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PRIMARY INTESTINAL LYMPHOMA: CLINICAL AND THERAPEUTIC FEATURES OF 32 PATIENTS

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ABSTRACT

Background and Objective. Lymphomas of the gastrointestinal tract are the most common type of primary extranodal lymphomas, accounting for 5 to 10% of all non-Hodgkin's lymphomas. In particular, primary intestinal lymphomas represent about 15-20% of gastrointestinal lymphomas. New multimodal therapeutic approaches have improved the prognosis of this once deadly disease: we report a retrospective analysis of our experience with 32 cases of primary western intestinal lymphomas, presenting clinical, therapeutical and prognostic data.

Patients and Methods. From March 1989 to November 1995, 32 patients with untreated primary western intestinal lymphomas were submitted to radical surgery plus polychemotherapy (early stages, I and II; 22 patients), or polychemotherapy alone (advanced stage, III and IV; 10 patients). The most frequent symptoms were abdominal pain, nausea, vomiting and weight loss. The tumor was located in the jejunum in 2 cases (6.2%), in the proximal small bowel in 15 cases (46.9%), in the distal and terminal ileum in 8 cases (25%), in the colon and rectum in 4 cases (12.5%), and multiple sites were found in 3 cases (9.4%). According to histology, 26 patients had high-grade and 6 low-grade non-Hodgkin's lymphoma.

Results. Stage I-II patients underwent radical resection of the tumor and chemotherapy; advanced (III-IV) stage patients were treated with chemotherapy alone as first-line approach. Of the 32 patients, 24 (75%) achieved a complete response (CR); according to stage, all stage I-II patients had CR, while only 2 of the 10 stage III-IV patients reached CR. The risk of a lower response rate was significantly correlated with the presence of advanced stage (III-IV) ($p = 0.000001$). The overall 5-year survival rate was 59%, with a relapse-free survival rate of 72% among the 24 complete responders.

Interpretation and Conclusions. Intestinal lymphomas differ significantly from their gastric counterpart, not only in pathology, but also with regard to clinical features, management and prognosis. Our experience confirm the efficacy of the surgery-chemotherapy combination in obtaining a good remission rate for localized early primary intestinal lymphoma and indicates that this combination represents the only means for managing complications.

Key words: lymphoma, intestinal tract, radical resection, chemotherapy

Primary gastrointestinal (GI) lymphomas are not common accounting for between 1 and 4% of all gastrointestinal tumors,[1] but they represent the largest group among all extranodal non-Hodgkin's lymphomas (NHL).[2] GI lymphomas are predominantly located in the stomach (50-60%),[3-6] whereas intestinal lymphomas are more infrequent and appear in the small bowel (20-30%)[3-6] and the colon and rectum (10-20%).[7]

Intestinal lymphomas differ from gastric ones not only in pathology, but also as regards their clinical features, treatment and prognosis.[8] The term *primary intestinal lymphoma* includes some particular entities: the western type, immunoproliferative small-intestinal disease (IPSID or Mediterranean lymphoma), the enteropathy-associated T-cell lymphoma, and the childhood type.

In particular, the western type is an uncommon malignancy with a challenging differential diagnosis and an urgent need for therapy. Recent reports[9-13] have demonstrated that although resection plays an important role in local control of the disease and in the prevention of bleeding and/or perforation, by itself it rarely eradicates the lymphoma. In addition, the lymphoma is often diagnosed in an advanced stage, so that only 30-40% of such patients are eligible for surgical treatment. Consequently, adjuvant chemotherapy and radiotherapy are essential in the therapeutic approach.

The single most important prognostic factor in western intestinal lymphomas is clinical stage; in fact, the 5-year survival rate is 40-50% in stage I-II patients and less than 10% for those in advanced stage.[14-17] We report a retrospective analysis of our

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experience with 32 cases of primary western intestinal lymphomas, presenting clinical, therapeutical and prognostic data.

