Pediatric B-cell Non-Hodgkin Lymphoma: 21-year Experience with FAB-LMB Protocols in a Single Institute in Greece

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Abstract

Aims and background: Our objective was to analyze the clinical and demographic characteristics of children with B-cell lymphoma treated in a single center over the last two decades.

Methods: Data was collected by a retrospective review of the charts of all 76 patients treated to our unit, from 1990 to 2010, with FAB LMB 89, 96 protocols and 2003 modifications.

Results: The median age was 8.03 years, with a male predominance 3.7:1. According to LMB staging criteria, 7 patients (9.2%) were classified as Group A, 53 (69.7%) as B and 16 (21.1%) as C all but 1 with bone marrow involvement and in 8 combined with CNS involvement. Most of our patients (46/76 - 60.5%) had abdominal tumours. Eight children of A and B Group (8/60, 13.3%) were upgraded to Group C due to poor treatment response. Regarding outcome, 11 patients died, 8 due to disease, 3 due to toxicity, 2 in induction and 1 post autograft. Relapse occurred in 10 children (13.2%), all with abdominal disease, one of them with concurrent mediastinal involvement. Most relapsed patients (7/10) were initially treated as Group B (7/53, 13.2%), 2 as C and 1 as Group A. The outcome of relapsed children was dismal, as 6/10 (60%) died.

Conclusions: In our results, the survival rate is generally excellent (65/76, 85.53 %) more than one year off treatment, which generally means cure in B-cell lymphomas. Children with unsatisfactory response to treatment and recurrent disease have a dismal prognosis.

Keywords
Non-Hodgkin lymphoma, B-cell lymphoma, FAB-LMB protocol

Introduction

B-cell Non-Hodgkin Lymphoma (BL), is the third most common childhood lymphoid malignancy among children younger than 15 years after acute lymphoblastic leukemia (ALL) and Hodgkin lymphoma [1,2]. The most common subtype of Non-Hodgkin Lymphoma (NHL) is Burkitt lymphoma, which is characterized by a high growth fraction and a short doubling time, making necessary the administration of intensive treatment with short gaps between the courses. The adaptation of treatment intensity to recognized prognostic factors resulted in high cure rates, mainly with the use of FAB-LMB protocols [3-6].

The aim of our study was to analyze our experience of the treatment with FAB-LMB protocols and analyze the clinical and demographic characteristics of children with BL, treated in our Institute, the last two decades.

Patients and Methods

From January 1, 1990 to December 31, 2010, a total of 76 children with BL were treated in our Institute, all with FAB-LMB protocols, and more specifically with 89, 96 versions and 2003 modifications. Diagnosis was based on histomorphology and immunohistochemical analysis of lymph node or tumor mass biopsy, or on cytologic and immunophenotypic examination of malignant effusions. In more recent years, fluorescence in situ hybridization (FISH) for the specific for Burkitt lymphoma chromosomal translocation was also available. Disease staging was performed according to protocol staging system, dividing patients into 3 therapeutic groups (A - resected stage I and abdominal stage II); B - not eligible for A or C; and C - stages IV and L3 Acute Lymphoblastic Leukemia (ALL) with central nervous system (CNS) involvement or bone marrow involvement >25%. Response to treatment was assessed at 2 time points. Initially, at day 7 after COP (Cyclophosphamide / Vincristine / Prednisone): patients from Group A and B with tumour reduction less than 20% (poor response to COP) were switched to the more intensive group C regimen. The second evaluation was performed after the first consolidation course. Residual mass was recommended to be removed for histology or at least to be biopsied. Patients from Group B who had malignant cells in residual mass were also switched to group C.

The SPSS 17.0 software program was used for statistical analysis.

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Table 1. Clinical and demographic characteristics of the patients.

