

Clinico-Pathological Features and Outcome of Management of Pediatric Gastrointestinal Lymphoma

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ABSTRACT

Purpose: The purpose of this study is to evaluate pediatric GIT lymphomas as regards clinico-pathological features, controversies in surgical treatment, role of chemotherapy and the prognostic features.

Patients and Methods: This study included forty three patients with pediatric GIT Non-Hodgkin's lymphoma collected over 7 years at the NCI Cairo University between January 1997 and December 2003. The data of every patient included: Age, sex, presenting symptoms and signs, preoperative investigations, extent of the disease at diagnosis and the type of resection performed, histopathological examination, details of chemotherapy and state at follow up. Overall and disease free survival were calculated and correlated with all parameters.

Results: The study included 30 boys and 13 girls with median age 5.00 years (range: 0.4:17). The lesions were located in the small intestine (n=15), the large intestine (n=14), the ileocecal region (n=10), stomach (n=2), and multifocally (n=2). Burkitt's Lymphoma was the commonest histological type (n=24). The majority were stage IIE and IIIE (22 and 17 respectively). Exploration was done in thirty nine patients (complete resections were done in 23 cases, incomplete resections (debulking) were done in 14 cases and in 2 cases only lymph node biopsies were done). All patients received a sort of systemic chemotherapy. The median follow up duration was 44 months (range 4-116 months). The only parameters that had significantly affected the overall survival were localized disease, complete resection, earlier stage and response to chemotherapy with *p* values, (0.005, 0.001, 0.005 and <0.001 respectively). As regards the disease free survival the only significant factor was localized disease (*p*=0.035).

Conclusion: The extent of disease at presentation is the most important prognostic factor in pediatric GIT lymphoma. Surgery still plays an important role such as complete resection in localized disease, management of complicated disease and diagnostic biopsy. There is no value of debulking and surgery is not advised for gastric lesions. Chemotherapy represents a cornerstone in the

treatment and offers an excellent chance for long term, disease free survival.

Key Words: Pediatric - GIT - Lymphoma.

INTRODUCTION

Primary Non-Hodgkin's lymphomas (NHL) of the gastrointestinal tract are the most common extranodal lymphoma with increasing incidence in recent years, yet they are rare tumors [1]. Between 1952 and 1996, 54 patients [from a total of 4547 tumor registrants (1.2%) at the Children's Hospital, Columbus] were reported for intestinal lymphoma [2]. Unlike adult patients in whom stomach is the most frequent site (50-60%) [3], small and large intestine are the most frequent sites of involvement in the pediatric age group [4]. The prognosis for childhood gastrointestinal NHL improved significantly with the realization that virtually all cases were disseminated at diagnosis and systemic therapy is necessary for long term disease free survival [5]. The role of surgery in gastrointestinal NHL remains controversial. Magrath et al., supported aggressive operative debulking, defined as >90% tumor removal, prior to chemotherapy after analysis of a large single institutional series of patients with Burkitt's lymphoma in Uganda [6]. Others cautioned against extensive initial surgery which might delay institution of systemic therapy [7]. The aim of this study was to clarify the clinico-pathological features of pediatric gastrointestinal B-cell lymphoma in Egypt. We also aim to identify the preferred lines of treatment and to correlate them with the outcome and to identify the significant prognostic factors.

PATIENTS AND METHODS

Patients Selection: Between January 1997, and December 2003, we studied 55 pediatric patients with provisional diagnosis of extranodal NHL in the gastrointestinal tract at the National Cancer institute, Cairo University. According to the criteria developed by Dawson and colleagues, primary lymphoma of the gastrointestinal tract includes cases with no superficial adenopathy at diagnosis, no mediastinal adenopathy at chest radiography, a normal blood cell count, no involvement of the liver and spleen, and involvement of only regional lymph nodes at laparotomy [8]. In our study we excluded cases with peripheral adenopathy (6 cases), mediastinal adenopathy (3 cases), liver involvement (2 cases), or involvement of the spleen (1 case). Thus only forty three patients were eligible for the study and twelve cases were excluded (All were pathologically proved).

