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PROGNOSTIC SIGNIFICANCE OF SERUM ALBUMIN IN DIFFUSE LARGE B-CELL LYMPHOMA IN THE PRERITUXIMAB AND RITUXIMAB ERA

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Diffuse large B cell lymphoma (DLBCL) is the most frequent subgroup of non-Hodgkin lymphoma. The aim of the author was to verify the existence of important pretreatment serum albumin (SA) level as an independent factor of disease prognosis in patients with DLBCL in the territory of Southeast Serbia, in the era of prerituximab and rituximab.

A total of 55 patients with DLBCL (R-CHOP group) and 14 patients (CHOP group) were included in the study. Patients were divided into 2 groups according to the value of pretreatment SA: SA 30 g/l and ≤ 30 g/l. We analyzed the correlation of SA value with clinical stage and age, as well as the survival of patients with DLBCL compared to SA according to a therapeutic protocol.

There was no significant correlation of SA with age ($p = 0.630$), clinical stage ($p = 0.943$) and survival ($p = 0.638$) in CHOP group. There was significant correlation between SA levels with survival ($p = 0.001$) in R-CHOP group. No significant correlation of SA with age ($p = 0.141$) and clinical stage of disease ($p = 0.305$). There was no significant difference in survival compared to the value of SA in CHOP group/Log-rank = 0.782. There was significant difference in survival compared to the value of SA in R-CHOP group/Log-rank = 0.002.

The relationship between the predictive value of SA and the treatment protocol for DLBCL evaluated by the logistic regression analysis showed that the level of SA was not a significant predictor for the choice of treatment (Wald = 1.540, $p > 0.05$)

Our research has confirmed a negative predictive value of pretreatment serum albumin levels in patients with DLBCL treated according to R-CHOP protocol. Retrospective studies with a larger number of DLBCL patients who were treated with CHOP protocol, would give more significant results for the predictive importance of SA. Prognostic indexes, which as part of the point system include the value of SA, can be very useful in predicting patients with DLBCL.

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Key words: *DLBCL, albumin, R-CHOP, CHOP*

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Introduction

Diffuse large B cell lymphoma represent a diffuse proliferation of large neoplastic B-lymphocytes and is the most frequent subgroup of non-Hodgkin lymphoma.

It is a heterogeneous group of diseases with a spectrum of clinical, biochemical and immunohistochemical markers that have their own prognostic significance. Immunochemotherapy changes the approach in the prediction of patients with DLBCL. The value of albumins in the serum (SA) marker with potential prognostic significance in patients with DLBCL and may be considered as a surrogate for catabolic processes that occur within tumor affected organism. The inflammatory response in the malignant disease, is associated with a reduced concentration of SA and loss of cell mass. It is hypothesized that the increased demand for specific amino acids is necessary for the production of mediators of the immune response that are mobilized from available proteins, including albumins (1). Loss of body weight is traditionally associated with poor prognosis of disease (2).

The aim of the study was to identify the impact of pretreatment SA level on prognosis in patients with DLBCL in a real situation in the territory of southeast Serbia and compare its predictive value between patients treated in the era of prerituximab and those treated with rituximab containing therapy.

Methods

Demographics of 55 patients with DLBCL, including age, Ann Arbor clinical stage, and SA were collected. They were all treated by therapeutic protocol R CHOP (rituximab, cyclophosphamide, doxorubicin chydrochloride, vincristine, prednisolone), according to the standard procedure in the period 2009 to 2013 at the Clinic of Hematology and Clinical Immunology, University Clinical Center in Niš, Serbia. Patients included in this study were newly diagnosed DLBCL, previously untreated , age 24-82 years. An overview was made by 31 December 2015.

The historical control group included 14 patients with DLBCL age 41-75, treated during the period from 1991 to 2002 according to the protocol CHOP (cyclophosphamide, doxorubicin chydrochloride, vincristine, prednisolone), at the Clinic of Hematology and Clinical Immunology, University Clinical Center in Niš, Serbia, according to standard procedure. All patients were from the same geographical area. Patients with incomplete clinical data were excluded.

Value of SA was determined using standard diagnostic procedures with automated spectrophotometric method, before the start of treatment. According to the value of pretreatment SA, the patients were divided into 2 groups: SA > 30 g/l and ≤ 30 g/l. Clinical stages of disease were determined by Ann Arbor classification. According to their age, the patients were divided into 2 groups: ≤ 60 years and > 60 years. The histological sections were processed by standard techniques, and stained with hematoxylin and eosin (HE) at the Center of Pathology, University Clinical Center Niš, Serbia. Inclusion criteria consist of de novo CD20 + DLBCL.