Patients and Methods

From March 1989 to November 1995, 32 consecutive patients with primary intestinal NHL were managed in our institute. Criteria for entry into the study included: previously untreated patients, histological diagnosis of non-Hodgkin's lymphoma according to the Kiel Classification,[18] HIV negativity. Primary intestinal lymphoma was defined according to the criteria of Dawson *et al*.[19] for primary gastrointestinal lymphoma, including the satisfactory operational definition that the lymphoma presents with the main bulk of disease in the GI tract, necessitating treatment in that site. For staging, an adaptation of the Ann Arbor system for extranodal lymphomas[20] and its modification by Musshoff[21] were used.

Staging evaluation included initial hematologic and essential surveys in addition to chest radiograms and computerized tomography of the chest and abdomen, radiographic study of the duodenum and small bowel, and upper endoscopy. Bone marrow biopsy and abdominal ultrasonography were performed in all patients.

Patient characteristics (Table 1)

Of the 32 patients with primary intestinal lymphoma, 16 were males and 16 females, and age ranged from 18 to 85 years (median 55 years). The most frequent symptom was abdominal pain (87.5%); the most common presenting symptoms are listed in Table 2. The median duration of symptoms before diagnosis was 5 months (range 1 week-12 months). With respect to stage at diagnosis, the 32 primary intestinal lymphomas consisted of 22 cases (68.8%) in stages I and II, 6 cases (18.7%) in stage III and 4 cases (12.5%) in stage IV; among stage IV patients, 2 showed massive intestinal involvement and 2 presented lymphoma in other sites. Three (9.3%) patients suffered from bulky disease.

Table 1. Characteristics of 32 primary intestinal lymphoma patients.

Age (yrs):	median	55
	range	18-85
Sex:	M/F 16/16	
Histology:	High grade:	26/32
	- centroblastic	14/26
	- immunoblastic	3/26
	- anaplastic large cell	3/26
	- Burkitt's lymphoma	4/26
	- MALT	2/26
	Low grade:	6/32
	- immunocytoma	2/6
	- centroblastic/centrocytic	2/6
	- MALT	2/6
Stage:	I-II 22/32	
	III-IV 10/32	
Bulky:	No/Yes	29/3
Distribution:	jejunum	2/32
	proximal small bowel	15/32
	distal and terminal ileum	8/32
	colon and rectum	4/32
	multiple sites	3/32

Distribution and histology

Twenty-two patients underwent surgical resection of their lymphomas, while in the remaining 10 only a biopsy was performed. In 2 cases (6.2%) the lymphoma was located in the jejunum, in 15 cases (46.9%) in the proximal small bowel, in 8 cases (25%) in the distal and terminal ileum, in 4 cases (12.5%) in the colon and rectum, and in 3 cases (9.4%) multiple sites were found.

By histological features, there were 26 (81.2%) high-grade (HG)-NHL and 6 (18.8%) low-grade (LG)-NHL; of the 32 lymphomas, 4 (12.5%) were mucosa-associated lymphoid tissue (MALT) lymphomas (2 HG and 2 LG MALT types). Among the HG-NHL there were 14 centroblastic (Cb), 3 immunoblastic (Ib), 3 anaplastic large cell (ALCL), 2 MALT and 4 Burkitt's lymphomas (BL). Among the LG, we found 2 immunocytomas (Ic), 2 centroblastic/centrocytic (Cb/Cc), and 2 MALT lymphomas.

HG-NHL were localized as follows: of the 14 Cb types, 7 were present in the proximal small bowel, 3 in the terminal ileum (ileocecal region) and 1 in the colon; of the 3 Ib types, 2 were in the proximal small bowel and 1 in the rectum; all ALCL types were located in the small bowel; the 2 MALT lymphomas were localized in the distal and terminal ileum. All BL were situated in the ileocecal region. Three patients (all HG-NHL, Cb types) presented multiple intestinal sites (terminal ileum and colon).

All the LG-NHL were located in the proximal small bowel.

Treatment

All 22 patients in stages I and II underwent primary radical resection of the tumor followed by multiagent chemotherapy [CHOP-like (6 cycles) or MACOP-B-like regimens (12 weeks) for HG-NHL, and COP-like (6-8 cycles) or CHOP-like (6 cycles) regimens for LG-NHL]. The 10 patients in stages III and IV received only polychemotherapy, e.g. MACOP-B-like regimens.