<table>
<thead>
<tr>
<th>Localization</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>4</td>
<td>11</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>ORL</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Cervical</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Bone</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Other / combination</td>
<td>9</td>
<td>3</td>
<td>10</td>
<td>22</td>
</tr>
</tbody>
</table>

Results after COP

| > 25% response   | 48      | 15      | 63      | 126   |
| < 25% response   | 2       | 1       | 3       | 6     |

Results after CYM/CYVE

| CR | 37 | 14 | 51 |

Residual mass

| Necrotic tissue | 7 |

Primary treatment outcome

| Abdominal | 6 |

| 2-year OS | 100% | 83.1% | 86.7% | 81.3% |
| 2-year EFS | 85.7% | 81.1% | 81.3% |

Relapse

| Local | 1 | 4 | 5 |
| BM | 2 | 2 |
| BM ± CNS | 2 | 0 |
| BM + CNS | 0 |
| CNS | 1 | 1 |
| Survival rate |

Results after COP

| CR | 37 |
| PR | 14 |
| Death due to disease | 7 |
| Death due to toxicity | 2 |
| Relapse | 1 |

Eight of the 60 children of A and B Group (13.3%) were treated in our country, with very good results. As reported in other studies, the outcome of relapsed patients was in 2 as salvage treatment, post disease progression during treatment and in the second, as initial treatment with steroids. Only 1 of them has entered remission.

Five children underwent SCT, 4 due to relapse and 1 due to primary treatment failure. Only 1 of these children survived, 1 died from transplant toxicity and the other 3 died from disease progression following successful engraftment.

Monoclonal antibody anti-CD-20 was administered in 3 patients, in 2 as salvage treatment, post disease progression during treatment and in the second, as initial treatment with steroids. Only 1 of them has entered remission.

Treatment outcome according to initial therapeutic group is described in Table 1. The OS for the entire cohort of 76 patients was 85.5% (65/76) and the EFS 83.78%, at 2 years, with a median follow-up time of 9.5 years (2-12). The survival analysis was performed based on intention to treat, as 1 patient died prior to commencing chemotherapy. According to the therapeutic group, the OS and the EFS was 100% and 85.7% for A, 83.1% and 81.1% for B, and for group C, 86.7% and 81.3%, respectively.

Grade 3 and 4 hematological toxicity with profound neutropenia and thrombocytopenia was noted in all patients following COPADM and CYVE (Cytarabine/Etoposide). At least one episode of neutropenic fever was noted in all 69 patients of group B and C, 60 of them had more than one episodes. Overall, we had 34 episodes of sepsis in 26 children. Twenty-five developed sepsis on the grounds of neutropenic fever following a course of chemotherapy and 1 before initiation of treatment. Other kind of infections were pneumonia in 8 cases, 1 of them fatal with ARDS picture, central venous catheter exit site infection in 5 cases, VZV infection in 2 cases, HSV in 2 patients, CMV in 1 child, H1N1 in 1 child, urine tract infection in 1 child, acute otitis media in 2 children, periodontal abscess in 1 child and genital infection in 1 child. Five children had more than 1 septic episode and 1 died from septic shock post COPADM #1, the cause unspecified. Twenty-one episodes were attributed to Gram negative bacteria (E.coli 5, Klebsiella 8, Pseudomonas 2, Enterobactera 2, Citrobacter 1, Acinetobacter 1, Achromobacter 1 and Proteus 1), 9 to Gram positive (Streptococcus 5, Staphylococcus coagulase negative 3, Staphylococcus coagulase positive 1), 1 to Candida, 2 to a combination of Gram positive and Gram negative (Streptococcus with Klebsiella in the 1st child and with Acinetobacter in the 2nd) and in 1 case, the only fatal, the cause was unspecified.

Mucositis was the second most frequent toxicity. It varied from grade II to IV and was noted following COPADM, mainly attributed to the combination of high-dose Methotrexate and Adriamycine. The development of mucositis did not correlate necessarily with delayed Methotrexate clearance. Oral mucositis was reported in 57 children post COPADM, in 14 of them post CYVE or 1st maintenance also.

