EUR. J. ONCOL., vol. 18, n. 3, pp. 121-128, 2013 © Mattioli 1885

Association of FCGR2A and FCGR3A gene polymorphisms with clinical characteristics and course of diffuse large B-cell lymphoma

Jovana Trimčev[1], Bojana Cikota-Aleksić[2], Ljiljana Tukić[3], Olivera Tarabar[3], Zvonko Magić[2]

[1] Institute of Pathology and Forensic Medicine, Military Medical Academy, Belgrade, Serbia; [2] Institute of Medical Research, Military Medical Academy, Belgrade, Serbia; [3] Clinic for Hematology, Military Medical Academy, Belgrade, Serbia

Summary. *Aim:* This study aims to assess whether FCGR2A and FCGR3A gene polymorphisms may affect clinical course and outcome in diffuse large B-cell lymphomas (DLBCL) patients treated with R-CHOP therapy. *Materials and methods:* The study included 64 DLBCL patients treated with R-CHOP. Genotype analyses were performed through PCR-RFLP method. *Results:* The trend of higher incidence of FCGR3A VF and FF genotypes in patients aged 60 or older (χ^2 test, p=0.07) was observed. Significant statistical association between different FCGR2A and FCGR3A gene polymorphisms/genotypes and clinical characteristics (clinical stage, bulky disease, IPI, response to therapy, incidence of relapse and outcome) was not observed, except for FCGR2A HR genotype, which was more frequent in patients with advanced clinical stage (III and IV) (OR 6.11 95% CI 1.18-31.54; RR 1.43 95 CI % 1.06-1.93; p=0.02). However, we observed a trend of better disease free survival (DFS) in patients with FCGR3A FF genotype than in those with VV and VF genotype (log rank test, p=0.05). FCGR2A genotypes did not influence DFS. No association between FCGR2A and FCGR3A gene polymorphisms/genotypes and event free survival (EFS) and overall survival (OS) was observed. *Conclusions:* Considering clinical features and course of DLBCL, FCGR2A HR genotype is associated with advanced clinical stage of DLBCL. A higher frequency of FCGR3A F allele in DLBCL patients older than 60 years and impact of FCGR3A FF genotype on DFS were noticed only as a trend.

Key words: diffuse large B-cell lymphoma; FCGR2A and FCGR3A receptors; gene polymorphisms

«Associazione dei polimorfismi dei geni **FCGR2A** e **FCGR3A** con le caratteristiche e il decorso del linfoma a grandi cellule B»

Riassunto. *Scopo:* Questo studio intende valutare se i polimorfismi dei geni FCGR2A and FCGR3A possono influire sul decorso clinico e sull'esito della terapia nei pazienti con linfoma a grandi cellule B (DLBCL), trattati con R-CHOP. *Materiali e metodi:* Lo studio ha interessato 64 pazienti DLBCL trattati con R-CHOP. L'analisi dei genotipi è stata fatta con metodo PCR-RFLP. *Risultati:* È stata osservata una più alta incidenza dei genotipi FCGR3A VF e FF nei pazienti di 60 anni o più (χ^2 test=0.07). Non è stata osservata una significativa associazione statistica tra i diversi polimorfismi/genotipi dei geni FCGR2A and FCGR3A e le caratteristiche cliniche (stadio clinico, interessamento massivo linfonodale, IPI, risposta alla terapia, incidenza di ricadute ed esito), ad eccezione del genotipo FCGR2A HR, che risultava essere più frequente in pazienti con stadio clinico avanzato (III e IV) (OR 6,11 95% CI 1,18-31,54; RR 1,43 95 CI% 1,06-1,93; p=0,02). Tuttavia, è stato osservato un andamento di miglior sopravvivenza libera da malattia (DFS) in pazienti con genotipo FCGR3A FF rispetto a quelli con genotipo VV e VF (log-rank test, p=0,05). I genotipi FCGR2A non hanno influenzato la DFS. Non è stata osservata alcuna associazione tra i polimorfismi/genotipi dei geni FC-

