

FcγRIIIA receptor genotype does not influence an outcome in patients with follicular lymphoma treated with risk-adapted immunochemotherapy

V. PROCHAZKA¹, T. PAPAŽIK¹, J. GAZDOVA¹, M. DIVOKA¹, S. ROZMANOVA¹, E. FABER¹, L. RAIDA¹, L. KUCEROVA², K. LANGOVA³, M. JAROSOVA¹, K. INDRAK¹

¹Department of Hemato-Oncology, University Hospital, I.P.Pavlova 6, 77520 Olomouc, Czech Republic, e-mail: vit.prochazka@fnol.cz; ²Department of Pathology, Faculty of Medicine and Dentistry, Palacky University, Olomouc; ³Department of Medical Biophysics, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic

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Antibody (rituximab) dependent cellular cytotoxicity is a key mechanism in killing CD20+ lymphoma cells. FcγRIIIA-158 V/F gene polymorphism results in expression of 3 variants of the FcγRIIIA receptor (FcγRIIIA) on cytotoxic lymphocytes with different receptor affinity.

We studied 102 patients with newly diagnosed FL to assess whether the FcγRIIIA genotype influences outcome in patients treated with risk-adapted immunochemotherapy. The median age was 52 years (31-84); 90% of the patients had advanced (III/IV) clinical stages.

The Follicular Lymphoma International Prognostic Index (FLIPI) scores were as follows: low 18.9%, intermediate 33.7% and high 47.4%. The front-line treatment was stratified according to the commonly used risk factors (FLIPI, beta-2-microglobuline and serum-Tyrosine-Kinase levels, bulky disease) into 3 treatment groups: (1) patients with FLIPI 0-1 treated with (R)-CHOP (51%), (2) patients under 60 (65) years of age with intermediate-risk disease (FLIPI 2) indicated for an intensive protocol (ProMACE-CytaBOM or sequential chemotherapy) (21%), and (3) patients under 60 (65) years with high-risk disease (FLIPI ≥3) treated with intensive chemotherapy plus autologous stem cell transplantation (28%). Rituximab was added to front-line chemotherapy in 59% of the patients. Generally, complete remission (CR) or unconfirmed CR was achieved in 85% of the patients, 11% had partial remission and 4% stable disease. Molecular CR (CRm) was achieved in 67.4% of 86 evaluable patients. Overall survival (OS) at 5 years reached 84% (95% CI 0.74-0.93); event-free survival (EFS) at 5 years was 58% (95% CI 0.45-0.71). The frequencies of FcγRIIIA-158 gene polymorphisms V/V, V/F and F/F were 8%, 50% and 42%, respectively. The FLIPI score distribution was not different in F/F patients as compared to V/F+V/V carriers (chi-square, P=0.7). The treatment modalities (treatment arm or rituximab administration) had the same distribution in V/V+V/F vs F/F patients (chi-square, P=0.16 and P=0.62, respectively). The CRm rates were similar in both subgroups of V/V+V/F vs F/F patients (chi-square, P=0.92). Survival curves for OS and EFS were not significantly different when comparing the subgroups of V/V+V/F vs F/F patients (P=0.28 and P=0.57, respectively). We found no difference in the quality of treatment response or survival after front-line immunochemotherapy between FcγRIIIA subgroups. FcγRIIIA polymorphism have no influence on the outcome of patients treated with risk-adapted chemotherapy with or without rituximab.

Key words: Follicular lymphoma, chemotherapy, autologous transplantation, FcγR polymorphisms, rituximab, BCL2/IgH rearrangements

The introduction of rituximab into the treatment of B-cell non-Hodgkin's lymphoma has brought unprecedented improvements in treatment outcomes across the whole population of patients [1-4]. Although resistance to rituximab is rare, some patients show a poorer treatment response.

