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ORIGINAL ARTICLE

Pretreatment risk factors for overall survival in patients with gastrointestinal and non-gastrointestinal mucosa associated lymphoid tissue lymphomas

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Summary

Purpose: *The aim of this 10-year retrospective study was to investigate prognostic clinical and laboratory factors significant for the outcome of patients with mucosa associated lymphoid tissue (MALT) lymphoma.*

Methods: *The study involved 87 patients diagnosed with MALT lymphoma: 37 (42.5%) with gastrointestinal (GI) and 50 (57.5%) with non-GI localization. The following pretreatment laboratory parameters were analyzed: hemoglobin, serum albumin and lactate dehydrogenase (LDH) level, beta2-microglobulin (β_2-M) and bacteriological (H.pylori) status. Estimated clinical features were: stage of disease, ECOG performance status (PS), tumor mass, number of extranodal localizations, presence of B symptomatology, splenomegaly and enlarged lymph nodes. Diagnosis of MALT lymphoma was based on histopathological analysis of tissue samples, obtained by endoscopy or surgery.*

Results: *The median disease-free survival (DFS) was 36 months and the 5-year overall survival (OS) was 64%. OS rate of patients with non-GI localization was higher compared with patients with GI localization (p=0.001). Multivariate analysis showed hypoalbuminemia to be the most significant parameter associated with poor OS (p<0.001) for both patient groups. The most significant prognostic factor for poor OS in patients with GI localization was LDH level (p=0.031), while hypoalbuminemia was the most significant prognostic factor for poor OS in the group with non-GI disease localization (p=0.001).*

Conclusion: *Proper therapeutic approach for MALT lymphoma patients could be planned taking into consideration poor prognostic parameters, i.e. hypoalbuminemia and elevated LDH for GI patients and hypoalbuminemia for non-GI lymphoma patients.*

Key words: *gastrointestinal, lymphoma, MALT lymphoma, non gastrointestinal, prognostic factors*

Introduction

Extranodal lymphomas of marginal zone MALT type account for approximately 7-8% of all B-cell NHL [1]. The most frequent GI localization is the stomach (85%). Among non-GI MALT lymphomas the most common disease sites are the orbit (12%), lung (10%), skin (9%), salivary glands (6%), thyroid gland (4%) and breast (2%) [2].

These tumors are characterized by an indolent course. They tend to remain localized for long periods of time and show good response to therapy. Some sites of MALT lymphoma have been associated with chronic infections (*H.pylori, Borrelia burgdorferi, Campylobacter intestini, Chlamidiae psittaci*) and autoimmune diseases (Sjogren's syndrome, Hashimoto's thyroiditis) [3-5]. Patients with MALT lymphoma have a favorable outcome with a long OS (5-year OS between 85 and 95%) [6,7]. The median time to progression is around 5 years, significantly better for the GI localization compared to non-GI ones [8]. Nevertheless, some patients have a shorter survival either because of transformation into a more aggressive subtype

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of lymphoma or due to yet unknown reasons [7]. Many authors investigating MALT lymphoma have aimed to find clinical, laboratory and biological parameters that, before starting treatment, would detect those patients with an increased risk of rapid disease progression [7-11].

The aim of this 10-year retrospective study was to investigate prognostic clinical and laboratory factors, significant for the outcome of patients with MALT lymphoma.

Methods

This study included 87 patients with MALT lymphoma with GI and non-GI localization, who were followed up during the period January 2000–December 2009 in the Clinic of Hematology, Clinical Center of Serbia. The diagnosis of MALT lymphoma was confirmed by histopathological and immunohistochemical (IHH) examination of tissue samples taken endoscopically in GI localizations and surgicallyin non-GI localizations. Histopathological diagnosis was made according to the WHO classification criteria [2]. The following pretreatment laboratory parameters were recorded: hemoglobin, serum albumin, LDH, and β_2-M serum levels, and *H.pylori* status. Estimated clinical features were: stage of disease, ECOG PS tumor mass, number of extranodal localizations, presence of B symptomatology, splenomegaly and/or enlarged lymph nodes. Determination of clinical stage was based on the Ann Arbor classification and the Lugano classification for MALT lymphoma with GI localization. The International Prognostic Index (IPI) score was calculated according to published criteria [16]. Therapeutic response after initial treatment was determined as complete clinical remission (CR), partial remission (PR), stable disease (SD) or progression of disease (PD). OS was defined as the time interval from diagnosis to death or last follow-up. DFS was defined as the time from achievement of CR until relapse. Several therapeutic options were used: wait-and–see strategy in 21 patients (24.1%), CHOP chemotherapy in 39 patients (44.8%), and chlorambucil in 27 patients (31.0%).

