ABSTRACT

Introduction: Lymphomas are the third most common malignant tumor in the pediatric age group after leukemia and brain tumors. Outcome has improved remarkably over the past decade because of improvements in imaging and staging systems that more accurately reflect the clinical behavior, and the development of risk-adapted multi-agent chemotherapeutic regimens.

The aim of this work is to study the outcome, Overall Survival (OS) and Event Free Survival (EFS) of patients receiving FAB LMB96 protocol applied for treatment of mature B cell lymphoma.

Patients and Methods: This is a retrospective study analyzing the data of 103 newly diagnosed pediatric NHL (Burkitt’s lymphoma/leukemia, Diffuse Large B Cell Lymphoma (DLBCL)) who received LMB96 protocol at Department of Pediatric Oncology, National Cancer Institute, Cairo University, during the time period from 1st of January 2006 to the end of December 2008. A total of 103 patients were included in the study, and were followed-up till 31st December 2009.

Results: This study included were 80 males (77.7%) and 23 females (22.3%), their mean age was 6.55±3.9 years ranged from 2 to 16 years.

Abdominal presentation was the most common clinical presentation seen in 85 patients (82.5%) followed by thoracic mass in 27 patients (26.2%) and cervical mass in 22 patients (21.4%).

CNS involvement occurred in 16 patients (15.5%) while bone marrow infiltration occurred in 18 patients (17.5%).

The most common pathological subtype was Burkitt’s lymphoma seen in 83 patients (80.6%) followed by DLBCL in 12 patients (11.7%). Stage III was the most commonly seen; detected in 65 patients (63.1%). The commonest treatment group seen was group B in 80 patients (77.7%) followed by group C in 19 patients (18.4%) then group A in 4 patients (3.9%).

Conclusion: FAB LMB96 protocol is well tolerated, giving results close to the international literature for both group A and B patients, while it seems toxic for group C patients.

Key Words: NHL – FAB LMB96 – Pediatric – Lymphoma.

INTRODUCTION

Lymphomas are the third most common group of malignant tumors in the pediatric age group after leukemia and brain tumors worldwide [1]. Among pediatric non-Hodgkin’s lymphomas (NHL), B-cell constitutes the largest group. NHL of childhood are comprised of three principal histotypes: Small noncleaved cell (SNCC), lymphoblastic lymphoma (LL), and diffuse large B-cell Lymphoma (DLBCL) [2]. In contrast with the adults, childhood NHL are diffuse, aggressive neoplasms with a tendency to widespread dissemination [2].

Advances in histopathology, immunology, cytogenetics, and molecular biology have promoted enormous progress in the understanding of the biology of the NHLs, which, consequently, has led to more rational classification of these diseases [1].

Outcome has improved remarkably over the past decade because of improvements in imaging and staging systems that more accurately reflect the clinical behavior, and the development of risk-adapted multi-agent chemotherapeutic regimens [3].
Progress in therapy of childhood NHL is one of the successful stories of the past two decades. More than 75% of children with NHL can now be cured with modern therapy, and many recent studies have focused on reduction of therapy to reduce the acute and long-term consequences of treatment [3].

Advances in supportive care to reduce the life-threatening complications of therapy; and more rational application of chemotherapy with the development of intensive regimens for children presenting with advanced-stage disease have all contributed to gratifying improvements in outcome for children with NHL [4].

The aim of this work was to study the outcome, OS and EFS of patients who received FAB LMB96 protocol applied for treatment of mature B cell lymphoma at Pediatric Oncology Department, NCI, Cairo University in a 3 year period (2006-2008).

**PATIENTS AND METHODS**

This is a retrospective study analyzing the data of 103 newly diagnosed pediatric patients with NHL (Burkitt lymphoma/leukemia, Diffuse DLBCL) admitted to the Department of Pediatric Oncology, National Cancer Institute, Cairo University, during the time period from 1st of January 2006 to the end of December 2008. Patients were followed-up till 31st December 2009.

