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ORIGINAL ARTICLE

Clinical implications of glutathione S-transferase genotyping in patients with diffuse large B-cell lymphoma

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Summary

Purpose: *Polymorphic deletions in glutathione S-transferase (GST) genes are recognized as a risk factor for lymphoma, other hematological and non-hematological malignancies.*

The purpose of the present study was to investigate whether deletions of GSTT1 and GSTM1 as well as GSTP1 Ile-105Val single nucleotide polymorphism influence clinical presentation, response to therapy and outcome in patients with diffuse large B-cell lymphoma (DLBCL).

Methods*: The study included a total of 82 DLBCL patients treated with rituximab-CHOP (R-CHOP) therapy (6-8 cycles). GST genes were analyzed with PCR-based methodology.*

Results: *The obtained frequencies of GSTT1 and GSTM1 null genotypes were 24 and 63%, respectively. The variant GSTP1 Val allele was present in 76% of the patients. No association between GST genotypes and clinical presentation was found. However, a higher frequency of GSTM1 null genotype was observed in patients who developed DLBCL before the age of 60 [odds ratio (OR) 3.12, 95% confidence interval (CI) 1.11-9.17; p=0.03]. Patients carrying at least one GSTP1 Val allele achieved remission in a shorter time period than patients with GSTP1 Ile/Ile genotype (p=0.05). GST genotypes didn't influence the incidence of relapse and survival. There were no toxic effects, life-threatening infections or significant delay in immunochemotherapy in the analyzed group of patients.*

Conclusion: *The present study showed the association of GSTM1 null genotype and DLBCL development before the age of 60 (prognostic cutoff). GST genotypes didn't influence survival, but patients with at least one low-producing GSTP1 Val allele achieved clinical remission in a shorter time period.*

Key words: *diffuse large B-cell lymphoma, gene polymorphism, glutathione S-transferase*

Introduction

DLBCL is the most common type of non-Hodgkin lymphoma (NHL), accounting for about one-third of all newly diagnosed lymphoma cases [1]. With respect to clinical features, response to treatment and outcome, DLBCL is highly multifaced [2]. Clinical studies identified five features as independent parameters for prognosis: age (cut point at 60 years), tumor stage, presence of B-symptoms (fever, night sweats, weight loss >10% of body weight), LDH level in serum and extranodal involvement. These clinical features are included into the IPI (International Prognostic Index) scoring system to categorize patients into one of four prognostic groups that correlate with both relapse-free survival and overall survival [3]. However, elucidation of etiologic factors and their role in the pathogenesis of DLBCL remains challenging. Molecular studies indicated that, beyond

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clinical and environmental factors, development and prognosis of DLBCL may be affected by genomic variations [4].

Several studies have provided evidence of higher risk for lymphoma in individuals with deletion polymorphisms of genes encoding GSTs [5-8]. GSTs comprise a family of enzymes that catalyze the conjugation of reduced form of glutathione to xenobiotic substrates creating less toxic compounds. Thus, GSTs are involved in the detoxification of a wide range of carcinogens, including benzene, organochlorine compounds, organophosphate pesticides, components of tobacco smoke, chemotherapeutic agents and reactive oxygen species [9]. However, conjugation of substrates is not necessarily beneficial. Some reports indicated that direct binding to alkylating agents and also detoxification of free radicals generated by anthracyclines may increase resistance to anticancer drugs [10].

Certain members of the GST family display phenotypically relevant genetic polymorphisms. Homozygous deletions of GSTM1 or GSTT1 (null genotypes) cause loss of GSTM1 or GSTT1 enzymatic activity [10,11]. If present, GSTM1 allele is represented by the variant GSTM1*A or GSTM1*B [12]. Previous studies have reported that GSTM1*A and GSTM1*B encode enzymes with similar catalytic activity, but do not necessarily have the same effect on susceptibility to different diseases [13,14]. A single nucleotide polymorphism (SNP) within coding region of GSTP1 (A313G) causes substitution of isoleucine to valine at codon 105 (Ile105Val) and consequently decreases activity of the enzyme [15,16].