Statistics

Descriptive statistics included measures of central tendency: mean, median; measures of variability: range (min-max), standard deviation (SD); and relative numbers. The significance of differences was assessed by chi square test, Student's t-test, Mann-Whitney U test (rank sum test) or Fisher's exact test as appropriate. Survival was evaluated by the Kaplan-Meier method and log rank test for comparison among the groups. To determine risk factors we used the univariate and multivariate Cox regression models. Statistical significance was set at $p<0.05$.

Table 1. Demographic and clinical-laboratory characteristics of GI/non-GI MALT lymphoma patients

Characteristics	*GI MALT (N=37) N (%)*	*Non-GI MALT (N=50) N (%)*
Gender: male/ female	16(43.24) / 21(56.76)	25 (50) / 25 (50)
Age, years, median (range)	65 (38-82)	57 (28-78)
CS I and II	13 (35.14)	32 (64)
CS III and IV	24 (64.86)	18 (36)
ECOG >1	9 (24.32)	4 (8)
B symptoms	26 (70.27)	15 (30)
Extranodal localization > 1	22 (59.46)	16(32)
Splenomegaly	10 (27.03)	1 (2)
Hemoglobin<12 g/dL	27 (72.97)	15 of 43 (34.88)
LDH (IU/L)	5 (13.51)	6 of 37 (16.22)
Albumin <34 g/l	15 of 31 (48.39)	4 of 34 (11.76)
ESR > 30 mm/h	14 of 36 (37.84)	22 of 45 (48.89)
β_2-M >3 g/l	5 of 10 (50)	7 of 29 (24.14)
H. pylori positivity	13 of 32 (40.6)	14 of 47 (29.8)
IPI score		
Low (0 or 1)	9 (24.3)	22 (50)
Intermediate	25 (67.6)	20 (45.5)
High (4 or 5)	3 (8.1)	2 (4.5)

GI: gastrointestinal, CS: clinical stage, IPI: international prognostic index, β2-M: β2 microglobulin, ESR: erythrocyte sedimentation rate, ECOG: Eastern Cooperative Oncology Group, LDH: lactate dehydrogenase

Results

The main clinical and laboratory characteristics of the patients are shown in Table 1. Their mean age was 58 years (range 28–82). Patients with GI lymphoma were older than patients with non-GI lymphoma. There were 46 (52.9%) women and 41 (47.1%) men. Female predominance was obvious in patients with GI lymphoma. The majority of patients with non-GI lymphoma had Ann Arbor clinical stage I, while most patients with GI lymphoma had stages III or IV. Patients with GI lymphoma had a higher percentage of B symptoms, more extranodal sites, splenomegaly and poorer laboratory results than patients with non-GI lymphoma. Relatively more GI lymphoma patients were *H.pylori*-positive (13 of 32; 40.6%). The majority of patients from both groups had intermediate IPI score. Stomach (N=29;33.3%), and orbit (N=13;14.9%) prevailed with skin and testis being the less frequent localizations (N=1;1.1% each). The most frequent site of origin of GI MALT lymphoma was the stomach (29;33.3%), and of

non-GI MALT lymphoma the orbit (N=13;14.9%). DFS was 36 months (range 2-72) and 5-year OS was 64%. Patients with non-GI localization had significantly longer OS than those with GI localization (p=0.001).

The probability of OS, as tested by the Kaplan-Meier method, correlated positively with the parameters: age (p=0.001), clinical stage (p=0.026), B symptoms (p=0.006), ECOG PS (p=0.005), *H.pylori* infection (p=0.015) and hypoalbuminemia (p<0.001). The impact of age on OS is shown in Figure 1. Figures 2 and 3 show the impact of LDH and hypoalbuminemia on OS in GI/non-GI MALT lymphoma. Univariate analysis including both GI and non-GI lymphoma indicated that the following features were significant prognostic factors for poor OS: age >60 years (p<0.001), clinical stage III and IV (p=0.026), presence of B symptomatology (p=0.006), ECOG PS ≥2 (p=0.005), *H. pylori* positivity (p=0.015) and hypoalbuminemia (p<0.001). In the group of patients with non-GI lymphoma, univariate analysis indicated clinical stage III and IV (p=0.020), hypoalbuminemia (p<0.001) and IPI score (p=0.037) as significant factors for poor OS, while in the group of patients with GI lymphoma, univariate analysis showed that elevated LDH was significant factor for poor OS (p=0.016). The results of univariate analysis for non-GI and GI lymphomas, are shown in Table 2.

