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Primary Gastrointestinal non-Hodgkin Lymphoma in Adults: Clinicopathologic and Survival Characteristics

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A B S T R A C T

Primary non-Hodgkin lymphomas of gastrointestinal tract (PGI-NHL) are the most common extranodal lymphomas with an increasing incidence. The incidence, clinicopathologic characteristics, treatment and survival were assessed in 39 successive, newly diagnosed PGI-NHL patients (23 male and 16 female) treated at »Merkur« University Hospital. The aim of the study was to precisely evaluate their characteristics and compare them with the results reported from other similar studies. The most common site of PGI-NHL was stomach (n=29, 74%), followed by small intestine (n=5, 13%), and colon and rectosigmoid (n=5, 13%). According to the Ann Arbor classification, 34 (87%) patients had stage IE and IIE, and five patients (12%) stage IIIE and IVE. According to World Health Organization (WHO) classification, 29 (87%) patients had diffuse large B-cell lymphoma (DLCBL), two had mantle cell lymphoma, and seven (18%) had marginal zone B-cell lymphoma-mucosa associated tissue (MALT). Twenty-six (66%) patients underwent surgical resection followed by chemotherapy, ten (26%) were treated with chemotherapy alone, and three (8%) were treated surgically. Complete remission was achieved in 28 (72%) and partial remission in seven (18%) patients. Four (10%) patients had progressive disease. In our patients, the major prognostic factor for outcome was the stage of disease. Patients with localized lymphoma (stage IE and IIE) had a significantly longer overall survival: 85% at five years and 65% at ten years. Patients with extended disease (stage IIIE and IVE) had overall survival less than 33%. The prognostic power of erythrocyte sedimentation rate (ESR), total protein, serum albumin, LDH concentration and activity was analyzed. Of these parameters, only LDH had a statistically significant effect on overall survival. In conclusion, our patient group was comparable to other literature reports on PGI-NHL patients according to clinicopathologic characteristics. Disease stage and LDH were the only parameters that had a statistically significant effect patient survival.

***Key words**: lymphoma, extranodal lymphoma, stomach, intestine*

Introduction

Primary non-Hodgkin lymphomas of gastrointestinal tract (PGI-NHL) are the most common extranodal lymphomas, with an increasing incidence[1,2]. They account for 30–50% of all extranodal lymphomas and constitute a heterogeneous group of diseases with different clinical and pathologic features[3–5]. The most common primary site is stomach (60–75%), followed by small intestine, colon, and rarely other gastrointestinal organs including pancreas and liver[5,6]. Esophageal lymphoma is extremely unusual, e.g. Mayo Clinic has reported only three primary cases in 47 years[7].

There are many classifications of gastrointestinal tract lymphomas, but none of them covers all requirements for clinical and histopathologic use. For simplicity, clinical staging has been evaluated according to Ann Arbor classification[8] and histopathologic according to World Health Organization (WHO) classification[9]. According to this

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classification, lymphomas of the gastrointestinal tract generally fall into one of six categories (extranodal marginal zone-mucosa associated lymphoma tissue, MALT lymphoma; follicular lymphoma; mantle cell lymphoma; diffuse large B-cell lymphoma, DLCBL; and Burkitt's lymphoma)[9,10].

Approximately one half to two-thirds of PG-NHL are DLCBL[11,12]. MALT is the second most common type of PGI- NHL, occurring predominantly in individuals aged >50, with a peak in seventh decade, although it has been occasionally reported in younger patients as well. In 80% of cases, there is strong association between chronic *Helicobacter (H.) pylori* infection and MALT gastric lymphoma[13–15]. Mantle cell, follicular and Burkitt's lymphomas are encountered less frequently[15].