GR2A and FCGR3A con eventi liberi da malattia (EFS) e sopravvivenza globale (OS). *Conclusioni:* Considerando le caratteristiche cliniche e il decorso di DLBCL, il genotipo FCGR2A HR risulta essere associato ad uno stadio clinico avanzato di DLBCL. Sono stati osservati una più alta frequenza dell'allele FCGR3A F in pazienti con DLBCL di età superiore a 60 anni ed un impatto del genotipo FCGR3A FF sulla DFS

Parole chiave: linfoma a grandi cellule B, recettori FCGR2A eFCGR3A, polimorfismi del gene

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of Non Hodgkin's lymphoma (NHL) that accounts for almost one third of all NHL cases (1). The incidence of DLBCL increases, but underlying etiologic factors remain largely unknown. Considering clinical course and outcome, DLBCL represent a heterogeneous group of lymphoproliferative disorders (2). After conventional therapy, some patients will achieve complete clinical remission (CR), but others will relapse or manifest progressive clinical course.

For many years, cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) chemotherapy has been the standard therapy for advanced DLBCL providing a long-term overall survival rate (OS) of about 40%. Introduction of rituximab (R) in the treatment of DLBCL has improved OS and relapse free survival (RFS) and established R-CHOP therapy as the standard care in DLBCL (3). Rituximab is a monoclonal IgG1 antibody against CD20, but its exact mechanism of activity is not completely understood. Possible mechanisms of action include antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and induction of apoptosis (4). However, it is assumed that ADCC plays a major role in the clinical activity of rituximab. Recent studies demonstrated that rituximab induces polarization of B-cells, involving a reorganization of CD20; such polarized cells are preferentially killed by natural killer (NK) cells (5).

ADCC is modulated by FCGRs that are expressed on leucocytes including monocytes, NK cells, macrofages, dendritic cells, plateles and endothelial cells. "Auto" antibodies bind to FCGRs and activate immune cell functions, including phagocytosis and the release of inflammatory mediators. Binding affinity of FCGR may be determined by gene polymorphisms. In FCGR2A, the presence of histidine (H) or arginine (R) at amino acid position 131 is encoded by A519G SNP. It is known that the H isoform (encoded by FCGR2A 519G allele) has a higher affinity to IgG2 than the R isoform (encoded by 519A allele) (6). Considering FCGR3A, 559C allele encodes the high-binding isoform to IgG1 and IgG3 with valine (V) at amino acid position 158, while 559A allele encodes the low-binding phenylalanine (F) isoform (7, 8). Previously, FCGR2A and FCGR3A SNPs have been analyzed in the context of susceptibility to different autoimmune diseases (8-12). Also, extensive studies assessed the relationship between FCGR2A and FCGR3A SNPs and response to therapy containing monoclonal antibodies in cancer patients: cetuximab in colorectal cancer (13), trastuzumab in breast cancer (14), alemtuzumab in CLL (15) and rituximab in DLBCL, follicular lymphoma and CLL (16-19). Previous reports about association of different allelic variants of FCGRs and clinical course of DLBCL (RFS OS) are not consistent (16, 18, 20, 21).

The aim of the present study was to investigate whether FCGR2A (CD32a) and FCGR3A (CD16a) gene polymorphisms corresponding to amino acid positions 131 and 158, associate with clinical presentation, course and outcome in DLBCL patients treated with R-CHOP.

Patients and methods

Patients

The present study included 64 patients (39 men and 25 women) with the newly diagnosed DLBCL, aged 18 to 74 (median 47.5). Patients with previous

history of low-grade lymphoma, other type of malignant disease and HIV-related lymphoma were not included in the study. All patients were diagnosed and treated in our hospital. Diagnosis was based on histopathology and immunohistochemistry according to the World Health Organization (WHO) classification (2). The extent of the disease was categorized according to Ann Arbor classification and the risk score was determined by International Prognostic Index (22).