Pretreatment Evaluation and Stage Classification: The presenting symptoms were registered, extent of disease was determined by history, physical examination, baseline complete blood picture, liver function tests, kidney function tests, lactate dehydrogenase (LDH) as a tumor bulk indicator, uric acid and serum electrolytes in addition to bone marrow aspiration/biopsy and CSF cytology, abdominal ultrasound and/or CT scan of the abdomen. GIT endoscopy was done in cases of haematemesis and/or bleeding per rectum and cystoscopy was done in suspected urinary bladder invasion.

Treatment:

Initial Surgery: Patients were candidates for complete surgical resection if they had localized disease and the operation can be performed safely without any significant delay in beginning chemotherapy. In patients without completely resectable disease, initial surgery included the least invasive procedure to establish the diagnosis and correct any complicated disease (e.g. obstruction, intussusception, etc.). Patients were grouped on the basis of localized disease versus extensive disease. Localized disease was defined as tumor confined to the bowel, adjacent mesentery, or adjacent structures amenable to resection along with the main bulk of the tumor itself. In addition, resections were defined as complete gross resections if all gross tumor was excised, or incomplete gross resection if gross

tumor was left in situ. Those patients undergoing incomplete gross resection and those undergoing biopsy only were compared as a single group with those undergoing complete gross resection.

The staging system adopted was the St. Jude staging system for childhood Non-Hodgkin's lymphoma [9] (Table 1).

Table (1): The St. Jude staging system for childhood Non-Hodgkin's lymphoma.

Stage	Description
I	A single (extranodal) or single anatomic area (nodal), excluding mediastinum or abdomen
II	A single tumor (extranodal) with regional node involvement on same side of diaphragm: Two or more nodal areas Two single (extranodal) tumors with or without regional node involvement A primary gastrointestinal tract tumor with or without associated mesenteric node involvement, grossly, completely resected
III	Tumor on both sides of the diaphragm: a- Two single tumors (extranodal) b- Two or more nodal areas Or all extensive primary intraabdominal disease, unresectable Or all primary paraspinal or epidural tumors regardless of other sites Or all primary intrathoracic tumors (mediastinal, pleural, or thymic)
IV	Any of the above with initial central nervous system or bone marrow involvement

All pathologic specimens were reviewed and classified according to new WHO-Real classification [10]. Five micron thick sections were cut on L-olylysine coated glass slides. Antigen retrieval was performed using antigen retrieval solution at a dilution of 1:4 with deionized water (Biogenex cat no HK 090-5K). Immunostaining was applied using the labeled streptavidin-biotin-immunoenzyme antigen detection system (ultra Vision Detection System Antipolyvalent HRP/DAB ready to use). The monoclonal antibodies CD20 (Dako M0774) for B-cell lineage, CD45RO (Dako N1520) and CD3 (Dako A0452) for T-cell typing were used.

Chemotherapy:

After surgery, and establishment of the exact pathology and stage of disease and as soon as

the patients general condition allows, base line investigations were repeated and systemic chemotherapy was started. Those who presented with bulky tumor size after incomplete resection or biopsy taking only were candidates for a cytoreductive prephase in the form of "COP" (vincristine, prednisolone and fractionated cyclophosphamide) [11]. Further chemotherapy was then decided according to the implemented specific B-cell lymphoma protocols at the NCI-Pediatric Unit. Accordingly, our study group of patients were enrolled on one of two protocols that we chronologically defined them as protocol "I" and protocol "II". Before the year 2001, protocol "I" was applied which classified patients into either low risk (localized disease that was completely resected) or high risk that included all other patients. Patients had received alternating cycles of chemotherapy; "A" (vincristine - cytarabine - cyclophosphamide - fludarabine - IT); and "B" (vincristine - etoposide - ifosfamide - methotrexate - IT) with a total of 4 cycles for low risk versus 8 cycles for high risk patients [12]. Since January 2001, another protocol (protocol "II") adopted from the FAB-LMB 96 has been started [9,13]. Its primary aim was to reduce chemotherapy duration, toxicity and induced late sequelae as much as possible without compromising the final outcome and the achieved good survival on previous protocols. Patients under this protocol were allocated into one of three arms (A, B or C).