Treatment strategies for nodal NHL are well established, but there are still controversies concerning optimal treatment of PGI-NHL, particularly gastric lymphoma. Surgery, radiotherapy, and chemotherapy have been used alone or in combination[16–20]. Recently, important improvement in the response rate for B-cell lymphomas has been achieved with CD20, a cytolytic antibody, a direct agonist of the B cell specific antigen. Rituximab as a single agent can induce overall objective response rates in follicular lymphomas[21].

In our retrospective study, the incidence, clinical features, histology and treatment of PGI-NHL patients treated at »Merkur« University Hospital during a 10-year period were analyzed.

Patients and Methods

From January 1997 to January 2007, 548 patients with NHL were diagnosed and treated at »Merkur« University Hospital in Zagreb. Among them, 39 (7%) patients with gastrointestinal symptoms or predominant lesions in the gastrointestinal tract were selected for our study as PGI-NHL. Characteristics of patients included in the study are presented in Table 1. Diagnostic procedure consisted of history and physical examination, complete blood count and basic biochemical serum tests (including lactate dehydrogenase, LDH), serum electrophoresis with total proteins and chest X-ray and/or computerized tomography, abdominal ultrasound, and endoscopic examination of the gastrointestinal tract. Bone marrow biopsy and aspirate were also obtained.

Twenty-two patients underwent esophagogastroduodenoscopy and seven colonoscopy, with multiple biopsies. Four patients with stomach lymphoma had bleeding and/or perforation and needed urgent surgical treatment. Six patients with intestinal lymphoma also underwent urgent surgical treatment because of obstructive symptoms. All tissue specimens were analyzed in the same department and were classified according to the WHO classification of neoplasms of hematopoietic and lymphoid tissues[9,10]. Clinical staging was done according to Ann Arbor classification[8].

Patients were treated surgically, followed by chemotherapy, or by surgery or chemotherapy alone. None of the patients was treated with radiotherapy. Antibiotic therapy for *H. pylori* eradication was used in six positive patients. Therapeutic response was assessed according to standard criteria. Complete response was defined as complete disappearance of all lymphoma signs, maintained for at least 6 weeks. Reduction of the disease burden by at least 50% with disappearance of systemic manifestation for at least 6 weeks was considered as partial response. Patients with stable or progressive disease were classified as having no response[22]. Overall survival was measured from the point of inclusion in the study to the time of death from any cause or loss to follow up[23].

On statistical analysis, χ^2-test was used to compare response rates in the same groups of patients. Log-rank test was used to compare survival between the groups. Survival rate was calculated according to Kaplan-Meier method. The level of significance was set at $p<0.05$. Statistical tests were performed by use of the Stat View v. 5.0.1 software (SAS Institute, Cary, NC, USA).

Results

Clinical and histologic findings of all patients are presented in Table 1. Out of 39 patients with PGI-NHL, 23 were males and 16 females (M:F ratio, 1.6:1) aged 20–74 (median 58) years. Most patients reported epigastric pain (85%) and dyspepsia (30%). The duration of symptoms before the diagnosis varied from a few weeks to several

TABLE 1
CHARACTERISTICS OF 39 PATIENTS WITH PRIMARY GASTROINESTINAL NON-HODGKIN LYMPHOMA

Age (yrs) Median	58
Range	20–74
Sex: M/F	23/16
Histologic Subtypes	
High grade	
Diffuse large cell B lymphoma (DLCBL)	29
Mantle-cell lymphoma	2
Low grade	
Mucosa associated lymphoma tissue (MALT)	8
Stage	
I	13
II	21
III–IV	5
Bone Marrow	
Positive	4
Negative	28
Not done	7
Distribution	
Stomach	29
Jejunum/ileum	5
Colon/ rectosigmoid	5

months. Weight loss before the diagnosis was reported by 40% of patients. At the time of diagnosis, gastric bleeding was the main symptom in 15%–20% of patients, while perforation was rare.

Thirty four (88%) patients had disease stage IE and IIE, while five (12%) patients had stage IIIE and IVE. B symptoms (fever, weight loss of more than 10 percent of body weight and night sweats) were present in 33% of our patients, most of them with DLCBL.