Response criteria

Complete response (CR) was defined as a complete disappearance of the signs and symptoms due to lymphoma that was maintained for at least 6 weeks; a reduction of at least 50% of the known disease with the disappearance of systemic manifestations for a duration of at least 6 weeks was judged a partial response (PR). Patients with stable or progressive disease were considered as having no response.

Survival and relapse-free survival curves were calculated according to the method of Kaplan and Meier.[22] The survival curve was measured from diagnosis until death; the relapse-free interval was calculated from the end of induction therapy to the first evidence of disease relapse.

Results

All 22 stage I and II patients obtained a CR. Eighteen of them are still in remission at a median follow-up of 34 months (range 6-80 months), one of these being in second CR after a 28-month relapse; the other 4 early stage patients relapsed after 8, 10, 12, and 14 months, respectively, and

Table 2. Symptoms list of the 32 primary intestinal lymphoma patients at diagnosis.

Abdominal pain	28/32 (87.5%)
Nausea and/or vomiting	15/32 (46.8%)
Weight loss	12/32 (37.5%)
Constipation	10/32 (31.2%)
Diarrhea	5/32 (15.6%)
Gastrointestinal bleeding	3/32 (9.3%)

died of disease progression.

Among the 10 advanced stage patients, only two obtained a CR; of these, one suffered a relapse after 10 months and died of diseae progression, while the other is still in remission after 15 months. Among the remaining patients, 2 obtained PR and 6 were non-responders; all these patients showed disease progression that ranged from 4 to 15 months.

Figure 1 depicts the overall survival curve of all 32 patients (59% at 5 years), while Figure 2 shows the overall survival curves according to stages I-II versus stages III-IV. Figure 3 reports the relapse-free survival curve of all 24 CRs (22 early stage and 2 advanced stage; 72% at 5 years).

The relapses pattern of early-stage patients was characterized by: 3 local recurrences (relapse in the vicinity of the removed tumor), 1 gastrointestinal tract dissemination (recurrence distant from the primary site but restricted to the gastrointestinal tract), and 1 generalized dissemination (involvement of lymph nodes or organs unrelated to the gastrointestinal tract). No relationship between response and the presence of bulky disease, histologic subtype, age or sex was observed. In particular, all 4 BL suffered relapse and/or progression independently of the stage. By contrast, the advanced stage patients who relapsed or progressed showed local and /or generalized relapse and/or recurrences. No cases of hemorrhage and/or perforation were recorded in these patients during chemotherapy.

A significant difference was seen in the survival rate between early stage disease patients (with resection in the therapeutical approach) and the advanced stage ones ($p = 0.000001$).

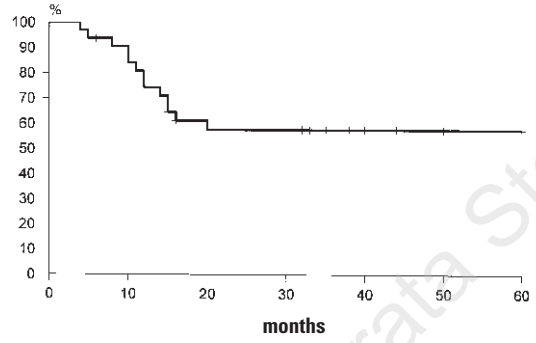

Figure 1. Overall survival curve of all 32 primary intestinal lymphoma patients.

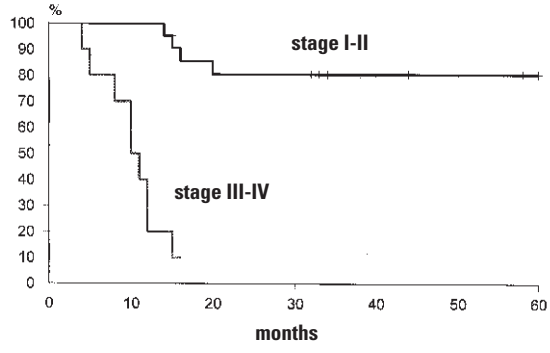

Figure 2. Overall survival curves according to stage: stage I-II versus stage III-IV.

