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Evaluation of parameters with potential prognosis impact in patients with primary gastric diffuse large B-cell lymphoma (PG-DLBCL)

IONELA ROTARU[1)], GABRIEL DRAGOŞ GĂMAN[1)], CASIANA STĂNESCU[2)], AMELIA MARIA GĂMAN[3)]

[1)]*Department of Hematology, University of Medicine and Pharmacy of Craiova, Romania*
[2)]*Department of Obstetrics and Gynecology, Faculty of Medicine, "Vasile Goldiş" Western University, Arad, Romania*
[3)]*Department of Pathophysiology, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

Background: Primary gastric lymphoma is the most common malignancy of the stomach after gastric adenocarcinoma. Most cases are represented by the aggressive histological type (diffuse large B-cell lymphoma). *Aim*: Identification of factors with potential prognosis impact in the aggressive primary gastric lymphoma and the prognosis profile of the patient with impact on the response to therapy and overall survival. *Patients and Methods*: The study group is composed of 49 patients diagnosed with primary gastric diffuse large-cell non-Hodgkin's malignant lymphoma at "Fundeni" Hematology Clinic of Bucharest and at the Hematology Clinic of Craiova, Romania, in the period 2005–2010. There were evaluated the following parameters in the attempt to establish correlations between the various studied parameters and the response to treatment, in order to establish the prognosis factors: erythrocyte sedimentation rate (ESR), hemoglobin, serum albumin, serum lactate dehydrogenase (LDH), beta-2 microglobulin, presence of serous infiltration, presence of locoregional adenopathies, bulky tumor, stage of disease, international prognostic index (IPI), quick response to therapy (reduction of >50% in tumor volume after two courses), presence of disease relapses, type of treatment – resection + chemotherapy *versus* chemotherapy alone, chemotherapy *versus* chemotherapy + Rituximab. *Results*: We found the following negative prognosis factors: the presence of disease relapse, the value of beta-2 microglobulin higher than 3 mg/dL, the presence of serous infiltration, IPI 3. *Conclusions*: Identifying prognostic factors is important for personalized therapy approach to obtain optimal response with minimal adverse reaction.

Keywords: primary gastric diffuse large B-cell lymphoma, prognosis factors, overall survival.

Introduction

Gastric lymphoma is considered to be primary when the initial symptoms of the disease are located in the stomach or when the tumor mass is located in the stomach. The gastrointestinal tract is a common localization of non-Hodgkin's lymphomas with extranodal onset (30–40% of extranodal forms). Compared to all non-Hodgkin's lymphomas regardless of location, primary gastric lymphoma represents 4–20% of all cases of non-Hodgkin's malignant lymphomas [1]. As for the primary gastric location, primary gastric non-Hodgkin's malignant lymphomas are the most common malignancy of the stomach after gastric adenocarcinoma. On the contrary, the primary or secondary involvement of the stomach in Hodgkin's lymphoma is extremely rare [2]. Clinical manifestations are unspecific and they are similar to those found in gastro-duodenal ulcer, in ulcerative dyspepsia or in gastric adenocarcinoma [3]. Accurate diagnosis is established by histopathological and immunohistochemical examination, supplemented by cytogenetic and molecular biology tests. A complete diagnosis requires a histopathological classification and a correct staging, both of them having an impact on the therapeutic decision.

Aim

The aim of our study was the identification of the factors with potential prognosis impact in the aggressive primary gastric lymphoma and the prognosis profile of the patient with impact on the response to therapy and overall survival.

Patients and Methods

The study group is composed of 49 patients diagnosed with primary gastric diffuse large-cell non-Hodgkin's malignant lymphoma at "Fundeni" Hematology Clinic of Bucharest and at the Hematology Clinic of Craiova, Romania, in the period 2005–2010. The inclusion criteria were: primary tumor location in the stomach with or without intra-abdominal structures involved; histopathological examination of gastric lesions, which indicated the diagnosis of non-Hodgkin's malignant lymphoma; positive diagnosis established on the histopathological examination of the gastric tumor, even in the context of the existence of supra-diaphragmatic adenopathies or of the damage of the hematogenous bone marrow at the biopsy bone puncture. There were excluded from the study the patients diagnosed by lymph node biopsy with histopathological and immunohistochemical examination, and who have also presented gastric lesions in evolution. Resection pieces were initially examined and studied at the Laboratory of Anatomical Pathology of "Fundeni" Clinical Institute, Bucharest and at the Laboratory of Anatomical Pathology of the Emergency County Hospital, Craiova. The anatomopathological examination consisted in the macroscopic

