Evaluation of 22 Primary Gastrointestinal Lymphoma Patients

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ABSTRACT

Objective: Primary gastrointestinal non-hodgkin lymphomas (PGI-NHL) are uncommon diseases with treatment modalities including chemotherapy, surgery, and radiotherapy. Our aim is to analyze the demographic and clinical features and treatment results of PGI-NHL.

Materials and Methods: 286 patients diagnosed with lymphoma who referred to Ataturk University Medical Faculty Hospital between July 2001 and April 2014 were surveyed retrospectively and 22 (7.6%) PGI-NHL cases whose primary lesions were in gastrointestinal system were included.

Results: Mean age was 47 (min.25- max.77) and 14 (63.6%) of them were men. The origin was determined as small intestines (50%), stomach (31.8%) and colon (18.2%), respectively. The most common complaint and pathologic subtype were abdominal pain (68.2%) and diffuse large B cell lymphoma (86.4%), respectively. The Lugano Classification was as follows: stage 1 (18.2%), stage 2 (59.1%), and stage 4 (22.7%). Surgery and chemotherapy were administered to 40.9% of patients. Complete and partial response and disease progression were established in 72.1%, 4.5% and 13.6% of the patients, respectively. Mean survival time was 99.6±16 months. Mean overall survival time was determined significantly longer in small bowel group than gastric group (119±15 vs. 50±24 months) (p=0.039). Age, gender, Eastern Cooperative Oncology Group performance status, International Prognostic Index, stage, histological type, tumor size, LDH level, albumin level, Hemoglobin level and treatment options were not associated with survival.

Conclusion: Demographic and clinical characteristics of our series were similar with Middle Eastern and African countries. Optimal treatment options or prognostic factors for PGI-NHL are not clear. There is a need for randomized prospective studies including large number of patients and long follow-up period.

Keywords: Primary gastrointestinal system lymphoma, prognostic parameters

Introduction

Primary Gastrointestinal Non-Hodgkin Lymphoma (PGI-NHL) was first described by Billroth in 1871 [1]. PGI-NHL represents only 1-4% of all gastrointestinal malignities [2]. The most frequent localization of extranodal NHLs is gastrointestinal system (GIS) and it presents 30-50% [3]. The incidence of primary GI-NHL is reported to be higher in Eastern countries than in Western countries, and high-grade histopathological types of gastric lymphoma are more common in Turkey and Middle Eastern countries than in Western countries [4, 5]. Stomach is the most affected site, followed by colon and small bowels [6]. The most frequent pathological subtype is diffuse large B cell lymphoma (DLBCL). Some potential risk factors like immunosuppression, Helicobacter Pylori (Hp) infection, human T-cell leukemia/lymphoma virus tip 1 (HTLV-1) infection, Celiac disease, Epstein-Barr virus (EBV), exposure to environmental agents and occupational risks were studied so far [7]. Clinical indicators of PGI-NHLs are not specific and may not be distinguished from other benign and malign gastrointestinal tumors, and this may lead diagnostic failure or misdiagnosis [8]. In recent years, because of the common use of endoscopic methods and radiological imaging, it is diagnosed at relatively early stages. Due to the heterogeneities, especially in patients at advanced stage, the optimal treatment modality is not established for PGIL yet [9]. Localization, histological type, immunophenotypical features and stage are important for treatment approaches. Additionally PGI-NHLs with different localizations have various clinicopathological features and prognosis.

In this retrospective study, we aimed to evaluate the demographical features, clinical follow ups, treatment outcomes and survival analysis of our PGI-NHL cases collected in 13 years.

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Materials and Methods

Two hundred eighty-six patients diagnosed with lymphoma who referred to Ataturk University Medical Faculty Hospital between July 2001 and April 2014 were surveyed retrospectively and 22 PGI-NHL cases whose primary lesions were in gastrointestinal system were included. PGI-NHL was defined as predominant lesions in the gastrointestinal tract or gastrointestinal symptoms according to the definition provided by Lewin *et al* [10]. Age, gender, diagnosis date, stage at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, serum LDH, Hemoglobin and Albumin levels, extranodal involvement, localization, tumor size of the patients at diagnosis and applied treatment modalities, treatment response status, follow-up periods and life status were recorded. Cases were staged according to the modified Lugano Classification System which was developed for GIS lymphomas [11]. The pathological classification of all cases was accomplished according to the morphological and immunophenotypical criteria of World Health Organization (WHO) [12]. Risk classification of the cases was fulfilled according to the International Prognostic Index (IPI) [13]. Patients were grouped according to the prognostic factor counts as follows: low risk group (prognostic factor count: 0-1), intermediate risk group (prognostic factor count: 2-3), and high risk group (prognostic factor count: 4-5).

Statistical analysis was performed using Statistical Program for Social Sciences (SPSS) verison 20.0 (IBM Corp., Armonk, NY, USA). Overall survival was calculated from the date of diagnosis to the date of death. Patients who were alive at the last follow-up were censored at that time. Life curves were estimated with Kaplan-Meier method. The association of each marker with survival was analyzed using Log-rank test. A $p<0.05$ was considered significant.