All patients received R-CHOP therapy (6-8 cycles). As a consolidation therapy for high-risk patients, autologous stem cell transplantation (ASCT) was performed in 27 cases. Response to the therapy was assessed using the International Working Group criteria (23). The study included patients diagnosed and treated from October 2000 till November 2009. Patients were systematically followed till April 2012. The follow-up period ranged from 1 to 147 months (median 73 months). The overall characteristics of the study population are shown in Table 1.

All DLBCL patients were ethnically matched.

Informed consent was obtained from all patients or patients' close relatives. The study was approved by Ethic committee of Military Medical Academy, Belgrade.

FCGR2A and FCGR3A genotyping

Peripheral blood was collected in EDTA tubes and stored at -40°C. Each patient's DNA was extracted from blood samples by Blood Prep™ Chemistry for ABI PRISM™ 6100 Nucleic Acid PrepStation (Applied Biosystems, USA).

The PCR primers 5'-GGAAAATCCCAGAAATTCTCGC-3'and 5'-CAACAGCCTGACTACCTATTACGCGGG-3' were used to amplify the sequence of FCGR2A gene that includes locus 131 (35 cycles at 94°C for 15 seconds, 55°C for 30 seconds, 72°C for 40 seconds) (24). PCR products were incubated with *Bst*UI according to manufacturer's instructions (Fermentas, Latvia), electrophoresed on 3% high resolution agarose gels and stained with ethidium bromide. The H allele was identified as a band of 337 bp, while the R allele was presented as a band of 316 bp and 21 bp.

Table 1. Characteristics of DLBCL patients treated with R-CHOP

Characteristics	Patients No (%)
Men	39 (61)
Women	25 (39)
Age < 60 years	49 (77)
≥ 60 years	15 (23)
IPI 0-2	28 (44)
IPI 3-5	36 (56)
Stage I and II	18 (28)
Stage III and IV	46 (72)
Extranodal disease	50 (78)
No extranodal disease	14 (22)
Bulky disease	32 (50)
No bulky disease	32 (50)
B symptoms	44 (69)
No B symptoms	20 (31)
Achievement of complete remission	55 (86)
No complete remission	9 (14)
Relapsed	15 (27)
No relapsed	40 (73)
Autologous stem cell transplantation	27 (42)
No autologous stem cell transplantation	37 (58)
Died	21 (33)
Alive	43 (67)

The DNA sequence of FCGR3A gene that includes locus 158 was amplified by two-step PCR. The first PCR step (35 cycles at 95°C for 1 minute, 57°C for 1 minute and 30 seconds, 72°C for 1 minute and 30 seconds) was performed with the following primers: 5'-ATATTTACAGAATGGCACAGG-3' and 5'-GACTTGGTACCCAGGTTGAA-3'. The second PCR step (35 cycles at 95°C for 1 minute, 64°C for 1 minute, 72°C for 1 minute) was performed with 5'-ATCAGATTCGATCCTACTTCTGCAGGGGGCAT-3' and 5'-ACGTGCTGAGCTTGAGTGATGGTGATGTTCAC-3' and generated a fragment of 94 bp (25). PCR products were incubated with *Nla*III according to manufacturer's instructions

(Fermentas, Latvia), electrophoresed on 3% high resolution agarose gels and stained with ethidium bromide. The V allele was identified as a presence of two bands at 61 bp and 33 bp, while the F was presented by one band at 94 bp.

Statistical analysis

The differences in genotype frequencies between DLBCL patients with different variables of disease were assessed using the χ^2 test and, if required, Fisher's exact test. In order to estimate the relative risk of DLBCL stage III or IV in relation to FCGR2A genotype, we calculated odds ratio (OR) and 95% confidence intervals (95% CI) for each genotype, using the homozygous HH genotype as the referent group. Event-free survival (EFS) was defined as time from first day of therapy to progressive disease (PD), relapse or death from lymphoma. Disease free survival (DFS) was calculated as time from first day of therapy to relapse. Overall-survival (OS) was defined as time from first day of therapy to death from lymphoma. Survival curves were generated using the method of Kaplan and Meier and compared by log-rank test. A p value < 0.05 was considered as statistically significant.