evaluation of the gastric tumor and of the other resected tissue fragments (lymph nodes and other tissue fragments suspected of neoplastic invasion) and subsequently in the preparation of tissue for histopathological and immunohistochemical evaluation. Histopathological examination involved the paraffin inclusion of tissue fragments and subsequently the achievement of usual Hematoxylin–Eosin (HE) stained histological sections, following the next steps: fixation in 10% buffered formalin, washing with 80% alcohol, dehydration through successive alcohol bath, clarification on benzene, toluene, xylene and paraffin embedding. Preparations were microscopically examined in order to define the histological type, the degree of differentiation, and the invasion of gastric wall structures. For immunohistochemistry, the LSAB – Dako manufacturer, code K0679 (HRB), method (LSAB – Labeled Streptavidin–Biotin; HRP – Horseradish Peroxidase) and the antibodies: CD20, CD10, CD5, κ light chain and Ki-67 were used. The signal was detected with 3,3'-diaminobenzidine (DAB) (Dako) chromogen substrate solution. The 4-µm sections were collected on special slides covered with a layer of poly-L-Lysine. The antigens dilutions and performed pre-treatments are presented in Table 1.

Table 1 – ***The antigens dilutions and performed pre-treatments of the gastric biopsy or gastric resection pieces***

Antibody	Source	Clone	Dilution	Antigen retrieval	Clonality
CD20	Dako	L26	1:100	Three cycles, citrate buffer	Monoclonal, mouse
Ki-67	Dako	MIB-1	1:20	Seven cycles, citrate buffer	Monoclonal, mouse
CD10	Leica	56C6	1:100	Five cycles, citrate buffer	Monoclonal, mouse
CD5	Leica	NCL-L-CD5-4C7	1:100	Five cycles, citrate buffer	Monoclonal, mouse
K light chain	Dako	MHK-49	1:1000	Seven cycles, citrate buffer	Monoclonal, mouse

Data processing was made using Data Analysis module of Microsoft Excel application (Microsoft Corp., Redmond, WA, USA), XLSTAT suite for MS Excel (Addinsoft SARL, Paris, France) and also SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Entering patient data in the EXCEL application produced the initial database from which there were extracted significant aspects of this study. There were evaluated the following parameters in the attempt to establish correlations between the various studied parameters and the response to treatment, in order to establish the prognosis factors: ESR value, hemoglobin value, serum albumin value, serum LDH value, beta-2 microglobulin value, presence of serous infiltration, presence of locoregional adenopathies, bulky tumor, stage of disease, B symptoms (fever, weight loss, physical asthenia), international prognostic index (IPI), quick response to therapy (reduction of >50% in tumor volume after two courses in 33 patients without resection), presence of disease relapses, type of treatment – resection + chemotherapy *versus* chemotherapy alone, chemotherapy *versus* chemotherapy + Rituximab. The international prognostic index (IPI) was calculated for 40 of the patients with primary gastric diffuse large B-cell lymphoma, the ECOG performance status not being able to be evaluated for the other patients. Thus, in the case of primary gastric lymphomas, IPI includes the following parameters: age >60 years, elevated serum LDH values, ECOG performance status > or = 2, more than one extranodal determination of the disease, excluding the stomach. Disease staging was done by using the Lugano system, in which stage III is not defined, and stage IV corresponds to the generalized disease with supradiaphragmatic damage or extralymphatic damage by hematogenous dissemination and not by contiguity. Extralymphatic determinations by contiguity are marked with E, and bulky tumor (having a diameter greater than 10 cm) with X. Final evaluation of patients was done was done after two and five years respectively.

Results

Characteristics of the studied group

There were 49 patients in the group diagnosed with primary gastric diffuse large B-cell lymphoma. The average age is of 52.20 years, with ages ranging from 21 to 79 years and with a standard deviation of 29.22%, as shown in Table 2.

Table 2 – ***The average age and standard deviation in patients with diffuse large B-cell lymphoma (DLBCL) [4]***

Age	DLBCL
No. of cases	49
Average age [years]	52.204
Standard deviation	15.412
CV [%]	29.22
Minimum	21
Quartile 1	40
Median	55
Quartile 3	65
Maximum	79

CV – Coefficient of variation.