Results

Demographical Features

Of the 22 patients diagnosed with PGI-NHL, 14 (63.6%) were men, 8 (36.4%) were women. Men/women ratio was 1.7/1. Median age was 47 (min 25-max 77).

Clinical course and tumor localization

The majority of PGI-NHL cases were localized at small bowel representing 50% of the cases (11 patients). Seven patients (31.8%) had gastric localized lymphoma, 4 (18.2%) patients had colon localized lymphoma. Tumor generally localized as a single lesion and tumor size was ranged 3-14 cm. The most frequent complaint at reference was abdominal pain and was presented in 68.2% of the patients, followed by nausea and vomiting (40.9%) (Table 1). Serum LDH level was high in 11 patients. B symptoms were determined in 6 of 22 patients. The IPI of the patients were as follows: 59.1% (13 patients) were in low risk group, 22.7% (5 patients) were in low-intermediate risk, and 18.2% (4 patients) were in intermediate-high risk group. (Table 2)

Histology and staging

According to the WHO Classification, 19 (86.4%) patients were classified as DLBCL, 1 (4.5%) patient was classified as mantle cell lymphoma (MCL), 1 (4.5%) patient was classified as follicular lymphoma, and 1 (4.5%) patient was classified as small lymphocytic lymphoma. Histologically, high grade lymphoma was determined as the most common type (42.3%). According to the Lugano staging system, of the patients 18.2% diagnosed in stage 1, 59.1% in stage 2 and 22.7% in stage 4. Bone marrow involvement was identified in none of the cases (Table 2).

Treatment strategies

Eleven patients (50%) had undergone surgical resection. Seven patients were undergone emergent surgery because of acute abdomen or GIS bleeding. Lesions of 6 patients who undergone emergent surgery were originated from intestines. Just one of the patients who undergone emergent surgery had stage 4 disease. Complete resection was performed in 1 (4.5%) patient. Complete resection + chemotherapy (CT) was performed in 8 (36.3%) patients, incomplete resection + CT was performed in 1 patient, incomplete resection + CT + radiotherapy (RT) was performed in 1 patient, only CT was performed in 10 (45.5%) patients, CT + RT was performed in 1 patient (Table 3). Rituximab, cyclophosphamide, vincristine, doxorubicin, and prednizolon (R-CHOP the most frequent, CHOP or R-CVP) including regimens were administered as CT to the patients.

Table 1. Clinical symptoms or sings of PGI-NHL*

Clinical symptoms or signs	No. of cases (%)
Abdominal pain	15 (68.2)
Nausea and/or vomiting	9 (40.9)
Loss of appetite	7 (31.8)
Anemia	8 (36.3)
Weight loss	5 (22.7)
Fever	5 (22.7)
Gastrointestinal bleeding	3 (13.6)
Melena	2 (9.1)
Obstruction	2 (9.1)
Abdominal mass	2 (9.1)
Shoulder pain	1 (4.5)
Oliguria	1 (4.5)

*PGI-NHL: Primary Gastrointestinal Non-Hodgkin Lymphoma

Prognostic factors and survivals

The median follow-up time of all patients was 113±13 months. Because the life status information couldn't be obtained, one patient wasn't involved to survival analyses. Complete response was obtained in 72.1% of the patients and partial response was obtained in 4.5%. Progression was observed in 13.6% of the patients (Table 4). Progression was observed in just one of the 9

Table 2. Demographic characteristics of PGI-NHL patients

	No. of cases (%) N:22
Gender	
Male	14 (63.6)
Female	8 (36.4)
Age	
Median (min-max)	47 (25-77)
Localization	
Gastric	7 (31.8)
Small intestine	11 (50)
Colon	4 (18.2)
Histological Type	
DLBHL**	19 (86.4)
MCL***	1 (4.5)
Follicular Lymphoma	1 (4.5)
Lymphocytic Lymphoma	1 (4.5)
Stage	
I	4 (18.2)
II	13 (59.1)
IV	5 (22.7)
IPI*	
Low-risk	13 (59.1)
Intermediate	5 (22.7)
High	4 (18.2)
B symptoms	
Yes	6 (27.4)
No	16 (72.6)
LDH level	
High	11 (50)
Normal	11 (50)

*IPI: International Prognostic Index, **DLBCL: diffuse large B cell lymphoma

***MCL: Mantle cell lymphoma

Table 3. Treatments of PGI-NHL patients

Therapy	Patients (n=19)	Overall survival (months)
Surgery + Chemotherapy	9	117±19
Chemotherapy	9	59±17
Chemotherapy + Radiotherapy	2	70±42
Surgery	1	119 (still alive)

Table 4. Treatment response of PGI-NHL patients

Response to First Line Therapy	n (%)
Complete	16 (72.1)
Partial	1 (4.5)
Progress	3 (13.6)
Ex. during therapy	1 (4.5)

patients who received only chemotherapy; complete response was obtained in the remaining. Progression was determined in only one of the 9 patients who undergone surgery and CT. Relapse was observed in follow-up in one patient who had complete response after surgery + CT and one patient who was administered CT + RT after incomplete surgery. One patient who had a diagnosis of DLBCL was administered 6 cycles of RCHOP treatment after surgery and in the fifth year of the follow-up had an additional diagnosis of second primary lung cancer.