**Eligibility criteria:** Patients were included in the study if they fulfilled the following criteria:

- Histologic diagnosis of a mature B cell lymphoma (e.g., Burkitt’s lymphoma/leukemia, atypical Burkitt’s lymphoma, diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, mature B-cell lymphoma).
- Newly diagnosed and previously untreated, (no more than 72 hours of steroids and/or emergency radiation).
- Pediatric age group (0-16 years) at the time of diagnosis.
- No prior organ transplantation.
- No previous malignancy of any type.
- No known HIV positivity.

**Initial evaluation:**

1. History and full clinical examination.
2. Laboratory evaluation: Complete blood count with differential, hepatic and renal function tests, serum uric acid, calcium, phosphorus, total protein, albumin, serum electrolytes; and coagulation screen (PT, PTT, fibrinogen) were obtained on admission and during chemotherapy.
3. Tumor tissue was obtained for determination of the histologic diagnosis by light microscopy. Immunologic and cytogenetic studies. The diagnosis of B-cell NHL was based on a biopsy and histopathology with cytomorphology and immunophenotyping.
4. Bilateral iliac crest bone marrow aspirates and biopsies including cytogenetic analysis.
5. Cerebrospinal fluid (CSF)-for cell count and differential, glucose, protein, and LDH.
6. Imaging studies: Chest X-ray (PA and lateral), CT or MRI scan of neck, chest, abdomen and pelvis (all patients), CT or MRI of head and neck (patients with head and neck disease).
7. Echocardiogram.

**Treatment:**

According to the treatment protocol (LMB-96), patients were stratified into three treatment groups [6]:

- **Group A:** Completely resected stage I or completely resected abdominal stage II lesions.
- **Group B:** All cases not eligible for Group A or Group C.
- **Group C:** Any CNS involvement and/or bone marrow involvement ≥25% blasts.

For CNS involvement one or more of the following applies:

1. Any L3 blasts in CSF.
2. Cranial nerve palsy (if not explained by extracranial tumor).
4. Isolated intracerebral mass.
5. Parameningeal extension: Cranial and/or spinal.

The drug combinations, doses and schedules in each treatment group are described in Table (1).
Patients in group B and C received initial cytoreductive chemotherapy for 7 days, consisting of Cyclophosphamide, Vincristine and Prednisolone (COP).

For patients in treatment group B, tumor response evaluation was done on day 7 and after CYM1. Non responding patients (<20% reduction in tumor size) were treated with Group C starting with COPADM3.

Definition of response criteria:

**Complete Response (CR):** Complete disappearance of all measurable or evaluable lesions (except bone), no L3 blasts in the bone marrow or in the CSF.

**Partial response (PR):** Twenty-99% reduction in the product of the two largest diameters (perpendicular) of measurable lesions and/or in the case of leukemia; 20-99% reduction in the number of L3 blasts in the bone marrow and/or in the CSF.

**No response (NR) or Stable disease (SD):** <20% tumor reduction of the product of the two largest diameters (perpendicular) of measurable lesions.

**Progressive disease (PD):** >25% increase in the product of the two largest diameters (perpendicular) of measurable lesions and/or the number of L3 Blasts in the bone marrow and/or CSP in the case of leukemia.

**Relapse:** Recurrence of disease at any site after achieving a CR.

**Statistical methods:**

Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows package version 15 (SPSS Inc., Chicago, Illinois, USA). Numerical data were presented as mean ± standard deviation (SD), median and range. Qualitative data were presented as numbers and percentages. The Chi-square test was used to examine the relation between qualitative variables. Comparison between numerical variables was done using the t-test as appropriate. Kaplan Meier was used to estimate survival and Log rank test for comparison. A p value ≤0.05 was considered significant.
RESULTS

A total of 103 patients were diagnosed to have mature B cell NHL and received FAB/LMB96 protocol at the Pediatric Oncology Department of the National Cancer Institute, Cairo University during the years between January 1st 2006 and December 31st 2008, patients were followed-up till 31st December 2009.