Arm "A": Patients with resected abdominal stage II disease (receive COPAD-COPAD).

Arm "B": Patients not classified as "A" or "C" (receive - COP - COPADM1 - COPADM2 - CYM1 - CYM2 - COPADM3 - COPADM4).

Arm "C": Patients with either >25% BM-L3 blasts and CNS negative (receive COP COPADM1 - COPADM2 - CYVE1 - CYVE2 - COPADM3 - COPADM4) or CNS positive (receive COP + IT - COPADM1 - COPADM2 - CYVE1 + IT - MTX + IT - CYVE2 + IT - COPADM3 - COPADM4).

Regimens [9]:

- COPAD: Vincristine - cyclophosphamide - prednisolone - doxorubicin.
- COPADM: COPAD + high dose methotrexate.
- CYM: Cytarabine - high dose methotrexate.
- CYVE: Cytarabine - etoposide.

Definitions of Response to Chemotherapy [9]:

Complete remission: Complete disappearance of all measurable or evaluable lesions. No L3 blast cells in the BM nor in the CSF.

Tumor regression: Persistence of tumor, but tumor volume in aggregate decreasing.

Stable disease: Persistence of tumor with unchanged volume or with an increase insufficient to classify as progression.

Disease progression or relapse: Any progression of more than 25% of the product of the largest two diameters of measurable lesions or appearance of new lesions or reappearance or increase in "L3" blasts in the BM or CSF.

Non response to "COP" prephase: Is defined as <20% tumor reduction of the product of the largest two diameters of measurable lesions or <20% reduction in the number of "L3" blasts in the BM or CSF.

Patients who successfully ended their treatment protocol were indicated for complete re-evaluation (clinically, laboratory and radiologically) before being routinely followed up. Follow up of patients in complete remission was done according to a timed-schedule with gradually spaced visits. Treatment of relapsed patients was individualized, according to the ongoing investigational protocols at the NCI.

Statistical Analysis:

Data was analyzed using SPSSwin statistical package version 11. Numerical data were expressed as mean \pm standard deviation (SD), median, minimum and maximum. Qualitative data were expressed as frequency and percentage. The overall survival was calculated from the date of end of chemotherapy till the date of last follow up or the date of death. For those patients who achieved remission after chemotherapy (36 patients, 83.6%, 34 of them developed complete remission and 2 cases developed partial remission), the disease free survival was calculated from date of end of chemotherapy till date of relapse. Survival analysis was done using Kaplan-Meier test and presented as cumulative survival rates. Comparison between two survival curves was done using Breslow test. A probability (*p*-value) less than 0.05 is considered significant.

RESULTS

The study comprised 43 children collected over 7 years at the NCI Cairo University. They were 30 boys and 13 girls with median age 5.00 years (range: 0.4:17 years). The majority were stage IIE and stage IIIE (22 and 17 respectively), only 4 patients had stage IVE disease (all were due to isolated bone marrow involvement). The most common pathology was Burkitt's lymphoma that was diagnosed in 24 cases (55.8%) (Fig. 1). Other pathological types were small cell non-cleaved lymphoma (11 cases), large B-cell lymphoma (4 cases) and mixed type (4 cases).

Table (2) shows the presenting symptoms of the patients. The most common symptom was abdominal pain which was present in 35 patients (81.4%), followed by abdominal swelling which was present in 33 patients (76.7%). Five patients (11.6%) presented as emergency intestinal obstruction.

Table (2): Presenting symptoms in the study group.

*Symptom	Number	Percent
Abdominal pain	35	81.4
Abdominal swelling	33	76.7
Vomiting	16	37.2
Constipation	12	27.9
Diarrhea	5	11.6
Intestinal obstruction	5	11.6
Melena	5	11.6
Bleeding per rectum	4	9.3
Hematemesis	3	6.97
Pneumaturia	1	2.3

*More than one symptom may be present in the same patient.