Despite a proven association between polymorphisms within GST genes and susceptibility to lymphoma, data about the clinical impact of these polymorphisms are scarce. In the present study, we analyzed the association of polymorphisms within GSTT1, GSTM1 and GSTP1 genes with clinical characteristics of DLBCL patients. Since GSTs are involved in the conjugation of anticancer drugs, including alkylating agents, anthracyclines and cyclophosphamide, the association of GSTT1, GSTM1 and GSTP1 gene polymorphisms with the response to therapy and outcome was analyzed.

Methods

Patients

This study included 82 patients (45 men and 37 women) with the newly diagnosed DLBCL, aged 18 to 77 years (median 49) who were diagnosed, treated and followed-up at the Clinic for Hematology, MMA, Belgrade, Serbia. All patients were of the same ethnicity. Patients with previous history of hematological malignancy, cancer or HIV-related DLBCL were not included in this study.

Diagnosis of DLBCL was based on histopathology and immunohistochemistry according to the World Health Organization (WHO) classification [17]. All patients underwent clinical examination, laboratory testing, bone marrow biopsy, chest radiograph and computed tomography of the chest and abdomen. The extent of disease was categorized according to Ann Arbor classification and the risk score was determined by the IPI [3]. All patients received R-CHOP (rituximab–cyclophosphamide, doxorubicin, vincristine, prednisone) therapy (6-8 cycles). Response to therapy was assessed using the International Working Group criteria [18]. The follow-up period ranged from 1 to 147 months (median 55).

The study was approved by the Ethics committee of MMA, Belgrade, in accordance with the Helsinki Declaration (2008). Written consent for participation in the study was obtained from all patients or patients' close relatives.

Samples and genotyping

Blood was collected in EDTA tubes and stored at -40°C. DNA was extracted by a PureLink™ Genomic DNA MiniKit (Invitrogen, Carlasbad, USA) according to the manufacturer's instructions.

GSTT1 and GSTM1 genes were amplified in parallel with β-actin sequence by polymerase chain reaction (PCR) as previously described [19]. PCR products were analyzed on 2% agarose gels after electrophoresis and ethidium bromide staining.

GSTT1-null as well as GSTM1 - null genotype was visualized as a 289-bp band (β-actin) on the gel. GSTT1 positive genotype showed the presence of two bands (480 bp of GSTT1 and 289 bp of β-actin).

GSTM1-positive PCR products (132 bp of GSTM1 and 289 bp of β-actin) were further digested with restriction endonuclease HaeII according to the manufacturer's instructions (Thermo Scientific, Lithuania) and analyzed on 10% polyacrylamide gels (PAGs) after electrophoresis and silver nitrate staining. Genotypes were determined as GSTM1*A (112 bp, 20 bp), GSTM1*B (132 bp) or GSTM*AB (132 bp, 112 bp and 20 bp). Additional band of 289 bp (β-actin) was present in all samples.

GSTP1 gene was amplified by PCR method as previously reported [19]. PCR products were digested with restriction endonuclease BsmAI acording to the manufacturer's instructions (Thermo Scientific, Lithuania). After electrophoresis on 10% PAGs and staining with silver nitrate, genotypes were determined as Ile/Ile (329 bp,113 bp), Ile/Val (329 bp, 216 bp, 113 bp, 107 bp) or Val/Val (216 bp, 113 bp, 107 bp).

Statistics

The observed frequencies of GSTP1 and GSTM1-positive genotypes were tested by Hardy-Weinberg equilibrium. The association between genotypes and clinical characteristics and outcome were analyzed using the chi-square or Fisher's exact test. OR and 95% CI were used to estimate the risk of unfavorable clinical features. Event-free survival (EFS) was defined as the time from the start of treatment to progressive disease (PD) under therapy, relapse or death from any reason. Disease free survival (DFS) was calculated as the time from the start of treatment to relapse. Overall-survival (OS) was defined as the time from the start of treatment to death or to the date of the last follow-up. Survival curves were generated using the method of Kaplan and Meier and compared by the log-rank test. The Cox proportional hazards model was used to estimate the effect of gene polymorphisms along with DLBCL features for OS. Time to remission between patients with different genotypes was compared using the Mann-Whitney U test. A p value < 0.05 was considered statistically significant.