The largest number of patients is found in the age groups of 50–59 and 40–49 years, followed by those aged between 60–69 and 70–79 years, as presented in Table 3.

Table 3 – ***Distribution by age groups of patients with DLBCL***

Age groups [years]	No. of patients	Percentage
20–29	5	10.20%
30–39	6	12.24%
40–49	10	20.41%
50–59	12	24.49%
60–69	8	16.33%
70–79	8	16.33%

In the studied group of patients, there were 23 men and 26 women. As for the place of origin that is presented in Table 4, most patients (71.43%) come from urban areas and only 28.57% from rural areas.

Table 4 – ***Distribution of DLBCL cases according to the year of diagnosis***

Year of diagnosis	No. of patients	Percentage
2005	8	16.33%
2006	9	18.37%
2007	8	16.33%
2008	11	22.45%
2009	4	8.16%
2010	9	18.37%

The histopathological exam shows a proliferation of large cells (the nucleus size is double in relation to the nucleus size of a normal lymphocyte), prominent nucleoli, basophilic cytoplasm, as shown in Figures 1 and 2. All of the diffuse large B-cell lymphoma revealed B-cell phenotype as immunohistochemistry showed CD20 expression in all cases (Figures 3 and 4). Regarding proliferation index, Ki-67 positivity (Figure 5) was usually observed in the blastic cells. Moderate (10–20%) or high Ki-67 index (>20%, maximum found 45%) was observed in eight diffuse large B-cell lymphoma of 12 cases tested.

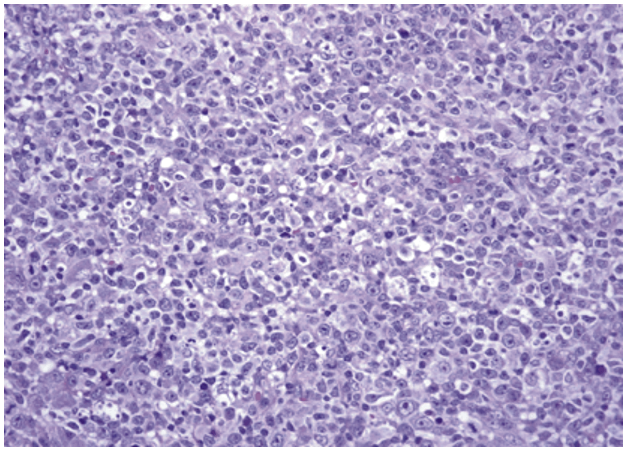

Figure 1 – ***Primary gastric diffuse large B-cell lymphoma. Infiltrated with neoplastic large cells with reduced cytoplasm, basophilia with hypertrophic nuclei, irregular, with multiple nucleoli, some of them attached by nuclear membrane. HE staining, 100×.***

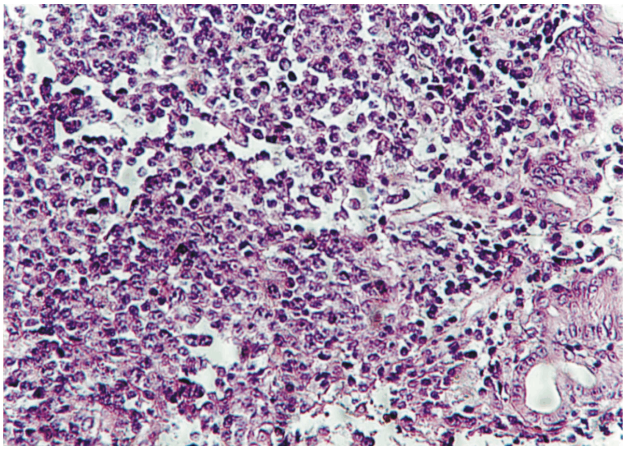

Figure 2 – ***Primary gastric diffuse large B-cell lymphoma with MALT component. Large cells, mostly with low quantitative cytoplasm, with round nucleus centrally placed nucleoli (lymphoplasmocytic cells)/peripheral (centroblast-like cells), with discrete lymphoepithelial lesions. HE staining, 200×.***