Thirty nine patients were submitted to abdominal exploration. Thirty four patients underwent elective abdominal exploration. In 11 cases the pathology was established preoperatively by endoscopy or ultrasound or CT guided biopsy, while in 23 cases exploration was done based on radiological and clinical data only. The aim of surgery was to establish the diagnosis, evaluate the disease extent and remove the whole lesion if possible. In 5 patients emergency abdominal exploration was done due to acute intestinal obstruction. Four patients were not submitted to abdominal exploration; (Two patients of them were diagnosed by upper GIT endoscopic biopsy, one of them had a lesion in the esophagus and stomach and the other one had two lesions one in the stomach and the

other in the left colon. The other two patients had bulky abdominal disease and were diagnosed by CT guided biopsy. Their general condition was risky for performing laparotomy). Table (3) shows the site of the disease in all the 43 patients.

Table (3): The site of the lesion in the 43 children with gastrointestinal lymphoma.

Site	Number	Percent
Stomach	2	4.6
Small bowel	15	34.9
<i>Large bowel:</i>		
Rt colon	12	27.9
Lt colon	2	4.6
Small and large bowel (all in the ileoaeical region)	10	23.25
Stomach and esophagus	1	2.3
Stomach and left colon	1	2.3

In the thirty nine explored patients, 23 patients had limited disease and complete resection could be safely accomplished, while 16 patients had extensive disease. Two patients had gastric lesions with large celiac nodes and only lymph node biopsy was taken. One patient had other abdominal organs direct infiltration (the right kidney) and in this case only debulking was done leaving a residual over the kidney. The remaining 14 patients had enlarged lymph nodes related to the major vascular mesenteric vessels, accordingly, only the tumor mass involving the gastrointestinal tract was resected leaving the centrally involved nodes. So, we had 23 complete resections, 14 incomplete resections (debulking) and 2 cases with lymph node biopsy only. The type of the operations performed in the 37 patients for whom resection (complete or incomplete) was performed were; 22 right hemicolectomy (Figs. 2,3a-b), 12 small intestinal resections, 2 left hemicolectomy and small intestinal resection with partial sigmoidectomy and partial cystectomy in one case (Fig. 4).

There was no postoperative mortality. Five surgical complications were reported in the thirty nine explored patients (12.8%). Four of these complications (persistent ileus, blood loss >250c.c., wound dehiscence, and subhepatic abscess which required operative drainage) occurred in patients with incompletely excised tumors who also had extensive disease. The

remaining complication developed in the child who presented with pneumaturia and was found at exploration to have small intestinal lesion involving the bladder and the sigmoid colon which were partially resected with the lesion and primarily repaired. This patient developed a urinary leak in the first postoperative day secondary to urinary catheter obstruction. Re-exploration was done with primary closure of the bladder and suprapubic cystostomy.

Chemotherapy:

All patients received a sort of systemic chemotherapy with 21 of them (48.8%) were candidates for pre-phase "COP" because of bulky tumor size. Further treatment was according to

criteria of protocol "I" in 29 patients (67.44%), and protocol "II" in 13 patients (30.2%). One patient (2.3%) received "COP" only.

Response to chemotherapy was collectively reported as complete remission in 34 patients (79%), tumor regression in 2 (4.6%) disease progression in 6 (13.9%) and no response after "COP" in 1 patient (2.3%).

Three patients (6.9%) developed a primary site relapse of their disease, two followed protocol "I" and one after protocol "II". All relapses were pathologically documented with unchanged histological subtype. Only 1 patient additionally had a bone marrow disease spread revealed by BM aspirate.

Table (4): Overall and disease free survival.