Discussion

The incidence and localization of primary gastrointestinal lymphomas vary around the world.[6-14] The stomach is the most common site of primary GI lymphomas in Western countries, but in the Middle East most primary gastrointestinal lymphomas arise in the small intestine, followed closely by the stomach.

Intestinal lymphomas differ significantly from their gastric counterparts, not only in pathology but also with regard to clinical features, management and prognosis. Unfortunately there is no information about their molecular pathogenesis[23] which might be possibly useful also from a clinical point of view.

Surgical resection should always be attempted for localized disease. The management of extensive gut lymphoma remains controversial; a conservative approach consists of limited resection of obstructed or perforated segments followed by whole-abdomen radiation. However, several authors[6,12,15,24,25] have argued for aggressive surgical debulking of all intestinal lymphomas, including those of stage III and stage IV. However, such comparative studies cannot completely resolve the question of whether the nonresected patient would fare poorly because the primary tumor was not removed (debulking procedure), or because nonresection selects advanced and prognostically unfavorable cases. Recent data suggest that extensive resection may improve local control and eliminate early mortality from visceral perforation or hemorrhage in unresected lesions during adjuvant therapy. The latter observation is highly significant, since these complications have been reported to account for 22% to 78% of treatment failures.[15-17]

There is a trend towards utilizing chemotherapy and radiotherapy after surgery. If radiotherapy alone is used, recurrence outside a confined radiation field may be as frequent as 60%.[6] In addition, radiation poses the risk of such late complications as vasculitis and radiation enteritis.

In the current study, 24/32 (75%) of the patients

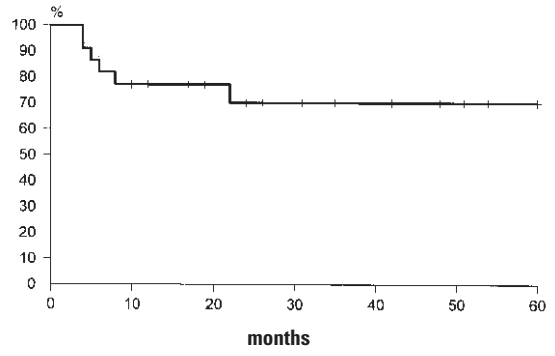

Figure 3. Relapse-free survival curve of all 24 CR patients.

achieved CR. The patients who failed to reach CR were all in advanced stages (III and IV). In fact, only 2/10 (20%) of the advanced stage patients obtained CR. Despite the fact that none of the responses were maintained, only 6 (25%) relapses were observed among the 24 CRs and relapse-free survival at a median follow-up of 30 months (range 6-80 months) was 72%.

Different therapeutic approaches were used in the two subsets: radical tumor resection plus polychemotherapy in early stage patients versus biopsy plus polychemotherapy in advanced stage patients. In fact, radical tumor resection was a major determinant of prognosis and was closely related to tumor stage as expressed by radical resectability for stage I and stage II ($p = 0.000001$).

The major prognostic factors for survival were early stage and radical resectability, with both factors being strictly correlated. In the literature recommendations for surgical treatment predominate, ranging from aggressive to rather limited surgical attitudes. As regards prognosis, patients with low-grade histology are generally reported to do better than those with high-grade tumors;[26] in our study, too few of the lymphomas were of the low-grade variety to allow any meaningful comparison.

In conclusion, our data confirm the findings of other investigators[25-27] that surgical resection is the mainstay of treatment for localized primary western intestinal lymphomas. In addition, in our retrospective study post operative chemotherapy positively influenced survival. Thus, our recommendation for early stage primary intestinal lymphomas is to adapt lymphoma resection in such a way as to make it as radical as is necessary. The role of selective postoperative chemotherapy for advanced primary intestinal lymphomas after surgical biopsy alone must be established by multicenter prospective clinical trials capable of accumulating a larger body of data so that these uncommon lymphomas can be better understood.

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