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