	No.	60-months overall survival rate	p-value	No.	60-months overall survival rate	p-value
All patients	43	80.6%		36	86.1%	
Age:						
≤5 years	25	82.9%		20	94.7%	
>5 years	18	76.9%	0.557	16	75.0%	0.268
Gender:						
Male	30	75.7%		23	84.3%	
Female	13	91.7%	0.204	13	91.7%	0.812
Extension:						
No B.M. infiltration	39	81.7%		34	84.9%	
B.M. infiltration	4	66.7%	0.510	2	100.0%	*
GIT involvement:						
Small intestine	14	84.6%		11	100.0%	
Large intestine	16	93.8%		15	93.3%	
Both	9	51.9%	0.075	6	60.0%	0.187
Stomach	4	100.0%	*	4	100.0%	*
Disease:						
Localized	24	95.8%		22	93.3%	
Extensive	19	60.6%	0.005	14	78.6%	0.035
Pathological types:						
BL	24	81.7%		20	89.5%	
Other types	19	78.9%	0.639	16	84.4%	0.922
Stage:						
II	22	95.2%		22	87.9%	
III & IV	21	63.2%	0.005	14	85.7%	0.383
Surgical resection:						
Complete	22	100%		21	92.9%	
Partial	21	59.6%	0.001	15	80.0%	0.05
Type of resection:						
Incomplete	15	53.3%		10	80.0%	
Biopsy	6	80.0%	0.255	5	80.0%	0.931
Preconditioning chemotherapy:						
Yes	21	84.7%		17	94.1%	
No	22	77.3%	0.323	19	78.3%	0.516
Chemotherapy complications:						
Yes	6	66.7%		31	80.0	
No	37	82.9%	0.255	5	86.2	0.365
Response to chemotherapy:						
CR	34	94.0%				
No CR	9	25.0%	<0.001			

B.M.: Bone marrow.

BL: Burkitt's lymphoma.

CR: Complete remission.

*No. of patients are small for comparison.

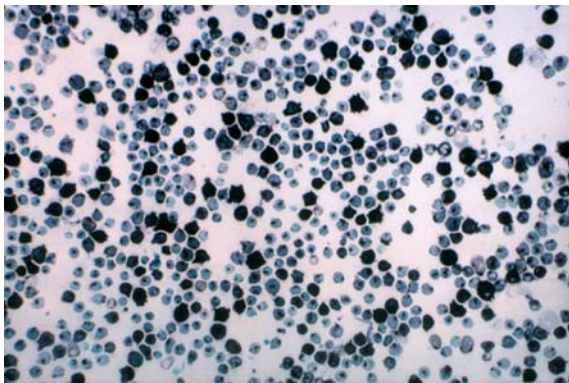


Fig. (1): Burkitt's lymphoma showing the starry sky appearance (Hx & E) (x400).



Fig. (2): Rt hemicolectomy postoperative specimen with lymphoma of the caecum showing multiple lesions.



Fig. (3-A): Rt hemicolectomy postoperative specimen with lymphoma of the distal ileum causing ileo-ileal and ileo-caecal intussusception.



Fig. (3-B): Same postoperative specimen was opened showing tumor of the distal ileum.



Fig. (4): Postoperative specimen showing Burkitt's lymphoma of the small intestine invading part of the sigmoid colon and urinary bladder. The ileum is in the back and the clamp is in the sigmoid.

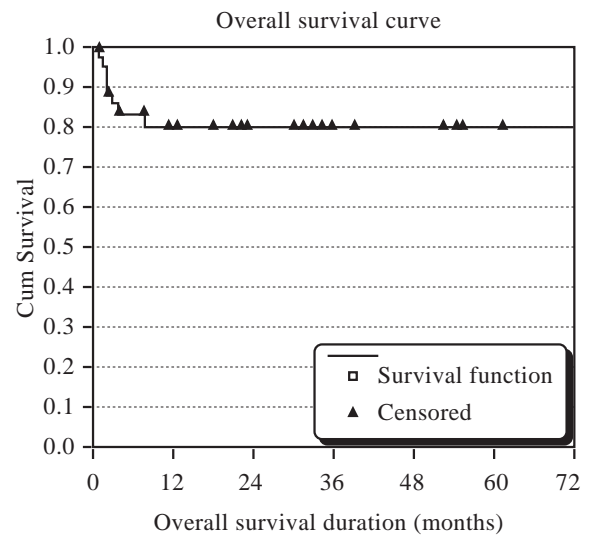


Fig. (5): Overall survival curve in all cases.