Table 2. Univariate analysis of prognostic factors for overall survival in GI/non-GI MALT lymphoma

Characteristics	*GI MALT p-value*	*Non-GI MALT p-value*
Gender: male/female	0.160	0.376
CS III and IV	0.895	0.020
ECOG >1	0.113	0.331
B symptoms	0.181	0.496
Extranodal localization> 1	0.960	0.069
Splenomegaly	0.586	/
Hemoglobin<12 g/dL		0.974
LDH (IU/L)	0.016	0.751
Albumin<34 g/l	0.116	p<0.001
ESR>30 mm/h	0.670	0.091
β_2-M >3 g/l	0.134	0.171
H. pylori positivity	0.071	0.266
IPI score		
Low (0 or 1)		
Intermediate	p=0.282	p=0.037
High (4 or 5)		

For abbreviations see footnote of Table 1

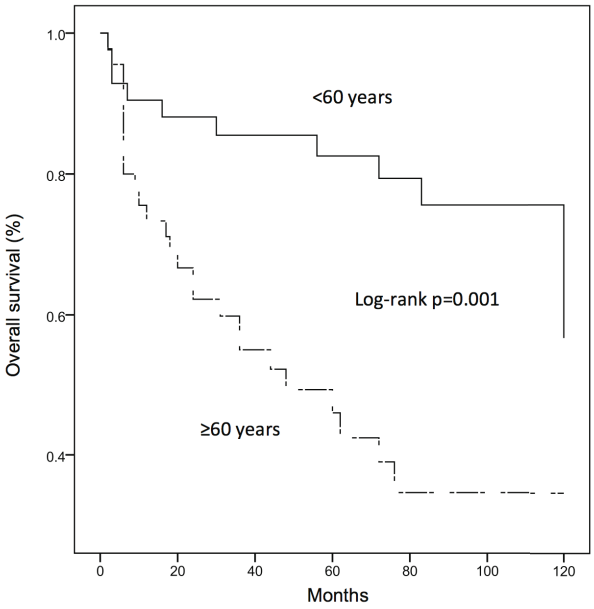

Figure 1. Impact of age on overall survival in non-GI and GI MALT lymphoma.

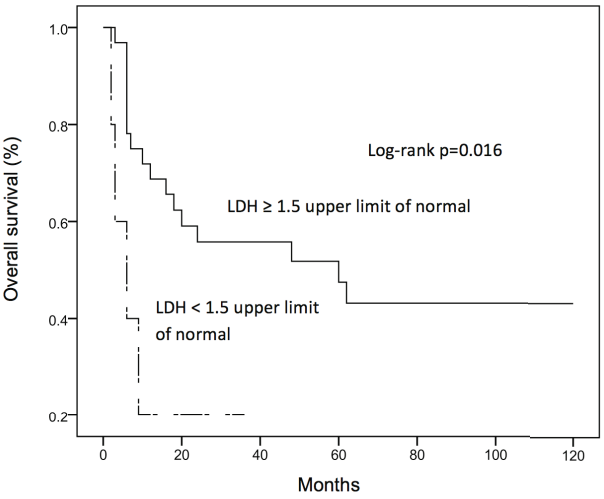

Figure 2. Impact of LDH level on overall survival in gastrointestinal MALT lymphoma.

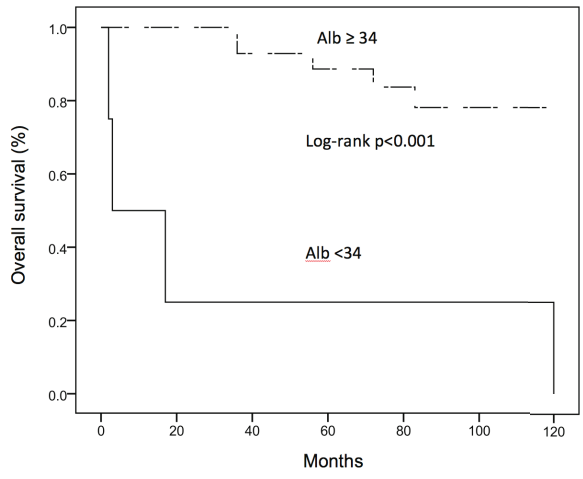

Figure 3. Impact of hypoalbuminemia on overall survival in non-gastrointestinal MALT lymphoma.