Mean survival time of the patients was 99±16 months. In the group which surgery and chemotherapy administered together (9 patients) survival was longer, but no statistically significant difference was observed in survival time compared to the group which received only chemotherapy (9 patients) (mean survival times: 117±19 months vs 59±17 months; p=0.22, respectively). Mean survival time was determined significantly longer in patients who had small bowel localized PGI-NHL than patients who had gastric PGI-NHL (119±15 vs 50±24 months) (p=0.039). Prognostic factors like age, gender, histological type, stage, IPI score, performance status, treatment modality, LDH, Hemoglobin, albumin levels and tumor size had no effect on survival time in our series.

Discussion

PGI-NHL shows heterogeneity in terms of patient characteristics, histological subtypes, stages and treatment outcomes [14]. Primary GI-NHL constitutes between 4% and 20% of all lymphoma cases [15]. In our study, PGI-NHL diagnosis was consisted of 7.6% of all lymphoma patients. It is comparable with the study by Erkurt et al. in our country as they found this ratio as 9.7% [4]. The median diagnosis age of patients was 47 (min.25-max.77). In gender distribution men/women ratio was 1.7/1, and our results showed that it was higher in men compatible with the existing literature [3, 8, 16]. The most frequent localization was stomach, and its frequency was reported in series between 37% and 86% [3, 5]. In some Middle Eastern Countries, the most frequent localization is small bowel [9, 17-19]. Also in our study, small bowel involvement was at the first place with a ratio of 50%, followed by stomach with 31.8% and colon with 18.2%. In another study from Turkey, small bowel was found as the most frequent localization [20]. Korelitz et. al have reported that diseases like immunosuppression, Human T lymphocyte virus (HTLV) and tropical sprue, ulcerative colitis were the predisposing factors of malign lymphoma [21]. In our patients, none of these risk factors were detected. Clinical course may vary according to the localization, but there are generally nonspecific gastrointestinal symptoms. The most frequent reference symptoms consisted of abdominal pain, nausea, vomiting, lack of appetite and weight loss similar with our study [3, 6, 8, 9, 22, 23]. Three patients diagnosed with gastric lymphoma were referred with GIS bleeding.

Also in our study, similar to the previous studies, DLBCL was the most frequent histological subtype and its ratio was found to be as 86.4% [3, 4, 8, 15, 22]. They include marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), which account for nearly 50% of gastric lymphomas, and diffuse large B-cell lymphomas (DLBCL), whilst both follicular and mantle cell lymphomas are infrequent [25, 26]. In recent years, increase in frequency of MALT/MZBCL was connected to developments in technological endoscopic procedures (like endoscopic ultrasonography) and multiple biopsies performed [6]. In our country where the frequency of H.Pylori is high, the reason of having no patients diagnosed with MALT/MZBCL may be associated with inadequate biopsies, frequent use of H.Pylori eradication treatments, and our low number of gastric lymphoma diagnosed patients.

The treatment is only surgery, chemotherapy and radiotherapy or the combinations of these. Although the role of surgery in PGI-NHL is still controversial, the most preferred treatment modality is combination chemotherapy with surgery. While in some studies surgery is preferred as the first option [27], in some studies it is reported that there was no difference in terms of survival between the administration of surgery with chemotherapy and chemotherapy alone [9, 28, 29]. On the other hand there are studies reporting combined treatment (surgery+chemotherapy) had been superior to surgery alone [8], or CT alone [4, 5, 20]. Supporting these results, in our study, in the group of patients whom surgery and chemotherapy were administered together, survival time was longer but did not reach statistical significance. In another study chemotherapy alone was reported superior to surgery alone or to surgery+chemotherapy [30]. Curative surgery may be recommended to patients who have localized disease. Palliative surgery procedures are important in patients with obstruction, perforation, bleeding and fistula [31]. CT is the first line treatment in rapidly progressing aggressive lymphoma, because it bears a role over local effect of surgery or RT. Because of the unresponsiveness to CT in mantle cell, follicular cell or T cell lymphomas, complete surgical resection or RT are the first choice [32].

In previous analyses, gender, age, pathological type, tumor localization, tumor size, IPI, stage, LDH, treatment modality were reported to be prognostic factors [3, 6, 14, 33]. In our study, from these parameters only tumor localization is found to be important and it is observed that intestinal group has a better prognosis than gastric group. In determining either optimal treatment options or prognostic factors, there is a need for randomized prospective studies including large number of patients, long follow-up period.

In conclusion, in our region, the most common localization of PGI-NHL is small bowel and the most common initial complaint is abdominal pain. Survival time is longer in intestinal group than the other localizations. In PGI-NHL patients, surgery + CT administration may be more efficacious.

Ethics Committee Approval: Ethical Committee approval was received for this study from the Ethics Committee of Ataturk University School of Medicine, dated 16.10.2015 and numbered 7/ 17.

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