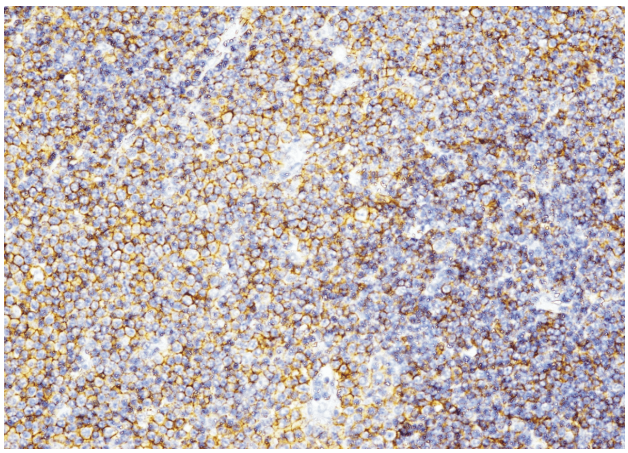

Figure 3 – ***Primary gastric diffuse large B-cell lymphoma with MALT component. CD20+ intense common in tumor cells. IHC, 100×.***

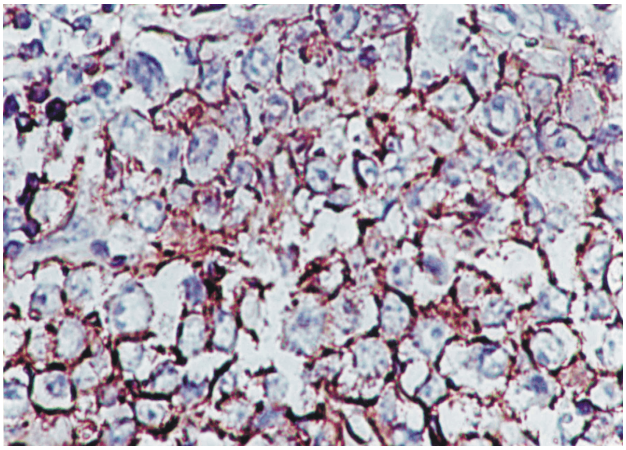

Figure 4 – ***Primary gastric diffuse large B-cell lymphoma with MALT component. CD20+ intense common in tumor cells. IHC, 400×.***

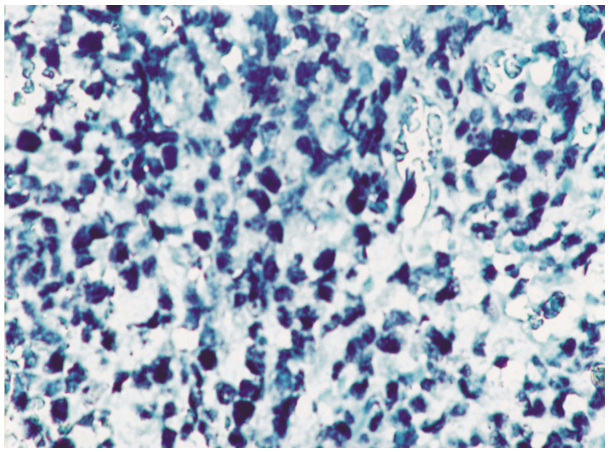

Figure 5 – ***Primary gastric diffuse large B-cell lymphoma with MALT component. Ki-67 diffuse intense positive in many tumor cells. IHC, 400×.***

The evaluation of the relationship between the studied parameters and patient status at final evaluation: there is a statistically significant dependence regarding sex (Fisher test = 0.0271), females being associated with a better response at final evaluation; the presence of B symptoms does not have a statistically significant influence on patient status at the end of the evaluation (chi-square test = 0.166796); hemoglobin value at diagnosis proved to be a factor without significant importance to patient status at the end of the evaluation for patients with diffuse large B-cell lymphoma (chi-square test = 0.8613828); as for the impact of serum albumin values at diagnosis, statistical analysis does not show any significant values concerning their influence on patient status at final evaluation (chi-square test = 0.646383). The discrepancy between these results and specialized literature data may be due to the small number of patients to whom there were determined serum albumin values (16 patients). The relationship