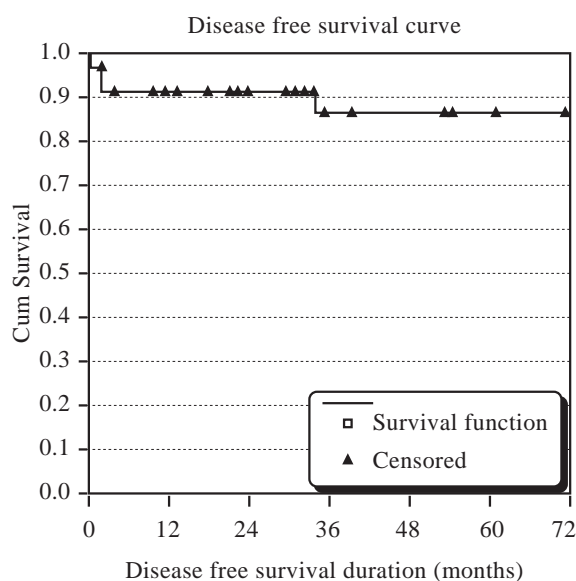


Fig. (6): Disease-free survival curve after excluding cases not responding to chemotherapy.

Seven mortality cases (16.2%) were reported, 4 of them died out of progressive disease on first line chemotherapy, 2 after relapse, and 1 due to septicemia with profound neutropenia as a chemotherapy related complication.

Survival Analysis:

The mean follow up duration was 44 months (range 4-116 months). The overall and disease free survival rates were 80.6% and 86.1% respectively (Figs. 5,6). Non responders with progressive disease and were not included in calculating the disease free survival. Correlation of the overall survival with various clinico-pathological and treatment parameters (Table 4) had shown that localized disease, complete resection, earlier stage (stage II) and response to chemotherapy had significantly affected the overall survival with p values, 0.005, 0.001, 0.005 and <0.001 respectively. When the disease free survival was correlated to the same parameters (except response to chemotherapy as all were responders), the only significant factor was localized disease ($p=0.035$).

Isolated bone marrow infiltration at presentation did not show to have a significant effect in decreasing the survival. Patients with gastric lesions also did very well. The 2 cases that were explored and biopsied and the 2 cases which were endoscopically diagnosed were still alive and on regular follow up.

DISCUSSION

The predominant GIT malignant tumor in children is NHL of the distal small bowel and the caecum [14]. The distribution of our cases fits with this fact as 37 of our 43 patients (86%) had their lesions in the areas of terminal small intestine (15 patients), ileocaecal region (10 patients), and right colon (12 patients). This was also reported in other series [2,5,15,16]. However, in our study we had 4 cases of pediatric gastric lymphoma (9%) which is a relatively large number.

The peak age for gastrointestinal NHL in children is 5-15 years with male sex preponderance 1.8-2.5 times that of females [2]. In our series, the age ranged from 0.4 to 17 years (mean 6.6 years), with a male to female ratio 2.3:1. The incidence of NHL is well known to vary on Geographic basis [17]. On our narrow local scale, we did not report any difference inside the country. Comparing Upper and Lower Egypt, there was no predilection to any of them regarding the number of patients, age distribution, sex, clinical presentation or histological pattern. Considering both the small size of patients' sample that can not give rise to a solid conclusion and the very close circumstances inside the same country, one can not anticipate any difference.

According to the WHO histological classification of NHL in children, B-cell immunophenotypes (Burkitt, Burkitt-like, large B-cell) most commonly predilect the abdomen as a primary site of presentation. Burkitt's NHL is by far, the most common subtype [18]. This fact matches with our results where the incidence of Burkitt's NHL in our study cases was (55.8%).