Results

FCGR2A genotyping

FCGR2A genotyping was performed in 57 DLBCL patients. HH genotype was found in 28 (49%) patients, HR in 24 (42%), while RR genotype was found in 5 (9%) patients. Genotype distributions were in Hardy-Weinberg equilibrium.

Distribution of FCGR2A genotypes with respect to patients' characteristic, DLBCL presentation and response to therapy is shown in Table 2.

We found that patients with HR genotype most often showed DLBCL in CS III or IV (OR 6.11 95% CI 1.18-31.54; RR 1.43 95 CI % 1.06-1.93; p=0.02) (Table 3). Comparing other clinical characteristics, we

Table 2. Distributions of FCGR2A and FCGR3A genotypes in DLBCL patients with respect to clinical characteristics

Patient/DLBCL characteristics	FCGR2A				FCGR3A			
	HH (%)	HR (%)	RR (%)	p	VV (%)	VF (%)	FF (%)	p
Men	28.1	22.8	5.3	NS	21.9	31.3	7.8	NS
Women	21.0	19.3	3.5	NS	7.8	18.7	12.5	
Age < 60 years	40.3	28.1	5.3	NS	25	34.4	17.2	NS
≥ 60 years	8.8	14	3.5		4.7	15.6	3.1	
IPI 0-2	24.6	14	5.3	NS	12.5	23.4	7.8	NS
IPI 3-5	24.6	28	3.5		17.2	26.6	12.5	
Stage I and II	17.5	3.5	5.3	0.009*	9.4	10.9	7.8	NS
Stage III and IV	31.6	38.6	3.5		20.3	39.1	12.5	
Extranodal disease	39.3	35.7	3.6	NS	25.4	38.1	14.3	NS
No extranodal disease	10.7	7.1	3.6		4.8	11.1	6.3	
Bulky disease	30.3	16.1	3.6	NS	11.1	25.4	12.7	NS
No bulky disease	19.6	26.8	3.6		19.0	23.8	8.0	
B symptoms	36.8	29.8	3.5	NS	20.3	34.4	14.1	NS
No B symptoms	12.3	12.3	5.3		9.4	15.6	6.2	
Achievement of complete remission	45.4	36.4	3.6	NS	22.6	41.9	17.7	NS
No complete remission	5.5	7.3	1.8		8.1	6.5	3.2	
Relapsed	14.6	10.4	2.1	NS	9.8	11.8	4.0	NS
No relapsed	37.5	31.2	4.2		17.6	39.2	17.6	

*p values were obtained by χ^2 test or Yate's corrected χ^2 test; NS- statistical significance not found

did not observe significant statistical difference in the frequencies of FCGR2A genotypes. Furthermore, no significant statistical difference in the CR rate, incidence of relapse, duration of DFS, EFS and OS in patients with different FCGR2A genotypes was observed.

FCGR3A genotyping

FCGR3A genotyping was performed in 64 DLBCL patients. VV genotype was found in 19 (30%) patients, VF in 32 (50%), while FF genotype was found in 13 (20%) patients. Distribution of FCGR3A genotypes was in Hardy-Weinberg equilibrium.

We did not observ significant statistical difference in frequencies of analyzed FCGR3A genotypes between men and women. However, we noticed the trend of higher incidence of genotypes containing F allele (VF and FF) in patients aged 60 or older (χ^2 test, p=0.07).

Considering characteristics of DLBCL, CR rate and incidence of relapse, we did not observe significant statistical difference in the frequencies of FCGR3A genotypes.

Distribution of FCGR3A genotypes with respect to patients' characteristic, DLBCL presentation and response to therapy is shown in Table 2.