We analyzed the correlation of SA value with clinical stage and age, as well as the survival of patients with DLBCL. Survival is calculated from the time of diagnosis (OS was defined as date of diagnosis to date of death or date of last contact for those censored), because the date of initiation of therapy in some cases was not known.

Statistical analysis

Comparison of the frequency of distribution of certain modalities of attributive characteristics between groups was performed by Pearson χ^2 test or Fisher exact test. The relationship of certain characteristics was measured by correlation analysis using Spearman's correlation coefficient. OS were estimated using the Kaplan-Meier method. The log-rank test was used in order to determine the difference in survival prognostic factor. The relationship between predictive value of the test variable (the SA value) and the dependent variable (treatment protocol) was established in the logistic regression analysis. Statistical analysis was performed using standard data processing programs and software package SPSS version 18.0.

The values < 0.05 were considered statistically significant

Results

The difference in the frequency of attributive characteristics between the groups (age, clinical stage of disease, the value of SA), was compared. The groups were homogenous in terms of all clinical prognostic characteristics (Table 1).

No significant statistical correlation between the values of serum albumin with age (p = 0.630), clinical stage (p = 0.943) and survival (p = 0.638) in patients with DLBCL treated with CHOP protocol, was found (Table 2).

Table 1. Comparative characteristics of groups

Variable	group CHOP		group R-CHOP		test
Age	N	%	N	%	
< 60 y.	5	35.7	27	49.1	χ^2 = 0.803 p = 0.370
> 60 y.	9	64.3	28	50.9	OR = 0.576
					CI (0.171 - 1.940)
Cl. stage	N	%	N	%	
1	1	7.1	4	7.3	χ^2 = 2.757 p = 0.431
2	4	28.6	23	41.8	
3	7	50.0	15	27.3	
4	2	14.3	13	23.6	
SA	N	%	N	%	χ^2 = 1.558 p = 0.208
> 30 g/l	10	71.4	29	52.7	Fisher exact T = 0.242
≤ 30 g/l	4	28.6	26	47.3	OR = 0.446
					CI (0.125 - 1.596)

Table 2. Correlation analysis of CHOP group

			Age	Cl. stage	Survival
Spearman's	SA	Correlation Coefficient	0.141	0.021	0.138
		Sig. (2-tailed)	0.630	0.943	0.638

Table 3. Correlation analysis of R-CHOP group

			Age	Cl.stage	Survival
Spearman's	SA	Correlation Coefficient	0.201	0.141	0.422
		Sig. (2-tailed)	0.141	0.305	0.001

Significant correlation between serum albumin levels with survival (p = 0.001) in patients with DLBCL treated with R-CHOP protocol was found. There was no difference in the levels of SA in respect of age (p = 0.141) or clinical stage of disease (p = 0.305) (Table 3).

There was no difference in survival compared to the value of SA ≤ 30 g/l vs. > 30 g/l in patients with DLBCL treated with CHOP protocol. Log-rank (Mantel-Cox) = 0.782 (Figure 1).