As known, patients with Burkitt's NHL in North Africa and the Middle East (including Egypt) appear to have a spectrum of organ involvement that more closely approximate that of sporadic rather than endemic form of the disease since most of patients present with abdominal tumor [9,19]. Large proportion of patients with sporadic form of Burkitt's NHL would present with abdominal pain, abdominal swelling, change in bowel habits, nausea, vomiting, intussusception related symptoms complex...etc [20]. Around 25% of such patients may come with a right iliac fossa mass [5]. Similarly, a very consistent pattern of clinical

presentation was reported in our series (Table 2).

The distribution of cases among different stages in the present study was also similar to most reported series where stages IIE and IIIE usually represent around 75% of cases [2,5].

The survival results of our study support several conclusions determining the appropriate role of surgical intervention in pediatric gastrointestinal NHL. Although, localized disease, complete resection, earlier stage (stage II) and response to chemotherapy had significantly affected the overall survival yet the strongest predictor of disease-free survival was tumor burden at diagnosis, as measured by extent of abdominal disease. This is consistent with other studies clearly showing that the outcome is most dependent on the number of malignant cells present at initiation of therapy [5,16] and can be predicted by measurement of serum LDH, interleukin II and B2 microglobulin levels [9].

Because children with partially resected or biopsied tumors are treated identically according to the extent of disease, partial resections neither add to survival (as shown in Table 4 when compared to cases where biopsy only was taken with no trials of debulking), nor prevent the patients from entering the higher risk group. Thus, in patients without completely resectable disease, with no evidence of extra-abdominal extension, and laparotomy is needed for diagnosis, surgery should be limited only to the least invasive procedure, such as biopsy or a simple intestinal resection-anastomosis. So, we could avoid any major surgical procedure that may lead to higher incidence of postoperative complications and more importantly may lead to delay in beginning chemotherapy. Due to the excellent results achieved by chemotherapy in the cases of pediatric gastric lymphoma, which were all not subjected to surgical resection, it is reasonable that surgical resection is not recommended in these cases. In a large review, patients with pediatric gastric lymphoma had a same 5-year survival rate irrespective of whether the primary tumor was resected or not [21].

Patients' assignment to an appropriately intensive therapy according to their risk group is becoming the rule with different protocols. Patients having minimal disease require less

intensive therapy than do patients with extensive one. It is important not to give more therapy to patients than they need. Pediatric gastrointestinal B-cell NHL patients in whom all disease has been resected are indicated for only few [2-3] courses of chemotherapy. Tolerance to therapy and short duration of treatment have been achieved without compromise to the final outcome. On the other hand, patients with a higher risk are usually treated with more intensive protocols including more than 6 drugs and 4 or more cycles of chemotherapy [9] as was the case in our patients under study.

Earlier reports about results of treatment showed overall survival results ranging from 60% [12] to 65% [5]. The disease free survival in patients with localized disease was reported to be 85% [5]. The results of several new protocols in which the principle of risk stratification is used, demonstrate better results with overall disease free survival approximates 90%. Patients with stage II has 98-100% disease free survival rate versus 76% in those with most extensive disease [22].

Despite the relatively lower rates in our hands with an overall survival 80.6% for all stages and 87.9% disease free survival for patients with stage II disease, yet our study results concerning its small sample size and different applied protocols (applying same policy of tailored treatment) can be more or less considered close to other reports in this regard.

In patients with B-cell NHL, partial response has become a more frequent cause of failure than recurrent disease [9]. This explains our results that show a relatively higher frequency of primary treatment failure in the form of partial response or disease progression than relapse after a period of remission.

Conclusively, extent of disease at presentation is the most important prognostic factor in patients with pediatric GIT lymphoma. Surgery still plays an important role in exactly defined situations such as complete resection in localized disease, management of complicated disease, and diagnostic biopsy. There is no value of debulking, and surgery is not advised for gastric lesions. Chemotherapy represents a cornerstone in the treatment of these patients and offers the patients an excellent chance for long term, disease free survival.

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