Patients characteristics are illustrated in Table (2). They were 80 males (77.7%) and 23 females (22.3%) at a ratio 3.4:1. Their mean age was 6.55±3.9 years ranged from 2 to 16 years.

Abdominal presentation was the most common clinical presentation seen in 85 patients (82.5%) followed by thoracic mass in 27 patients (26.2%), cervical mass in 22 patients (21.4%), generalized lymph nodes enlargement in 19 patients (18.4%) and bone infiltration in 5 patients (4.9%).

CNS involvement occurred in 16 patients (15.5%) in the forms of CSF infiltration with blasts in 4 patients (3.9%), cranial nerves palsy in 7 patients (6.8%), intra cerebral mass in 3 patients (2.9%) and parameningeal extension in 2 patients (1.9%).

Bone marrow infiltration occurred in 21 patients (20.3%).

The most common pathological subtype was Burkitt’s lymphoma seen in 83 patients (80.6%) followed by DLBCL in 12 patients (11.7%) then mature B cell (L3) leukemia in 8 patients (7.8%).

According to the St Jude classification system, stage III was the most commonly seen detected in 65 patients (63.1%) followed by stage (IV) BM <25% with CNS involvement in 11 patients (10.7%) then stage (II) unresected in 8 patients (7.8%).

According to the LMB96 protocol stratification, the commonest treatment group seen was group B in 80 patients (77.7%) followed by group C in 19 patients (18.4%) then group A in 4 patients (3.9%).

Evaluation of response to chemotherapy:

In groups B and C, two response evaluations were done. The first was post COP (in groups B and C), while the second was post CYM1 in (group B) and post CYVE2 in (group C).

Group B response to chemotherapy:

1- Response to COP: Evaluation of response to COP in (group B) revealed that 14/80 patients (17.5%) were in CR, and 60/80 patients (75%) were in PR. Less than 20% reduction of tumor size occurred in 4/80 patients (5%), those patients were upgraded to group C, and 2/80 patients (2.5%) died due to septicemia post COP.

2- Re-evaluation post CYM1: The remaining 74 patients had a second reevaluation post CYM1. Complete remission was achieved in 63/80 patients (78.7%), 1/80 patient (1.2%) was switched to (group C) as he had pathologically documented residual disease, 6/80 patients (7.5%) were incompliant and lost follow-up while on chemotherapy, and 4/80 patients (5%) died due to septicemia (2 post COPADM1, 1 post COPADM2 and 1 post CYM1).

Group C response to chemotherapy:

1- Response to COP: Evaluation of response to COP in group C revealed that 17/19 patients (89.5%) had partial remission, 2/19 patients (10.5%) died due to septicemia post COP.

2- Re-evaluation post CYVE2: Twenty two patients were re-evaluated post CYVE2, [17 patients in group C in addition to 5 patients upgraded from group B]. Complete remission occurred in 9/22 patients (41%), partial remission occurred in 7/22 patients (32%), stable disease occurred in 2/22 patients (9%), 1/22 patients (4.5%) lost follow-up while on chemotherapy, disease progression occurred in 2/22 patients (9%) and 1/22 patients (4.5%) died due to septicemia post CYVE2.

Treatment outcome:

CR for the whole group of patients was achieved in 76 patients (73.7%), PR in 7 patients (6.7%), relapses and disease progression occurred in 9 patients (8.8%) and SD in 1 patient (1%). Death due to septicemia occurred in 9 patients (8.7%). There were 8 patients (7.8%) who discontinued treatment (Table 3).

In (group A) complete remission (CR) was achieved in 4/4 patients (100%).
In (group B) CR was achieved in 63/80 patients (78.7%). Relapse occurred in 3 patients (3.7%) (2 patients after 1 month of ending treatment and 1 patient after 6 months of ending treatment), and disease progression DP occurred in 2 patients (2.5%).