Table 3. Univariate and multivariate analysis of significant parameters for overall survival in GI and non-GI MALT lymphoma

Parameters	*Patient groups*	*Univariate analysis p-value*	*Multivariate analysis*		
			p-value	*Relative risk*	*95% confidence interval*
Albumin<34 g/l		<0.001	0.001	28.195	3.590-221.456
CS III and IV	Non GI MALT	0.020	/	/	/
IPI score		0.037	/	/	/
LDH	GI MALT	0.016	0.031	3.452	1.121-10.630
Albumin<34 g/l	Non GI MALT & GI MALT	/	<0.001	5.060	2.055-12.458

For abbreviations see footnote of Table 1

Multivariate Cox proportional regression method pointed to low serum albumin level (p<0.001) as the most significant prognostic factor for poor OS in both groups of MALT lymphoma patients. For those with GI localization, the most significant prognostic factor for poor OS was LDH level (p=0.031), while for the group with non-GI localization was hypoalbuminemia (p=0.001; Table 3).

Discussion

GI and non-GI MALT lymphomas have an indolent course, a good response to therapy and long survival. We showed that some differences existed in laboratory and clinical characteristics on presentation.

The mean age of our patients was 58 years, which confirms earlier findings that this type of lymphoma occurs in older people [17]. There was a significant difference in survival in different age groups (p=0.001; Figure 1) as patients younger than 60 years lived longer. GI localization was more frequently found in women but there were no differences in survival between males and females or between the groups, which is consistent with published data [15]. The stomach with one third of our patients was the most frequent localization, also in accordance with literature data [8]. The most common sites of non-GI lymphoma were the ocular adnexa (14.9%), salivary gland (12.6%), lung (10.3%) and tonsils (9.2%), which are in agreement with reported data [6,8,11,12]. A low percentage of our patients had B symptoms, ECOG PS > 1 and increased LDH, which indicates an indolent course of MALT lymphoma, as found previously by others [6-8,11,12]. Advanced stages (III-IV) according to the Ann Arbor classification system occurred significantly more frequently in patients with GI lymphomas (64.86%) vs 36% in patients with non-GI lymphomas. This is contrary to the results of other studies [7-9]. It can be partly explained by the high percentage of non-GI ocular cases that were in clinical stage I among our group of patients. Determining the prognostic IPI score showed that most patients had a medium risk (51.7%) or low risk (35.6%) with only 5 (5.7%) at high risk. No statistically significant difference was seen in patient survival according to the IPI score. Patients with non-GI lymphoma were more likely to have localized disease, rarely with B symptoms and better ECOG PS, less than one extranodal place, rare splenomegaly, less frequent *H. pylori* infection, milder anemia and hypoalbuminemia compared with patients with GI lymphoma. Thus, there was a significant difference in survival in favor of non-GI lymphoma patients (p=0.001). *H.pylori* infection was found in 40.6% of patients with GI lymphomas and in 29.8% of those with non-GI lymphomas. Data from epidemiological, clinical and laboratory studies support the causative role of *H.pylori* in the development of gastric MALT lymphoma in 85-90% of the cases [3]. There was a significant difference in survival according to the presence of *H.pylori* infection groups (p=0.015), as patients without *H. pylori* infection lived longer.

The probability of 5-year OS survival was 64%, which was considerably lower than rates of 86 to 95% observed by others [6,7,9]. Three-year DFS was 36 months, which was shorter than DFSs found in many studies, with rates ranging from 5.6 to 7 years [6-8,11,12]. We observed a higher percent of relapses among the non-GI group patients. The probability of 5-year OS in relation to the occurrence of the first relapse was not statistically significant, as described earlier [7]. Our patients showed good response to therapy (CR:85;1%), which confirms earlier findings [8,9,12]. Only one patient (1.1%) developed transformation to diffuse large B-cell lymphoma.

Our results showed that there were statistically significant differences in survival according to clinical stage, ECOG PS, presence of B symptoms, *H.pylori* infection and hypoalbuminemia in agreement with the results of many studies [9,11,18-20]. Hypoalbuminemia had a marked impact on

the survival of both groups of MALT lymphomas. Multivariate analysis confirmed hypoalbuminemia as a poor prognostic factor for both groups of patients, especially for non-GI lymphoma. Elevation of LDH levels was adversely associated with the survival of patients with GI lymphoma and multivariate analysis characterized it as a poor prognostic factor, as reported in previous studies [8,12,20]. Thus, clinical and laboratory parameters at presentation (hypoalbuminemia and elevated LDH) could identify MALT lymphoma patients with an unfavorable prognosis.

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