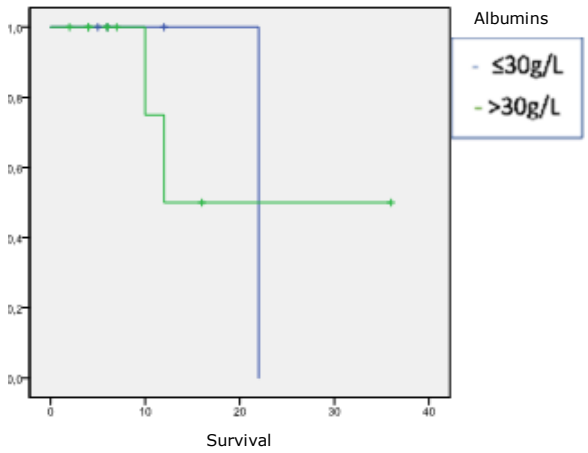

Figure 1. Survival in the CHOP group according to SA values

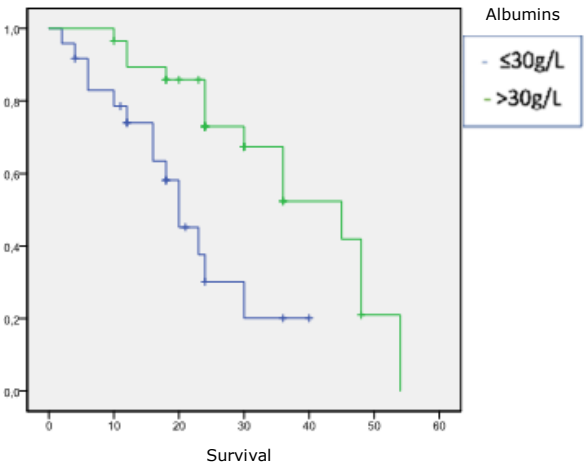

Figure 2. Survival in the R-CHOP group according to SA values

There was statistically significant difference in survival compared to the value of SA ≤ 30 g/l vs. > 30 g/l in patients with DLBCL treated with R-CHOP protocol. Log-rank (Mantel-Cox) = 0.002 (Figure 2). The relationship between the predictive value of SA and the treatment protocol for patients with DLBCL evaluated by logistic regression analysis showed that the level of SA was not a significant predictor of treatment choice (Wald = 1.540, p > 0.05) (Table 4).

Table 4. Logistic regression analysis of SA according to the therapeutic approach of DLBCL Patients

Omnibus Tests of Model Coefficients		Sig.		-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
	1.643	0.200		67.963[a]	0.024	0.037
Variable	B	S.E.	Wald	Sig.	Exp(B)	95% C.I.
SA	0.807	0.650	1.540	0.215	2.241	0.627

Discussion

The results of this study identified SA as a significant predictor of survival in patients treated with the R-CHOP protocol

The connection of hypoalbuminemia and poor prognosis in patients with malignant diseases, is well known (1, 3-7). In 2014, Eatrides et al. confirmed that the level of serum albumin in patients with DLBCL is a powerful predictor of risk (8). In a study with a cut off value of 37 g/l, albumins are marked as predictors of overall survival in patients with DLBCL treated with the R-CHOP protocol and which, together with the other clinical parameters can be useful in identifying patients with high risk of relapse.

A low SA is an independent prognostic marker in patients with DLBCL treated with standard R-CHOP. Low albumin was considered as SA level < 37 g/l. The mechanism by which low level of serum albumin has a negative predictive value in relation to the survival of patients with DLBCL is still not clear enough. There are theories that the low levels of serum albumin are associated with an increased inflammatory response in the tumor mass with a poor nutritional status, as well as the increased release of cytokines. Low SA may also be caused by reduced production in hepatocytes due to the release of cytokines from a tumor, such as IL-6, which blocks the production of albumin in the hepatocytes. Increased levels of TNF may also be associated with low levels of serum albumin (9). Elevated level of interleukin 6 in serum, as one of the cytokines, with almost the main role in the inflammatory process is a negative prognostic factor in patients with DLBCL (10-12). Low serum albumin may also be the result of a strong inflammatory response caused by the presence of the tumor mass.

Hypoalbuminemia is a sign of continuous systemic response (13, 14). Pretreatment albumin level is a strong prognostic factor for OS in patients with DLBCL and can discriminate high-risk patients with inferior prognosis (13, 15).

Poor nutritional status is associated with malignancies, poor performance status and co-morbidities, and could cause the inability to apply adequate therapeutic doses of chemotherapy (9).

Low SA levels are the indicator of the nutritional status and very useful prognostic factor (16).

A systematic review of Gupta et al. (2010) (17), emphasizes the general predictive significance of pretreatment SA in all cancers, including NHL. In order to confirm the level of causality of serum albumin and survival in malignant patients, clinical studies should demonstrate that raising albumin levels by means of intravenous infusion or by hyperalimentation could decrease the excess risk of mortality in cancer (17).

The advantage of pretreatment SA level as a prognostic factor in cancer patients is that it is inexpensive, reproducible and powerful.

There are different results in the literature which show that low SA level, elevated LDH and advanced clinical stage of disease in patients with DLBCL treated with CHOP protocol were poor prognostic factors but that in patients treated with R-CHOP protocol, survival was evident only in advanced clinical stage of disease, and male gender. Serum albumin had no predictive value (18).

The level of serum albumin in patients with DLBCL is very intriguing and because of that several authors proposed a new prognostic scores, including the value of serum albumins.

In 2013, Dalia et al. (19) proposed a new prognostic score "Albumin Adjusted IPI (A-IPI)" that counted: the value of SA < 37g/l, increased levels of LDH, ECOG ≥ 2 and clinical stage III-IV disease, in patients with DLBCL treated with R-CHOP protocol. A-IPI score identified three groups of patients: Very good: A-IPI = 0 Good: A-IPI = 1-2, Poor: A-IPI = 3-4. In the analyzed group of patients, the 4-year PFS (progression free survival) and OS (overall survival), were determined by comparing A-IPI and R-IPI (revised IPI). The comparing of these two prognostic scores, in their study, found that A-IPI score could accurately discriminate group of patients, "poor", with the ability to separate the good and "good" and "very good" risk group of patients with DLBCL. In conclusion, they suggested that SA could be a better surrogate for comorbidity and pro-inflammatory condition in DLBCL patients than their age (19).