In (group C) CR/PR was achieved in 16/24 patients (66.6%) and disease progression occurred in 4 patients (16.6%).

Duration of FU ranged from 6-42 months. Mean OS was 38.99±14.9 months and the mean DFS for all patients was 37.9±14.6 months. Median was not calculated as more than 50% were alive at end of follow-up.

For the whole group, the 3 year-OS survival was 86.6%, while the DFS was 83.7%. The 3 year-DFS for group A was 100%, for group B and group C patients was 82.3%.

The 3 years OS and DFS in relation to the treatment groups of studied mature B-cell NHL pediatric patients are illustrated in Figs. (1,2) respectively.

<table>
<thead>
<tr>
<th>Variable</th>
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</tr>
</thead>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
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<td></td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
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<td>80</td>
<td>77.7</td>
</tr>
<tr>
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</tr>
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</tr>
<tr>
<td>CSF involved</td>
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<td>3.9</td>
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<td>7.8</td>
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<td></td>
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<tr>
<td>I Incomplete resection</td>
<td>5</td>
<td>4.9</td>
</tr>
<tr>
<td>II Abdominal complete resection</td>
<td>4</td>
<td>3.9</td>
</tr>
<tr>
<td>II unresected tumor</td>
<td>8</td>
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<td>IV BM &lt;25% with CNS Involvement</td>
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<td>1.9</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Group C (CNS +ve)</td>
<td>16</td>
<td>11.7</td>
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</table>
DISCUSSION

Our study included 103 patients who were treated from mature B cell NHL at Pediatrics Oncology Department NCI, Cairo University during 3 years period (2006-2008). The aim of our work was to give a closer picture to the treatment outcome of FAB/LMB96 protocol. Patients were followed-up for a period of 3 years.

Cure rates of children with mature B-cell lymphoma have significantly improved over the past 25 years [5]. Based on the characteristics of this lymphoma, specifically a high growth fraction and a short doubling time, successful treatments were developed to be more intensive, delivering drugs either fractionated or by continuous infusion, maintaining serum drug level for at least 48 to 72 hours with the shortest delay between the courses [6].

In the LMB89 study (1989-1996), 3 risk groups were identified based on tumor bulk, and receiving treatment of progressive intensity. In addition, response to chemotherapy after the first week of treatment was also considered for adapting treatment intensity. Results of this study showed that intermediate-risk group B represented the majority of the patients (about two thirds), with a 5-course treatment as defined, and a treatment intensification for the small subgroup of “bad responders” after 1 week, or in partial remission after 3 courses, their 5-year overall survival (OS) and EFS were 94% and 92% respectively [7]. However, this successful treatment was associated with a high incidence of acute toxicity including severe mucositis and infection. It was also based on high doses of cyclophosphamide, a drug known to be associated with a risk of infertility. This led to an attempt to further reduce treatment without

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**Table (3): Outcome of 103 B cell NHL pediatric patients in different treatment groups.**

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>SD</th>
<th>PD</th>
<th>Relapse</th>
<th>Died</th>
<th>Lost FU</th>
<th>Switch</th>
<th>To group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Group A</td>
<td>4</td>
<td>100</td>
<td>0</td>
<td>0.00</td>
<td>0</td>
<td>0.00</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Group B</td>
<td>63</td>
<td>78.8</td>
<td>0</td>
<td>0.00</td>
<td>2.5</td>
<td>3.75</td>
<td>6</td>
<td>7.5</td>
</tr>
<tr>
<td>Group C</td>
<td>9</td>
<td>45.8</td>
<td>1</td>
<td>4.1</td>
<td>16.6</td>
<td>0.0</td>
<td>3</td>
<td>2.9</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>73.7</td>
<td>1</td>
<td>0.97</td>
<td>5.8</td>
<td>2.9</td>
<td>9</td>
<td>8.7</td>
</tr>
</tbody>
</table>

CR: Complete resection.  
SD: Stable disease.  
PD: Progressive disease.  
FU: Follow-up.