Results

Frequencies of GST genotypes

In the analyzed group of 82 patients with DLBCL, GSTT1 null genotype was found in 20 patients (24%), while GSTM1 null genotype had 52 patients (63%). Among the GSTM1 positive patients (N=30), 16 (20%) had GSTM1 AA, 4 (5%) had GSTM1 AB and 10 patients (12%) had GSTM1 BB genotype. GSTP1 Ile/Ile genotype was found in 20/82 patients (24%), 44/82 patients (54%) were carriers of Ile/Val genotype and 18/82 patients (22%) had Val/Val genotype (Table 1).

The observed frequencies of GSTP1 genotypes were in Hardy-Weinberg equilibrium.

Patient characteristics and clinical presentation

No association was found between GST genotypes and clinical parameters [sex, age (≤60 vs >60 years), clinical stage (CS) of DLBCL (I/II vs III/IV), B symptoms, bulky disease, extra-nodal disease and IPI score (low/low-intermediate vs intermediate-high/high)].

However, there was a higher frequency of GSTM1 null genotype in patients who developed DLBCL before the age of 60 (OR 3.12, 95%CI 1.11-9.17; p=0.03).

Table 1 displays the overall characteristics of the study population and distribution of GST genotypes in patients with different clinical characteristics.

Response to therapy and outcome

In the group of 82 patients analyzed, the overall response rate (ORR) was 85% (70/82) with complete response (CR) rate of 84% (69/82) and partial response (PR) in one patient (1%). PD under R-CHOP therapy was present in 12 patients (15%). CR was achieved in 80% of GSTT1 null and 85% of GSTT1 positive patients; in 81% of GSTM1 null and 90% of GSTM1 positive patients; and in 80% of patients with GSTP1 Ile/Ile genotype and 85% of patients with at least one GSTP1 Val allele. CR rates were not statistically different between patients with different GSTT1, GSTM1 or GSTP1 genotypes. Along with genotypes, the impact of clinical features (sex, age, CS, IPI, B symptoms, extranodal involvement and bulky disease) on the achievement of CR was assessed. CR rate was significantly higher in patients with DLBCL in CS I/II than in patients with CS III/IV (100% vs 78%; p=0.02). Also, patients with favorable low/low-intermediate IPI had higher CR rate than pa-

Table 1. Distribution of GST genotypes in DLBCL patients with different clinical characteristics

Patient characteristics	*GSTT1*			*GSTM1*			*GSTP1*	
	Present N (%)	*Null N (%)*	*p*	*Present N (%)*	*Null N (%)*	*p*	*IleIle*	*IleVal/ ValVal*
Gender, M/F	36/26	8/12		17/13	27/25		13/7	31/31
Age > 60 years	15 (18)	4 (5)	0.77	11 (13)	8 (10)	0.03*	4 (5)	15 (18)
CS III/IV	47 (57)	12 (15)	0.17	19 (23)	40 (49)	0.19	15 (18)	44 (54)
B symptoms present	44 (54)	14 (17)	0.92	19 (23)	39 (48)	0.26	41 (50)	17 (21)
IPI IH/H	34 (42)	10 (12)	0.71	16 (20)	28 (34)	1	10 (12)	34 (42)
Extranodal sites ≥2	52 (63)	12 (15)	0.21	24 (29)	40 (49)	0.74	17 (21)	47 (57)
Bulky disease present	29 (35)	10 (12)	0.81	15 (18)	24 (29)	0.74	12 (14)	27 (33)

p values were obtained using the chi-square or Fisher's exact test;
*GSTM1: null genotype was more frequently found in patients who developed DLBCL before the age of 60 (OR 3.12, 95% CI 1.11–9.17; p=0.03); p was obtained using the chi-square test
IH/H: intermediate-high/high, M: male, F: female