According to histopathologic classification, DLCBL accounted for 74%, MALT for 21% and mantle cell lymphomas for 5% of all PGI-NHL cases. Bone marrow infiltration was positive in only four (10%) patients. There was no age and sex difference in the relative incidence of MALT lymphoma and DLCB lymphoma. Disease characterization was similar, with the exception of LDH, which was more frequently elevated in DLCBL patients.

Out of 39 PGI-NHL patients, 26 patients with DLCBL underwent surgical resection followed by 3–6 cycles of chemotherapy. Twenty-one of them were treated with CHOP regimen that consists of cyclophosphamide, doxorubicin, vincristine, and prednisone. Therapy was repeated every three weeks. Four patients were treated with chemotherapy without an anthracycline (COP), because they were older than 65 or had cardiomyopathy with ejection fraction <55%. After surgical intervention, one patient was treated with an alkylating agent (chlorambucil) in combination with prednisone.

Three patients with DLCBL were treated with chemotherapy (CHOP) and immunotherapy (rituximab). They were administered rituximab several years ago, when it was registered for this indication. Two patients with mantle cell lymphoma were also treated with chemotherapy (CHOP) and immunotherapy (rituximab). One of them relapsed two years later and was then treated with myeloablative chemotherapy followed by autologous bone marrow transplantation, while the other was transplanted immediately after surgery. Now, both patients are in remission.

Five patients with MALT lymphoma were treated only with chemotherapy. Two patients had stage IE gastric MALT lymphoma and positive H. pylori test. They immediately received therapy for H. pylori eradication that consisted of amoxicillin, metronidazole, and omeprazole. Both achieved remission, however, relapse occurred at one year. Then, they were treated with chemotherapy with alkylating agents and prednisone. Three other patients with MALT lymphoma underwent surgery and adjuvant chemotherapy (COP).

The overall response rate was 84% at 5 years and 68% at 10 years (Figure 1). Complete response was achieved in 28 (71%) and partial remission in seven (23%) patients, whereas four patients had progressive disease. Patients with stage IE-IIE tended to live longer than those with stage IIIE-IVE ($p<0.005$), but there was no significant difference in the overall survival between patients with DLCBL and MALT (Figure 2). Furthermore, there was no difference in survival between patients with local-

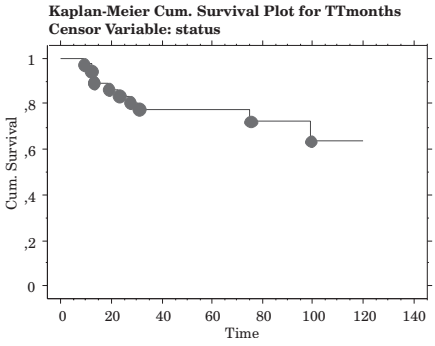

Fig. 1. Overall survival in 39 patients with primary gastrointestinal non-Hodgkin lymphoma.

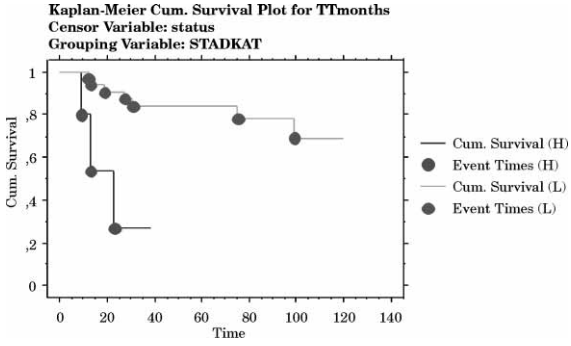

Fig. 2. Survival according to clinical stage: low stages I+II–L, high stages III+IV–H ($p=0.0008$).