between beta-2 microglobulin value and patient status at final evaluation showed that patients with values below 3 mg/dL are found in a greater number in complete remission of the disease at final evaluation. There is a statistically significant dependence between the presence of serous infiltration at diagnosis and the final status of patients with diffuse large cell lymphoma (Fisher test = 0.0271), the presence of serous infiltration representing a negative prognosis factor, the number of patients who died or who are in partial remission of disease at the end of evaluation being greater as regards serous membrane damage at diagnosis. The presence of locoregional adenopathies was found in a number of 14 patients whose presence was not of significant influence on patient status at final evaluation (chi-square test = 0.120). The evaluation of stage importance at diagnosis as regards the final response of patients showed a statistically insignificant relationship (chi-square test = 0.2484) between the stage of disease and the final evaluation. The evaluation of IPI impact on final status showed a significant difference (chi-square test = 0.0047) between cases with IPI<3 (low risk and low intermediate risk) and those with IPI=3 (high intermediate risk). DLBC patients with high intermediate risk have a significantly lower rate of complete remissions of disease at final evaluation and a higher death rate at final evaluation. Thus, IPI value at diagnosis is an important prognosis factor, patients with IPI between 0 and 2 having a favorable prognosis. The presence of bulky tumor was revealed in a number of 22 patients. It was noted the importance of reducing tumor after two courses of polychemical therapy, in 17 of these patients who did not have gastric resection, aiming for the impact of tumor reduction with >50% on the achievement of complete remission at the end of the therapeutic protocol and also on patient status at final evaluation. It was achieved complete remission at the end of the therapeutic protocol in all patients with diffuse large B-cell lymphoma who achieved a bulky tumor reduction of >50%. There was revealed a statistically significant relationship between tumor reduction of >50% for bulky forms and status at final evaluation. Patients who achieved a bulky tumor reduction of >50% after two courses of polychemical therapy, have a significantly better status, only one of the patients with tumor reduction of >50% being in partial remission of disease at the end of evaluation. Thus, tumor reduction is a prognosis factor with favorable impact on patient status at final evaluation. Gastric resection in 33 patients with diffuse large B-cell lymphoma does not bring any benefits to the final status of the patients, the differences between the two groups, with or without resection, being statistically insignificant (Fisher test = 0.2162). As regards polychemical therapy, we did not find any significant differences between patients treated with conventional courses (25 patients treated with CHOP) and those to whom molecular therapy (24 patients treated with R-CHOP) was added (Fisher test = 0.1223). We noticed a very statistically significant relationship (Fisher test = 0.0003) between the achievement of complete remission at the end of the therapeutic protocol and the patient status at final evaluation. Patients who achieve complete remission at the end of the therapeutic protocol have a favorable prognosis, all patients who are in complete remission of the disease after the end of therapy not presenting any disease signs at the end of evaluation. The occurrence of disease relapse has a significant influence on patient status at final evaluation (Fisher test = 0.0018); eight of the 49 patients of the group with diffuse large B-cell lymphoma had a relapse during evolution. Among these ones, two had an early relapse (in the first year after complete remission), dying in the first two and half years since diagnosis.

Statistical correlations

The encoding of the studied parameters in order to determine their correlations with patient status (complete remission, partial remission, death) at the end of evaluation is presented in Table 5. Table 6 contains the results of the correlations between the studied parameters.

Table 5 – ***Encoding of the studied parameters***

Encoding	-1	0	1	2	3	4	5	6	7
Age groups [years]				20–29	40–49	30–39	50–59	60–69	70–79
B symptoms		No	Yes						
ESR [mm/h]			<20	>20					
Hemoglobin [g/dL]			<10	10–12	>12				
Albumin [mg/dL]	<3.5		>3.5						
LDH [IU/mL]			<200	>200					
Beta-2 microglobulin [mg/dL]	<3		>3						
Stage			I1	I2	II1	II1E	II2	II2E	IV
Damage of serous membrane	Yes		No						
Bulky tumor		No	Yes						
Reduction of bulky tumors after two courses of treatment	No		Yes						
IPI			1	2	3	4			
Resection		No	Yes						
Treatment			Chemotherapy	Rituximab					
Maintenance		No	Yes						
End of courses of treatment			Complete remission	Partial remission	Death				
Relapse		No	Yes						
Final evaluation			Complete remission	Partial remission	Death				

ESR – Erythrocyte Sedimentation Rate; LDH – Lactate Dehydrogenase; IPI – International Prognostic Index.