Analyzing the duration of EFS and OS, no significant statistical difference between patients with different FCGR3A genotypes was shown. However, we observed the trend that patients with FF genotype showed better DFS than patients with VV and VF genotypes (log rank test, p=0.05) (Figure 1).

Discussion

FCGRs are an important part of the regulatory system which modulates antibody-dependent cellular cytotoxicity. Data from the literature indicate that single nucleotide polymorphisms of FCGR genes may influence the affinity of monoclonal antibodies to the Fc receptors on the effector cells (4, 26). In the current study, we analyzed the association of FCGR2A and FCGR3A SNPs with clinical characteristics and outcome of DLBCL treated with R-CHOP.

Frequencies of FCGR2A and FCGR3A genotypes obtained in this study are similar to those previously reported by Kim and coworkers (16), Mitrovic

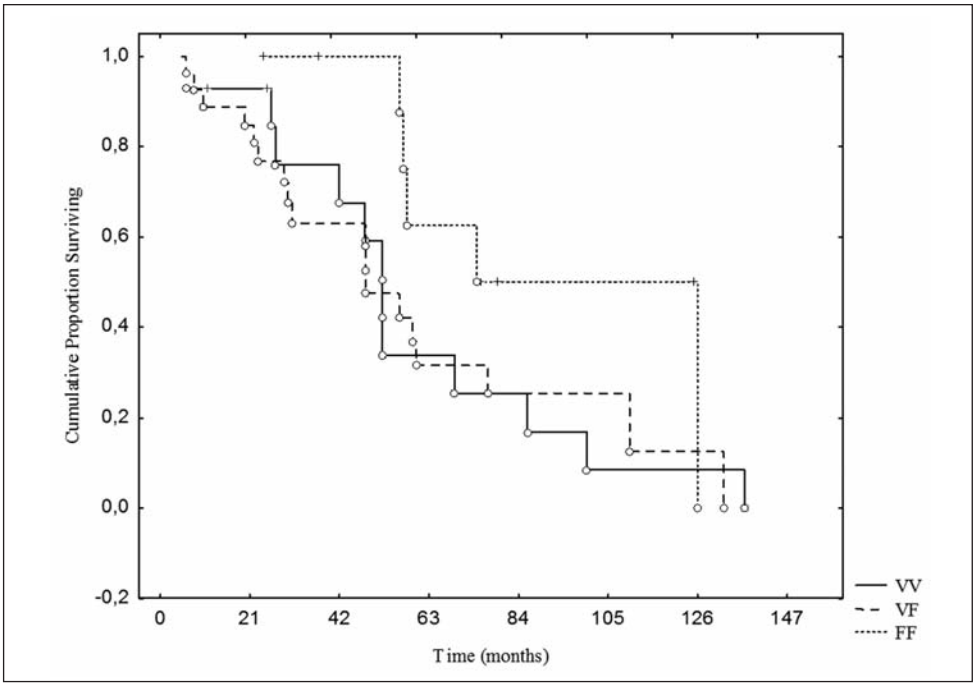

Figure 1. Disease free survival (DFS) by FCGR3A genotype. Survival curves were plotted by Kaplan Meier's method and compared by log-rank test (0.05)

Table 3. FCGR2A genotype frequences and risk for advanced clinical stage by SNPs

FCGR2A genotypes	CS I and II (%)	CS III and IV (%)	OR (95% CI)	RR (95% CI)	p*
HH	17.5	31.6	1		
HR	3.5	38.6	6.11 (1.18-31.54)	1.43 (1.06-1.93)	0.02
RR	5.3	3.5	0.37 (0.05-2.60)	0.62 (0.21-1.89)	0.29
HR+RR	8.8	42.1	2.67 (0.78-9.17)	1.29 (0.93-1.78)	0.10

*p values by Fisher exact test

and coworkers (20) and Ahlgrimm and coworkers (18).