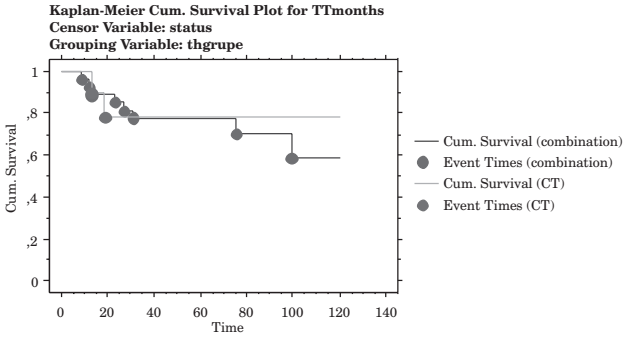

Fig. 3. Survival according to treatment: CT – chemotherapy, Combination – chemotherapy plus surgery ($p>0.05$).

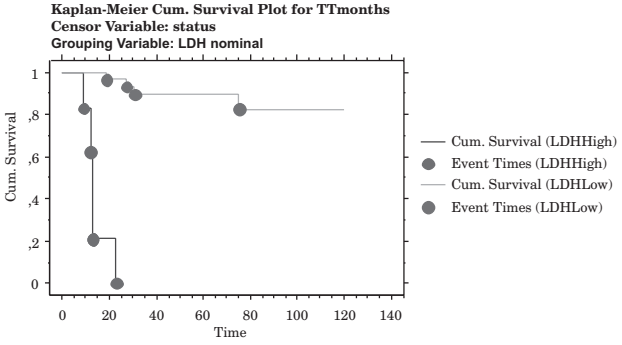

Fig. 4. Survival according to LDH: LDH≥400 – LDHHigh, LDH<400 – LDHLow ($p<0.0001$).

ized disease treated with surgery with or without chemotherapy, and those treated with chemotherapy alone (Figure 3). Finally, in our study LDH activity was found to be an important prognostic factor; patients with higher LDH levels had lower overall survival (Figure 4), whereas other parameters analyzed (ESR, albumin, total proteins, age and sex) had no statistically significant effect on patient prognosis.

Discussion and Conclusion

Primary gastrointestinal non-Hodgkin lymphoma is a heterogeneous disease regarding patient characteristics, histologic subtypes, stage, and treatment results. It is estimated that 11%–34% of all NHL are PGI-NHL[1]. The most commonly involved site is stomach with a frequency of 37.5%–86% in several studies, followed by small intestine, colon and rectum[2–7]. In our retrospective study, survival was analyzed in 39 patients with PGI--NHL. Out of 548 patients diagnosed and treated at »Merkur« University Hospital from January 1997 till January 2007, the prevalence of PGINHL was 7%. Stomach was the main site in approximately 74% of all PGI--NHL cases, which is in agreement with other literature reports[1–7]. Our results confirmed PGI-NHL to occur more frequently in men than in women[24]. The most common histologic subtypes were DLCBL and marginal zone B cell lymphoma-mucosa associated tissue. In our study, the percentage of DLCBL was higher than of MALT lymphoma (71% *vs*. 20%), which is consistent with literature data[7,11,15]. However, in the study by Papaxoinis et al., the percentage of indolent lymphoma (MALT) was slightly higher than that of aggressive lymphoma (DLCBL), probably because of the higher prevalence of H. pylori infection[20]. H. pylori infection is considered to be involved in the pathogenesis of MALT lymphoma, while its role in the etiology of DLCBL is controversial[22,23].

In the present study, the stage of disease was the major prognostic factor. Patients with localized lymphoma stage IE and IIE had a significant longer overall survival than patients with extended disease. At 3 years of the diagnosis, the overall survival in patients with stage IE and IIE (85%) was significantly higher ($p<0.05$) than in patients with stage IIIE and IVE. Similar results has been reported from other studies where overall survival in advanced PGI-NHL ranged from 25% to 47%[11,12,14,15,18]. Also, in our study LDH activity had a statistically significant effect on overall survival, while other study parameters such as ESR, albumin, total protein, age and sex had no statistically significant impact on prognosis. In our study, there was no difference in overall survival between patients with DLCBL and MALT lymphoma, which is in contrast with the study by Koch et al.[15], where a significantly shorter overall survival was only found in patients with high grade gastrointestinal lymphoma.