Table 2. Rate of complete response in relation to GST genotype, clinical stage and IPI score

Genotype	*Complete response rate N (%)*	*p value**
GSTT1 null	16 (80)	0.73
GSTT1 positive	53 (85)	
GSTM1 null	42 (81)	0.36
GSTM1 positive	27 (90)	
GSTP1 Ile/Ile	16 (80)	0.73
GSTP1 Ile/Val + Val/Val	53 (85)	
CS I/II	23 (100)	0.02
CS III/IV	46 (78)	
IPI low/low-intermediate	38 (100)	0.0001
IPI intermediate-high/high	31 (70)	

*p values were obtained using Fisher's exact test

Table 3. Time to remission in patients with diffuse large B-cell lymphoma with respect to genotype

Genotype	*Time to remission/days (median)*	*p value**
GSTT1		0.22
null	180-330 (300)	
positive	90-390 (210)	
GSTM1		0.53
null	90-390 (210)	
positive	90-360 (210)	
GSTP1		0.05
Ile/Ile	150-390 (300)	
Ile/Val + Val/Val	90-360 (219)	

*p values were obtained using Mann-Whitney U test

tients with unfavorable intermediate-high/high IPI (100% vs 70%; p=0.0001). The association between genotypes, CS and IPI score with CR rate is presented in Table 2.

GSTT1 positive patients had a shorter time to CR achievement (90-390 days, median 210 days) than GSTT1 null group (180-330 days median 300 days). However, this difference didn't reach statistical significance. A shorter time period to CR was observed in patients with at least one GSTP1 Val allele (90-360 days, median 219 days) compared to patients with Ile/Ile genotype (150-390 days, median 300 days) (p=0.05, Mann-Whitney U test) (Table 3).

In respect to the occurrence of side effects, there were no toxic effects, life-threatening infections or significant delay in immunochemotherapy in the analyzed group of DLBCL patients.

In the group of patients who achieved CR (N=69), 15 (22%) relapsed. The incidence of relapse wasn't associated with GST genotypes. In addition, no association between clinical features and incidence of relapse was found.

When we analyzed the impact of GSTT1, GSTM1 and GSTP1 genotypes on OS, DFS and EFS, no significant statistical association was found. OS and EFS were influenced only by CS (log-rank, p=0.04 for OS and p=0.09 for EFS) and IPI (log-rank test, p=0.01 for OS and p=0.04 for EFS). However, multivariate analysis using Cox regression model showed that only IPI was independent prognostic factor for OS [intermediate-high/high IPI vs low/low-intermediate IPI; hazard ratio (HR) 3.1, 95% CI 1.26-7.6; p=0.01] (Figure 1).

Discussion

An excessive risk of NHL has been linked to exposure to environmental carcinogens, and particularly in individuals with a positive family history of cancer. Phenotypically relevant polymorphisms in genes encoding GSTs and other enzymes involved in the metabolism of environmental agents have been recognized as factors of individual susceptibility to lymphoma [5]. The present study focused on the association of polymorphisms within GSTT1, GSTM1 and GSTP1 genes with the DLBCL characteristics and outcome.

According to published data, GSTT1 and GSTM1 genes are homozygously deleted in 15-30% and 40-60% of Caucasian populations, respectively [11]. The frequency of GSTP1 Val allele is about 30% in Caucasians [20]. In the present study that included DLBCL patients of Serbian origin, the obtained frequencies of GSTT1 null and GSTM1 null genotypes were 24% and 63%, respectively. Similar results were reported by Chiu and coworkers. In the case-control study, white ethnicity made more than 95% of the study population. GST1 null and GSTM1 null genotypes were found in 18% and 47% of DLBCL cases, respectively. In the same study, GSTP1 Val/Val was found in 2% of DLBCL cases [21]. In our study, the frequency of GSTP1 Val/Val genotype was 22%. Similar findings were reported for pediatric NHL by a German group [11].