With respect to patient characteristics, FCGR3A genotypes containing F allele (VF and FF) were more frequently found in patients older than 60 years. Similar results were reported in a German study (18). These authors found that the oldest patients (aged 61 to 80 years, median 70 years) most often showed FCGR3A VF genotype (DLBCL group treated with CHOP). Furthermore, in the same study, DLBCL patients with FCGR3A VV genotype were presented with a slightly decreased incidence of B-symptoms. In our study, the other clinical characteristics except age were not associated with FCGR3A genotypes.

Analyzing FCGR2A, we observed significant statistical association between HR genotype and adverse clinical stages III and IV. In the study of Ahlgrimm and coworkers, patients with bulky disease most often showed FCGR2A HR genotype (18). A Korean study reported that extranodal DLBCL involvement was more common with the FCGR2A HH genotype (16). In general, results reported by Kimm, Ahlgrimm (16, 18) and also by the present study, indicate the association between high-binding FCGR2A isoform H and adverse characteristics of DLBCL (advanced clinical stage, bulky disease and extranodal involvement). In contrast, high-binding FCGR3A isoform V was associated with favorable characteristics (decreased incidence of B-symptoms). Furthermore, the age over 60 years is considered as adverse characteristic in DLBCL patients. Both studies, Ahlgrimm's and ours, reported the higher incidence of low-binding FCGR3A isoform F in the group of oldest patients.

The impact of FCGR2A and FCGR3A SNPs on outcome of patients with B-cell malignancies has previously been investigated. Persky and coworkers reported an association of at least one FCGR3A V allele and improved overall survival in follicular lymphoma patients receiving therapy containing rituximab (19). Similar findings in follicular lymphoma were published elsewhere (27, 28). Analysis of FCGR2A and FCGR3A SNPs in CLL showed no apparent association with clinical outcome (17). However, there are conflicting data on association between FCGR2A and FCGR3A SNPs and outcome in aggressive NHL (16, 18, 20, 21). A Korean study reported a higher CR rate in the carriers of FCGR3A VV compared to VF and FF. A statistically significant difference in response rate was not observed according to FCGR2A genotypes. They also found that the group with FCGR3A VV genotype had a more rapid time to CR. A significant influence of FCGR2A genotypes on the time to achievement of CR was not observed (16). In the present study, we did not observe the difference in CR nor relapse rate according to FCGR2A and FCGR3A genotypes.

When comparing DFS, EFS and OS, we did not observe any impact of FCGR2A. With respect to FCGR3A, we observed a trend of better DFS, but not EFS and OS, in patients with FF genotype. German group reported that EFS and progression free survival, but not OS curves for FCGR3A FF showed a trend to be lower in DLBCL patients treated with R-CHOP (18). Kim and coworkers reported that neither FCGR2A nor FCGR3A showed any impact on EFS or OS (16).

It should be mentioned that B-cell malignancies display different sensitivity to rituximab. Anti-CD20 immunotherapy is rapidly evolving and the diversity of mAbs being tested in ongoing clinical trials reflects the uncertainty regarding the critical mechanism of action for this monoclonal antibody (29). Some of these new anti-CD20 antibodies show a higher

affinity for FCGR3A 158 F isoform, such as GA-101, AME-133v and rhuMAb v114 (4, 19). On the other hand, anti-CD20 antibodies are not specific for malignant cells, but for all B-cells expressing CD20. It is known that high affinity of FCGR may induce severe B-lymphocyte depletion. Furthermore, Weng and coworkers reported the association between high affinity FCGR3A V allele and rituximab-induced neutropenia in NHL patients subjected to autologous transplantation (30). Also, we should keep in mind the delicacy of the immune-effector mechanisms. For example, Alizadeh and coworkers indicated FCGR2A H allele as a crucial determinant of susceptibility to several autoimmune diseases and also confirmed an association of FCGR3A VV genotype with susceptibility to RA in Caucasian (12). Furthermore, beside binding affinity of different FCGR2A and FCGR3A allelic variants, efficiency of ADCC may be influenced by number of FCGR2A and FCGR3A expressed on effector cells. In addition, effects of FCGR2A and FCGR3A may be nullified by inhibitory FCGRs, such as FCGR2B and FCGR3B.