Table 6 – ***The main correlations found***

Parameter 1	Parameter 2	Pearson's correlation coefficient – *r*
Hemoglobin	*ESR*	-0.356
Beta-2 microglobulin	*B symptoms*	0.355
Bulky tumor	*Reduction of bulky tumors after two courses of treatment*	0.315
IPI	*Age*	0.427
IPI	*LDH*	0.28
End of courses of treatment	*IPI*	0.302
Relapse	*Age*	0.292
Relapse	*IPI*	0.376
Final evaluation	*Stage*	0.323
Final evaluation	*IPI*	0.393
Final evaluation	*End of courses of treatment*	0.532
Final evaluation	*Relapse*	0.599

ESR – Erythrocyte Sedimentation Rate; IPI – International Prognostic Index; LDH – Lactate Dehydrogenase.

Interpretation of the results

There can be noticed a correlation between IPI and the achievement of complete remission at the end of the therapeutic protocol: the more IPI value is higher the more the probability of not achieving complete remission is higher. Bulky tumor reduction of >50% after two courses of polychemical therapy in patients without gastric resection and bulky tumor, is also an important factor in the response to treatment, all patients with reduction after two courses being in complete remission of the disease at the end of specific therapy.

Disease relapse is directly influenced by patient age and IPI value, relapses being more common in elderly patients with high IPI values. Patient status at the end of evaluation is directly influenced by the stage of disease, the IPI value at diagnosis, the achievement of complete remission at the end of the therapeutic protocol and the presence of disease relapses.

In order to determine whether there is a statistically significant correlation between all these parameters and the final status of patients, we applied the multiple regression analysis as shown in Table 7. The results are presented in Table 8.

Some parameters, although directly analyzed in relation to the final evaluation, showed a statistically significant influence on patient status, but in the overall analysis, they did not show any statistically significant influence on status at the final evaluation. This is due to the use in multivariate analysis of some factors that depend on them, and the final evaluation result shows only the influence of the latter.

The parameter with a high statistically significant correlation in the group with diffuse large B-cell lymphoma is the presence of disease relapse ($p<0.00001$).

The achievement of complete remission at the end of the therapeutic protocol ($p=0.003$) and the beta-2 microglobulin value at diagnosis are also statistically correlated with patient status at final evaluation ($p=0.047$).

Table 7 – ***Multiple regression analysis***

Regression model	R (correlation coefficient)		R^2 (coefficient of determination)		Adjusted R^2
Values	0.84		0.705		0.557
ANOVA	**Sum of squared errors of prediction**	**Degrees of freedom (df)**	**Mean squared error**	***F***	***P***
Regression	21.435	16	1.34	4.777	0
Residual	8.973	32	0.28		
Total	30.408	48			

Table 8 – ***The results obtained by applying the multivariate analysis of the correlation between the studied parameters and the response to treatment in DLBCL***

Variable	Coefficient	*P*
Relapse	**0.563**	**<0.0001**
End of courses of treatment	**0.349**	**0.003**
Beta-2 microglobulin	**0.24**	**0.047**
Damage of serous membrane	-0.217	0.092
Reduction of bulky tumors after two courses of treatment	-0.145	0.2
Treatment (chemotherapy versus Rituximab – chemotherapy)	-0.166	0.251
Hemoglobin	0.13	0.357
ESR	0.115	0.363
Albumin	-0.087	0.445
Age	-0.06	0.618
Maintenance	0.055	0.632
Resection	0.057	0.661
IPI	-0.03	0.821
Stage	-0.013	0.929
B symptoms	0.005	0.969
LDH	-0.003	0.977

ESR – Erythrocyte Sedimentation Rate; IPI – International Prognostic Index; LDH – Lactate Dehydrogenase.

Discussion

Large B-cell lymphoma is the most common histological type of primary gastric lymphoma. It is an aggressive lymphoma that can occur *de novo* or by transformation of MALT lymphoma. Differentiating between the two types, *de novo* and resulted from a MALT lymphoma, is clinically and histologically difficult and can be done only immunohistochemically and by molecular biology techniques. The diffuse large B-cell lymphoma, which originates from the germinal centre cells, is CD10 positive, Bcl-6 negative and Bcl-2 positive, while the variant derived from MALT lymphoma is CD10 negative, Bcl-6 positive and Bcl-2 negative [5]. But, this differentiation is not clinically important and in terms of therapeutic attitude, both behaving as aggressive lymphomas and the therapeutic attitude being similar. Data provided by IELSG at Lugano in 2011, shows as factors with prognostic implications: the presence of lymph node damage, the presence of B symptoms, low serum albumin value, IPI values >3 [6]. In the studied group serum albumin value does not have prognosis importance (being discordant with specialized literature data), probably due to the small number of cases in which serum albumin dosage was made. There are also studies that identify as negative prognosis factors both the low hemoglobin value at