Some previous reports indicated association between GSTT1 null genotype and favorable clinical characteristics. In the study on Hodgkin's lymphoma, Hohaus and coworkers reported the association between GSTT1 null genotype and lymphoma risk particularly in young females, a patient group characterized by favorable prognosis. Also, the GSTT1 null genotype was associated with a limited stage of disease and low erythrocyte sedimentation rate, both well-established favorable prognostic factors [9]. Similar to Hohaus

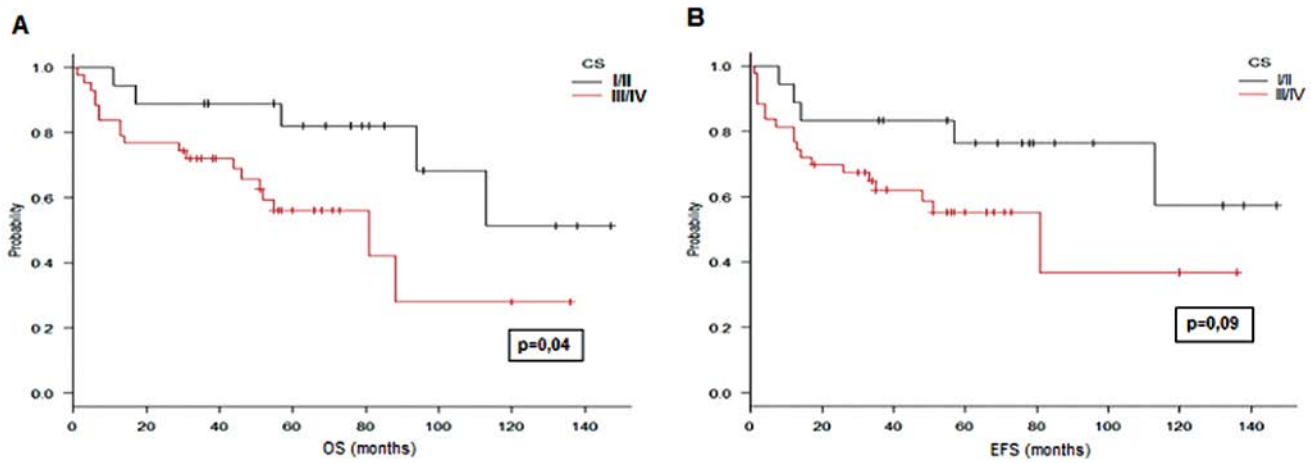

Figure 1. Overall survival **(A)** and event free survival **(B)** according to clinical stage. DLBCL patients with clinical stage (CS) I/II had better OS (p=0.04) and EFS (p=0.09) than patients with clinical stage III/IV.