In summary, we presented the results of a one-institution study that included ethnically matched DLBCL patients uniformly treated with R-CHOP. According to our knowledge this is the first study on FCGR2A and FCGR3A polymorphisms in lymphoma patients in our population. Obtained frequencies of FCGR2A and FCGR3A genotypes are similar to those previously reported by other European groups. Furthermore, we reported the association of FCGR2A HR genotype and adverse clinical stages III or IV. A higher frequency of FCGR3A F allele in DLBCL patients older than 60 years and impact of FCGR3A FF genotype on DFS were noticed only as a trend. This study and previous reports suggest the association of FCGR2A and FCGR3A genotypes with DLBCL characteristics, rather than the course and outcome of DLBCL. However, the possible approval of new anti-CD20 antibodies with better affinity for the FCGR3A F allele in clinical usage may impose the need for FCGR3A genotyping as an integral part of the routine diagnostic practice.

References

1. Lenz G, Staudt LM. Aggressive lymphomas. N Engl J Med 2010; 362: 1417-29.
2. Gatter KC, Warnke RA. Diffuse large B-cell lymphoma. In Jaffe ES, Harris NL, Stein H and Vardiman JWL: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, Lyon: IARC Press, 2001, 171-4.
3. Smith SM, van Besien K. Treatment approach to diffuse large B-cell lymphomas. In Sekers MA, Kalaycio ME, Bolwell BJ: Clinical malignant hematology, USA: McGraw-Hill, 2007, 543-54.
4. Aldulaij W, Illidge TM. The future of anti-CD20 monoclonal antibodies: are we making progress? Blood 2011; 117: 2993-3001.
5. Rudnicka D, Oszmiana A, Finch DK, *et al*. Rituximab causes a polarization of B-cells that augments its therapeutic function in NK-cell-mediated antibody-dependent cellular cytotoxicity. Blood 2013; 121: 4694-702.
6. Salmon JE, Edberg JC, Brogle NL, *et al*. Allelic polymorphisms of human Fc gamma receptor IIA and Fc gamma receptor IIIB. Independent mechanisms for differences in human phagocyte function. J Clin Invest 1992; 89: 1274-81.
7. Salmon JE, Edberg JC, Kimberly RP. Fc gamma receptor III on human neutrophils. Allelic variants have functionally distinct capacities. J Clin Invest 1990; 85: 1287-95.
8. Karassa FB, Trikalinos TA, Ioannidis JP. Fc gamma RIIIA-SLE meta-analysis investigators. The Fc gamma RIIIA-F158 allele is a risk factor for the development of lupus nephritis: a meta-analysis. Kidney Int 2003; 63: 1475-82.
9. Breij EC, van der Pol WL, van Winsen L, *et al*. No association of Fc gamma RIIa, Fc gamma RIIIa and Fc gamma RIIIb polymorphisms with MS. J Neuroimmunol 2003; 140: 210-5.
10. Morgan AW, Keyte VH, Babbage SJ, *et al*. Fc gamma RIIIA-158V and rheumatoid arthritis: a confirmation study. Rheumatology 2003; 42: 528-33.
11. Karassa FB, Trikalinos TA, Ioannidis JP. The role of FcgammaRIIA and IIIA polymorphisms in autoimmune diseases. Biomed Pharmacother 2004; 58: 286-91.
12. Alizadeh BZ, Valdigem G, Coenen MJH, *et al*. Association analysis of functional variants of the FcgRIIa and FcgRIIIa genes with type 1 diabetes, celiac disease and rheumatoid arthritis. Hum Mol Genet 2007; 16: 2552-9.
13. Zhang W, Gordon M, Schultheis AM, *et al*. FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor-expressing metastatic colorectal cancer patients treated with single-agent cetuximab. J Clin Oncol 2007; 25: 3712-8.
14. Hurvitz SA, Betting DJ, Stern HM, et al. Analysis of Fcγ receptor IIIa and IIa polymorphisms: lack of correlation with outcome in trastuzumab-treated breast cancer patients. Clin Cancer Res 2012; 18: 3478-86.