Although the management of primary gastrointestinal lymphoma, particularly of gastric origin, has been examined in several studies reported in the literature, it remains controversial. Many studies were focused on primary resection and chemotherapy[18,20,25]. However, other authors found no difference in survival between patients treated with chemotherapy and those treated with surgery plus chemotherapy[12–15]. In a randomized study of survival of patients with gastric DLCBL after chemotherapy or surgery combined with chemotherapy, survival was significantly longer (10-year survival rates 96% and 91%, respectively) than after surgery alone or surgery in combination with radiotherapy (10-year survival rate 53%)[17]. In our study, there was no difference in overall survival between patients treated with surgery plus chemotherapy and patients treated with chemotherapy alone (Figure 3).

In conclusion, PGI-NHL is a heterogeneous disease characterized by high variability of clinicopathologic and demographic features. Stage is the most important prognostic factor, with a significantly better survival in localized as compared with extended disease. Optimal treatment has not yet been established. New intensive combinations of chemotherapy, immunotherapy, radioimmunotherapy and radiotherapy, randomized clinical trials with a large number of patients and long-term follow up are needed to find out and validate the most appropriate treatment for PGI-NHL.

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PRIMARNI NE-HODGKINOV LIMFOM PROBAVNOG SUSTAVA

S A Ž E T A K

Primarni ne-Hodgkinov limfom (NHL) probavnog sustava najčešći je oblik ekstranodalnih limfoma s incidencijom rasta. U Kliničkoj bolnici »Merkur« retrospektivno smo analizirali 39 novodijagnosticiranih bolesnika (23 muškarca, 16 žena). Analizirali smo kliničko patološke karakteristike, način liječenja i preživljenje bolesnika u razdoblju od siječnja 1997. do siječnja 2007. godine. U 29 (74%) bolesnika dijagnosticiran je NHL želuca, u 5 (13%) tankog crijeva, a u 5 (13%) debelog crijeva. Klinički stadij bolesti odredili smo prema klasifikaciji Ann Arbor. Klinički stadij IE i IIE imalo je 34 (87%) bolesnika, dok je 5 (12%) bolesnika imalo stadij IIIE i IVE. Prema klasifikaciji Svjetske zdravstvene organizacije (SZO) 29 (87%) bolesnika imalo je B velikostanični limfom, 2 (5%) limfom plaštene zone, a 7 (18%) bolesnika imalo je limfom marginalne zone (MALT). Prema načinu liječenja 26 (66%) bolesnika liječeno je operacijski (potpuna ili djelomična gastrektomija ili resekcija) nakon čega su primali kemoterapiju, 10 (26%) bolesnika samo kemoterapijom, a 3 (8%) bolesnika samo operacijskim liječenjem**.** Kompletna remisija postignuta je u 28 (72%), djelomična remisija u 7 (18%) bolesnika, a u 4 (10%) bolesnika došlo je do progresije bolesti. Bolesnici s kliničkim stadijem IE i IIE imali su znatno duže preživljenje (5-godišnje preživljenje 85% bolesnika i 10-godišnje 65% bolesnika) od bolesnika u IIIE ili IVE stadiju bolesti koji su imali preživljenje manje od 33%. U studiji se analizirao i utjecaj ostalih parametara (dob, spol, SE, serumski albumini, ukupni proteini i laktat dehidrogenaza – LDH) na prognozu bolesnika. Jedini parametri koji su imali statistički značajan ($p<0,05$) utjecaj na preživljenje bili su stadij bolesti i vrijednost LDH.