**Fig. (1): Overall survival time (months) in relation to treatment groups of 103 mature B cell pediatric NHL patients according to LMB protocol.**

**Fig. (2): DFS (months) in relation to treatment groups of 103 mature B cell pediatric NHL patients according to LMB protocol.**
jeopardizing survival, which was the aim of the French-American-British (FAB) LMB96 international study [7].

In our present study, the male to female ratio was 3.4:1 similar to that reported by other authors [8,9].

According to the WHO histological classification of childhood NHL, mature B-cell most commonly predilect the abdomen as a primary site of presentation and Burkitt’s NHL is the most common subtype [2,10,11]. This finding matches with our results where Burkitt’s lymphoma represented 80.6% of the cases and abdominal stage III was the predominant site.

In our study, 4 patients (3.9%) were assigned to (group A) all of them were stage II who had completely resected abdominal lesions. They received 2 courses of COPAD post surgery, which was well tolerated without significant toxicity, and CR was achieved in all patients (100%). Our results were similar to the results of Gerrard et al., who conducted a study on 132 patients assigned to (group A) who received FAB/LMB96 protocol [12].

Intermediate-risk disease (group B) was studied in a series of 637 patients. Participants were randomized to either standard therapy, reduced dose of cyclophosphamide, omission of maintenance therapy, or both reductions. At 4 years, EFS did not differ among the different arms, suggesting that treatment could be safely reduced in intensity and duration [8].

In our study 80/103, (77.7%) patients were assigned to (group B). Complete remission was achieved in 78.7% of the patients, and 6.25% were switched to (group C). Deaths were 7.5%, relapse and disease progression occurred in 6.25%. Our results are worse than those reported by the original study group as complete remission was 90.7%, switched to (group C) 3%, deaths during treatment (post COP) 1% and relapse was 6% of the patients [7]. This difference might be explained by larger number, better control of infection in the original study, and lower patients compliance in our study. In addition, patients originally who suffered the most extreme toxicity and died within the initial stages of treatment (COP) were not eligible to be randomized and were not included in mortality rates [12].

High-risk patients, including those with CNS involvement, were randomization between a standard therapy and reduced intensification block and omission of 75% of the maintenance therapy in a study including 217 patients [12].

At 4 years, intention-to-treat analysis, EFS for full-intensity therapy was 90% (±3.1%) versus 80% (±4.2%) for reduced-intensity therapy. They concluded that for patients with either combined BM/CNS disease at diagnosis or poor response to initial COP, reduction therapy had a significantly inferior EFS (p<.001), and that standard-intensity FAB/LMB therapy is recommended for children with high-risk B-NHL (B-ALL with or without CNS involvement) [12].

In our study, 19 patients (18.5%) were assigned to group C initially, in addition to 5 patients who switched from group B. Our results showed CR/PR in 66.6%, disease progression in 16.6% and toxic death in 12.5% of the patients, compared to CR in 82%, relapse or progression in 6.5% and toxic death in 12.9% Cairo et al. 2007. Again, the differences could be explained by the previously mentioned reasons [12].

From both studies [7,12], we can conclude that a modest reduction in intensity of therapy is probably safe for children with a better prognosis, (good responders) while dose reduction for those with a worse prognosis (aggressive bulky disease) results in worse outcome.

In group B and C patients, partial response has become a more frequent cause of failure than recurrent disease [12]. This also could be illustrated in our results where primary treatment failure occurred in 5.8% in comparison to relapse seen in 2.9% of the patients.

Finally, the major problem that was illustrated from our study is the high rate of toxic deaths which was the sole cause of mortality in 12.6% of our patients.

In conclusion, FAB LMB96 protocol seems well tolerated giving results close to the international literature for both group A and B patients, while it seems toxic for group C patients. Long-term follow-up is vital to assess impact of the FAB/LMB96 protocol on fertility, cardiac toxicity the risk of second malignancies, and other late effects.
REFERENCES