15. Lin TS, Flinn IW, Modali R, *et al*. FCGR3A and FCGR2A polymorphisms may not correlate with response to alemtuzumab in chronic lymphocytic leukemia. Blood 2005; 105: 289-91.
16. Kim DH, Jung HD, Kim JG, *et al*. FCGR3A gene polymorphisms may correlate with response to frontline R-CHOP therapy for diffuse large B-cell lymphoma. Blood 2006; 108: 2720-5.
17. Dorman D, Spleiss O, Yeh RF, *et al*. Effect of FCGR2A and FCGR3A variants on CLL outcome. Blood 2010; 116: 4212-22.
18. Ahlgrimm M, Pfreundschuh M, Kreuz M, *et al*. The impact of Fc-γ receptor polymorphisms in elderly patients with diffuse large B-cell lymphoma treated with CHOP with or without rituximab. Blood 2011; 118: 4657-62.
19. Persky DO, Dornan D, Goldman BH, *et al*. Fc gamma receptor 3a genotype predicts overall survival in follicular lymphoma patients treated on SWOG trials with combined monoclonal antibody plus chemotherapy but not chemotherapy alone. Haematologica 2012; 97: 937-42.
20. Mitrovic Z, Aurer I, Radman I, *et al*. Fc RIIIA and FcγRIIA polymorphisms are not associated with response to rituximab and CHOP in patients with diffuse large B-cell lymphoma. Haematologica 2007; 92: 998-9.
21. Pennell NM, Bhanji T, Zhang L, *et al*. Lack of prognostic value of FCGR3A –V158F polymorphism in non-Hodgkin's lymphoma. Haematologica 2008; 93: 1265-7.
22. The International Non-Hodgkin's Lymphoma Prognostic Factors Project A predictive model for aggressive Non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987-94.
23. Cheson BD, Horning SJ, Coiffier B, *et al*. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma. NCI Sponsored International Working Group. J Clin Oncol 1999; 17: 1244-53.
24. Jiang X-M, Arepally G, Poncz M, *et al*. Rapid detection of the Fc gamma RIIA-H/R 131 ligand-binding polymorphism using an allele-specific restriction enzyme digestion (ASRED). J Immunol Methods 1996; 199: 55-9.
25. Koene HR, Kleijer M, Algra J, *et al*. FcγRIIIa-158V/F Polymorphism Influences the Binding of IgG by Natural Killer Cell FcγRIIIa, Independently of the FcγRIIIa-48L/R/H Phenotype. Blood 1997; 90: 1109-14.
26. Veeramani S, Wang SY, Dahle C, *et al*. Rituximab infusion induces NK activation in lymphoma patients with the high-affinity CD16 polymorphism. Blood 2011; 118: 3347-9.
27. Cartron G, Dacheux L, Salles G, *et al*. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgGFc receptor FcγRIIIa gene. Blood 2002; 99: 754-8.
28. Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol 2003; 21: 3940-7.
29. Beers SA, French RR, Chan HTC, *et al*. Antigenic modulation limits the efficacy of anti-CD20 antibodies: implications for antibody selection. Blood 2010; 115: 5191-201.
30. Weng WK, Negrin RS, Lavori P, *et al*. Immunoglobulin G Fc receptor FcγRIIIa 158 V/F polymorphism correlates with rituximab-induced neutropenia after autologous transplantation in patients with non-Hodgkin's lymphoma. J Clin Oncol 2010; 28: 279-84.

Received: 17.4.2013
Accepted:18.7.2013
Address: BojanaCikota-Aleksić
Institute of Medical Research
Military Medical Academy
Crnotravska 17
11000 Belgrade, Serbia
Tel. +381 11 3608 482
Fax: +381 11 662 722
E-mail: cbojana@ptt.rs