diagnosis and the low serum albumin value [7]. As regards IPI, our results are concordant with specialized literature data that identifies IPI as an important prognosis factor in DLBCL [8, 9]. The results obtained on the studied group did not reveal any statistically significant relationship between the presence of locoregional adenopathies or B symptoms, being discordant with the results published by the extranodal onset lymphoma study group at Lugano in 2011 [5]. The stage of disease is not a negative prognosis factor in the study group, being discordant with data published by Tanaka *et al.* in 2012, the advanced stage and the high value of serum LDH being identified as negative prognosis factors [10]. The achievement of complete remission at the end of the therapeutic protocol (p=0.003) and the beta-2 microglobulin value at diagnosis are also statistically correlated with patient status at final evaluation (p=0.047) in the studied group, as shown by Avilés *et al.* who identifies the importance of beta-2 microglobulin value at diagnosis that is correlated with the response to treatment [11]. Regardless of location, the diffuse large B-cell lymphoma is treated with aggressive polychemical therapy, the standard of treatment consisting in the combination of Rituximab with a polychemical therapy containing: Anthracycline (Epirubicin, Adriamycin or Mitoxantrone) with Cyclophosphamide, Vincristine and Prednisone (CHOP, CEOP or CNOP). The prescript of this therapeutic attitude is based on the excellent results obtained in the treatment of diffuse large B-cell lymphoma with nodal onset, confirmed by several clinical studies [12, 13]. For localized stages (I and II Lugano), first-line therapy consists of chemotherapy + immunotherapy. There are administered 3–4 courses of R-CHOP, followed by localized radiotherapy. Radiotherapy toxicity can be reduced by using techniques that minimize the radiation dose that reaches the liver and kidneys [14]. In advanced stages (stage IV according to Lugano staging), there are administered 6–8 cycles of R-CHOP. The effectiveness and safety of administering R-CHOP is high, even in the cases with bulky tumor [15, 16]. In the studied group, we did not find any significant differences between the results obtained in patients treated with conventional courses (CHOP) and those to whom molecular therapy (R-CHOP) was added (Fisher test = 0.1223). Our data is concordant with specialized literature data [12, 17–19], which does not indicate any benefits on the final status of patients by adding molecular therapy to conventional therapy (R-CHOP *versus* CHOP). The results of retrospective and prospective studies suggest that conservative therapy has equal or better results than gastrectomy [20]. Furthermore, data obtained from a randomized trial comparing the results obtained in patients with diffuse large B-cell lymphoma treated only with polychemical therapy *versus* chemotherapy + gastrectomy does not show any significant differences between the two groups in terms of up to 10 years survival (96% and 91% respectively), concluding that gastrectomy is not necessary [21].

In patients with diffuse large B-cell lymphoma of the studied group gastrectomy does not bring any benefits to the final status of patients, the differences between the two groups being statistically insignificant (Fisher test = 0.2162), as shown in specialized literature data, too [22]. The role of consolidation radiotherapy is still debated. The association of radiotherapy (40 Gy) to six cycles of CHOP polychemical therapy results in a 91% survival rate up to 42 months [23]. None of the patients in the studied group performed consolidation radiotherapy.

Conclusions

Summarizing all these data, there can be identified the following factors with prognosis impact for the studied group: *positive prognosis* (females, IPI 0–2, achieving a complete remission at the end of the therapeutic protocol, bulky tumor reduction of >50% after two courses of polychemical therapy in patients presenting a bulky tumor without gastric resection); *negative prognosis* (presence of disease relapses, value of beta-2 microglobulin higher than 3 mg/dL, presence of serous infiltration, IPI 3); *with no prognostic significance* (presence of B symptoms, gastric resection, adding Rituximab to the standard therapy, stage of disease, serum albumin value). Identifying prognostic factors is important for personalized therapy approach to obtain optimal response with minimal adverse reaction.

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Corresponding author
Ionela Rotaru, Assistant Professor, MD, PhD, Department of Hematology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Romania; Phone +40740–045 276, e-mail: rodirot@yahoo.com

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