In our population, 10 (13.7%) patients developed some form of impaired renal function or tumor lysis syndrome (TLS), which resolved in all cases. TLS was defined as an abnormally 25% increase in serum uric acid, potassium, and phosphorus levels over baseline and a 25% decrease from baseline in serum calcium levels. None of the children died because of TLS. Only 4 of those children (40% of TLS and 5.48% of the entire cohort) required haemodialysis. All of them had elevated LDH, bulk abdominal (one with concurrent EN1) disease and bone marrow involvement.

Discussion

The cure rates for B-cell mature lymphoma have substantially improved over the last decades, with the introduction of modern protocols (Table 2). Our OS and EFS were comparable to those reported in other countries, using FAB-LMB, BMF or CCG protocols [2,4,7-20]. This is the largest series of children with B-cell lymphoma, treated in our country, with very good results. As reported in other
countries, the children allocated to Group B represent the vast majority of patients [3,4]. Surprisingly, the cure rates for Group C are relatively higher than Group B; this could be attributed to the low number of patients in Group C.

Children from Group A have an excellent prognosis with minor treatment [5]. Children from Group B with unsatisfactory response at re-evaluation time points, and specifically following prophase and first consolidation course, seem to have dismal prognosis. In our cohort, the survival rate of children who were upgraded to higher regimen due to poor response to treatment was only 50% (4/8). Second-line treatment, targeted therapy and SCT might offer curable options for these children.

CNS involvement has been related to poor outcome in previous reports [21]. In our cohort, 9/76 (11.8%) children had CNS disease, percentage relatively higher to that reported by other Groups. On the contrary, this has not been a negative prognostic factor for our patients, as EFS and OS were 88.9% and 100%, respectively. Those patients with CNS and bone marrow involvement, classified as Group C, may have a very good prognosis, in view of the intensification of treatment and the improvement of supportive care, over the last two decades [22,23].

Only one of our patients who received a stem cell transplant, survived. The role of SCT in resistant and recurrent B-cell lymphoma has not been promising, apparently due to the aggressive nature of the disease [24].

Monoclonal antibody anti-CD20 has been administered in only 3 patients, in the first, as an upfront monotherapy (with steroids) and in the other 2, as part of second-line treatment for refractory disease. Only 1 of these patients reached remission. Even though the reports so far seem promising, we could not evaluate Rituximab in our population, due to the small number of recipients [23,25,26].

Myelosuppression was the main toxicity, as anticipated by such an intensive protocol. Despite the profound and long neutropenic periods in the children of our cohort, we had only one death due to sepsis. As a result, our EFS has not been particularly compromised. The increased supportive care measures with preemptive initiation of broad spectrum antibiotics and early diagnosis of infections are the main reason for their successful management. Children with neutropenic fever were treated with an antipseudomonal β-lactam, in combination with an aminoglycoside, until count recovery. A glycopeptide (mainly teicoplanin and rarely, vancomycin) was used in case of fever persisting more than 48 hours or if there was a suspicion of a Gram positive infection. Oral mucositis has been the second most frequent complication, related mainly to high-dose Methotrexate. Most episodes were noted following COPADM and less following CYVE and were predisposing to sepsis, as all children with sepsis had more severe than grade II mucositis. Mouth rines were used as a prophylaxis and treatment of mucositis. Acyclovir was used for severe mucositis and antifungals for severe oral thrush.

Elevated LDH and bulk disease are predisposing for TLS and increase supportive care measures are required. As it is reflected in our results, with the use of urate oxidase, which has been available in our country for more than a decade, the percentage of patients, even with advanced stage, who develop severe TLS, has fallen significantly [27].

In conclusion, the survival rates for children with B-cell Non-Hodgkin lymphoma in our Institution have been comparable to those reported in other developed countries. Children with poor response to treatment and recurrent disease have the worse prognosis. Larger sample, with multi-Institutional analysis should be performed in order to define prognostic factors and relate clinical and epidemiological variables with overall and disease-free survival.

References