Kobayashi et al. (2016) (20) proposed the formation of a new prognostic index "Kyoto Prognostic Index (KPI)" for patients with DLBCL in the rituximab era. KPI counted: > LDH, ECOG ≥ 2, SA < 35 g/l, EN events. Based on these parameters they formed 4 risk groups. Results showed that the KPI was highly predictive and sensitive when compared to the R IPI and the NCCN IPI (An enhanced International Prognostic Index). The same authors found that the age > 60 did not significantly affect the survival rate. "Glasgow prognostic score (GPS) and the modified Glasgow prognostic score" (mGPS), in their point system also contain SA (21, 22).

"The international staging system" contains only the value of SA and B2 microglobulin and is used in the prediction of patients with multiple myeloma, proved to be very useful in predicting patients with DLBCL who were treated with R-CHOP protocol. This score was not a significant predictor for patients with DLBCL treated with CHOP protocol (23).

Conclusion

Our research has confirmed a negative predictive value of pretreatment serum albumin levels in patients with DLBCL treated with protocol R-CHOP. Retrospective studies with a larger number of DLBCL patients who were treated with CHOP protocol would give more significant results of the predictor importance of SA. Prognostic indexes, which as part of the point system include the value of the SA, can be very useful in predicting patients with DLBCL.

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PREDIKTORNI ZNAČAJ VREDNOSTI ALBUMINA U SERUMU OBOLELIH OD DIFUZNOG B KRUPNOĆELIJSKOG LIMFOMA U PRERITUKSIMAB I RITUKSIMAB ERI

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Difuzni B krupnoćelijski limfom (*DLBCL*), predstavlja najprisutniju podgrupu ne-Hočkinskih limfoma. Cilj autora je da provere postojanje značaja vrednosti albumina u serumu pre početka lečenja, kao nezavisnog faktora prognoze bolesti, na prostoru jugoistočne Srbije, u prerituksimab i rituksimab eri.

U studiju je bilo uključeno ukupno 55 bolesnika sa *DLBCL* (*R-CHOP* grupa) i 14 bolesnika lečenih po *CHOP* protokolu (*CHOP* grupa). Bolesnici su podeljeni u dve grupe prema vrednostima SA: SA > 30 g/l i SA ≤ 30 g/l. Analizirana je korelacija vrednosti SA sa kliničkim stadijumom bolesti i godinama života, kao i preživljavanje obolelih od *DLBCL* u odnosu na vrednosti SA, prema terapijskom protokolu kojim su lečeni.

Nije bilo značajne statističke korelacije vrednosti SA sa godinama života (p = 0,630), kliničkim stadijumom bolesti (p = 0,943) i preživljavanjem (p = 0,638) kod obolelih od *DLBCL* lečenih po protokolu *CHOP*. Kod ispitanika u grupi *R-CHOP*, postoji značajna korelacija vrednosti SA sa preživljavanjem (p = 0,001), bez značajne korelacije vrednosti SA sa godinama starosti (p = 0,141) i kliničkim stadijumom bolesti (p = 0,305). Nije bilo značajne razlike u preživljavanju u poređenju sa vrednostima SA ispitanika iz *CHOP* grupe/Log-rank = 0,782. Postojala je značajna razlika u preživljavanju u poređenju sa vrednostima SA ispitanika u *R-CHOP* grupi/Log-rank = 0,002.

Odnos između prediktivne vrednosti SA i protokola lečenja *DLBCL*, procenjen logističkom regresionom analizom, pokazao je to da nivo SA nije značajan prediktor za izbor lečenja (Wald = 1.540, p > 0.05).

Naše istraživanje potvrdilo je negativan prediktorni značaj smanjenog nivoa SA pre početka lečenja, kod obolelih od *DLBCL*, lečenih po terapijskom protokolu *R-CHOP*. Retrospektivne studije sa većim brojem *DLBCL* obolelih, lečenih po protokolu *CHOP*, dalo bi značajnije rezultate o prediktornom značaju SA za ovaj terapijski modalitet. Prognostički indeksi, koji kao deo bodovnog sistema sadrže i vrednost SA, mogu biti vrlo korisni u predikciji obolelih od *DLBCL*.

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Ključne reči: *DLBCL, albumin, R-CHOP, CHOP*