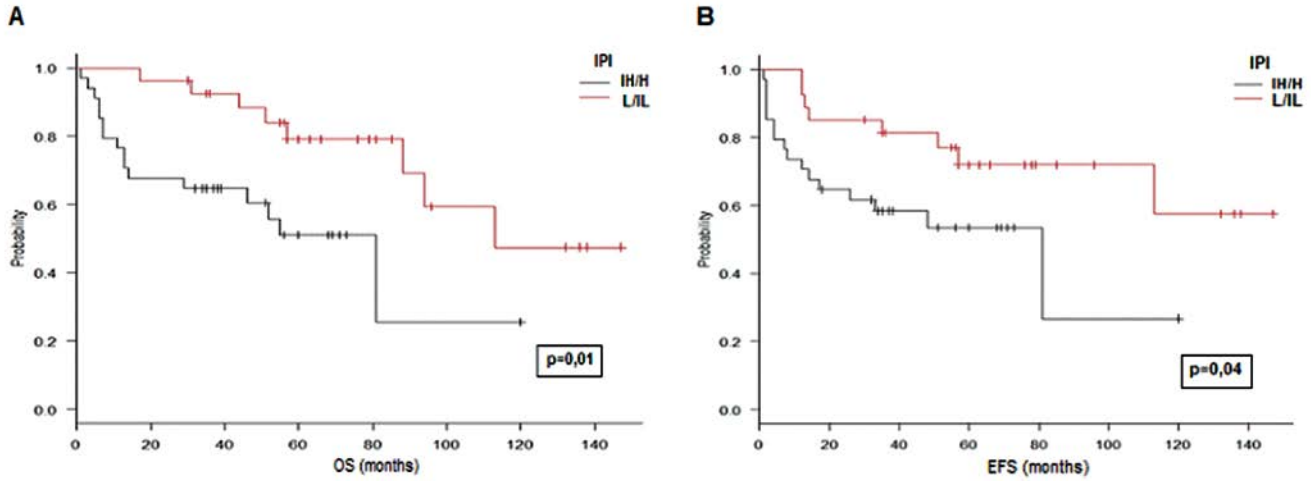

Figure 2. Overall survival **(A)** and event free survival **(B)** according to IPI score (low/ low-intermediate vs intermediate-high/high). DLBCL patients with low/low-intermediate (L/IL) IPI had better OS (p=0.01) and EFS (p=0.04) than patients with intermediate-high/high (IH/H) IPI. In Cox regression model IPI was only independent prognostic factor for OS (HR 3.1, 95% CI 1.26 – 7.6; p=0.01).

and coworkers, we found an association between deficit of GST enzymatic activity and age. However, in the present study the GSTM1 null genotype was associated with age under the prognostic cut-off point (<60 years). In addition, this finding may be discussed in the context of susceptibility to lymphoma in GSTM deficient individuals.

Previous reports suggested that GSTT1 deletion may significantly increase the risk of drug-related toxicity after R-CHOP in patients with DLBCL [22,23]. In the present study R-CHOP therapy was not accompanied with pronounced toxic effects, life-threatening infections or required a significant delay of immunochemotherapy. Furthermore, GSTs have been proven as important factors determining the efficacy of cyclophosphamide and doxorubicin, and possibly modulate the therapeutic effects of vincristine and prednisone [22]. In our patients with DLBCL, GSTT1, GSTM1 or GSTP1 genotypes were not associated with remission rate and incidence of relapse. However, patients with at least one GSTP1 105 Val allele had a shorter time period to remission than patients with Ile/Ile genotype. Since the GSTP1 105 Val allele is associated with decreased activity of the enzyme [20], our finding is in concordance with previous reports showing that tumor cells expressing high levels of GST enzymes were more resistant to chemotherapy [24,25]. Many reports have shown that the GSTP1 is largely expressed in lymphoid tissues than other GST izoenzymes, and is elevated in various cell lines resistant to anticancer agents such as adriamycin, cyclophosphamide, melphalan and chlorambucil [10]. Katahira and coworkers reported that patients with elevated GSTP1 plasma levels had lower complete response rate, OS and DFS rates than patients with normal GSTP1 plasma values [26]. In the

study of Ribrag and coworkers, DLBCL patients with high GSTP1 expression had a worse 5-year PFS and high GSTP1 expression was associated with a trend for lower survival [27]. In the study on Hodgkin's lymphoma, Hohaus and coworkers demonstrated that the GSTP1 Ile105Val polymorphism was associated in a dose-dependent fashion with an improved failure-free survival. The probability of 5-year survival for Val/Val homozygotes was 100%, for heterozygous patients 74% and for patients with the Ile/Ile genotype 43% [20]. In the present study only CS and IPI score significantly influenced CR rate and survival.

In conclusion, the results of the present study are consistent with previous reports indicating the clinical importance of GST genotyping. This study revealed the association of GSTM1 null genotype with DLBCL development before the age of 60 (prognostic cutoff). Previously, high expression level of GSTP1 was reported to increase resistance to chemotherapy in lymphoma patients and influence OS and DFS. Therefore, GSTP1 was designated as a potential therapeutic target. In this study, patients with at least one low producing GSTP1 105 Val allele achieved clinical remission in a shorter period of time, but GST genotypes didn't influence survival, probably due to the small study population. However, the present study was guided by strict inclusion criteria since all patients with DLBCL were ethnically matched, they were diagnosed, uniformly treated with R-CHOP and followed-up in one institution.

Conflict of interests

The authors declare no confict of interests.

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