Detailed study of the mechanisms of rituximab activity showed that the main effector mechanisms leading to the destruction of lymphoma cells are those related to a patient's antitumor immunity: complement-dependent cellular cytotoxicity (CDC) and antibody-dependent cellular cyto-

toxicity (ADCC) [5-6]. Study of rituximab interaction with a patient's T-lymphocytes and NK cells suggests considerable interindividual variability in the severity of the cytotoxic response. The first laboratory and clinical data show that variable quantity and quality of ADCC may be associated with the effectiveness of immunotherapy in a particular patient [7-10]. Rituximab molecule shares similar Fc portion with human IgG1 molecule. Strength of interaction between rituximab Fc portion and Fc Immunoglobulin G Fc receptor (FcγR) on cytotoxic cells is a key process in mediating rituximab dependent cytotoxicity. Immunoglobulin G Fc receptor (FcγR) gene single nucleotide polymorphism results in expression of different receptor variants with different binding affinity. This fact affects the ability of effector cells, like natural killer cells and macrophages to mediate ADCC against antibody-coated tumor cells. We recognize three subtypes of FcγR (FcγRI, FcγRIIA, FcγRIIIA), whereas FcγRIIIA-158 V/F gene polymorphism is the most studied one. Dimorphism located at amino acid residue 158 of the FcγRIIIA led to a substitution of the phenylalanine (FcγRIIIA-158F) by a valine (FcγRIIIA-158V). In vitro studies showed, that homozygous genotype for FcγRIIIA-158V (VV) is associated with much more effective rituximab-dependent cell cytotoxicity [7]. FcγRIIIA-158 V/V allotype was also found to be associated with better response to rituximab in patients with untreated follicular lymphoma [11]. The role of the FcγRIIIA polymorphism in patients with follicular lymphoma treated with chemoimmunotherapy is controversial. Carloti and colleagues analyzed 96 patients sequentially treated with CHOP and rituximab [12]. No correlation was found between FcγRIIIA-158VV/VF and FcγRIIA-131HH/HR polymorphisms and overall response rate, the molecular response and event free survival. On the other hand, Persky et al. analyzed 146 patients treated on SWOG clinical trials with chemotherapy alone or combined chemotherapy and monoclonal antibody rituximab or I-131 tositumomab. At least 1 FCGRIIIa V allele was strongly associated with improved OS vs F/F (HR 0.28, 95% CI 0.10–0.80, p=0.02), with 5 year OS of 72% for F/F, 97% for V/F, and 100% for V/V (13). The role of FCGRIIIa-158 V/F gene polymorphism in patients treated with a risk-adapted approach has not been studied yet. Therefore, we conducted a retrospective study

to evaluate the effect of these polymorphisms on the clinical, molecular response to treatment, and on the overall outcome in this population of FL patients.

Patients and methods

This retrospective study included 102 previously untreated patients with follicular lymphoma (grade I-IIIa), who were diagnosed and treated in Department of Hemato-oncology, University Hospital Olomouc between 1996 and 2008. These patients were chosen because their DNA samples were available for FcγR polymorphism analysis. Ninety-four patients had detectable bcl-2/IgH rearrangement in bone marrow and/or peripheral blood using standard or long-distance PCR method. Patients' clinical characteristics are summarized in Table 1.

Therapy stratification. All patients fulfilled GELF criteria for treatment initiation (14). The front-line treatment was stratified according to the commonly used risk factors (FLIPI, beta-2-m and s-TK levels, bulky disease) into 3 treatment groups: (1) patients with FLIPI 0-1 treated with (R)-CHOP (51%), (2) patients under 60 (65) years of age with intermediate-risk disease (FLIPI 2) indicated for an intensive protocol (ProMACE-CytaBOM or sequential chemotherapy) (21%), and (3) patients under 60 (65) years with high-risk disease (FLIPI ≥3) with additional risk factors were treated with intensive chemotherapy plus autologous stem cell transplantation (BEAM) (28%). Rituximab was added to front-line chemotherapy in 59% of the patients. Maintenance treatment after 1st line therapy was indicated in 35 (34%) of the patients. Twenty-four of them received rituximab (375mg/m² every 3 months for 24 months) and eleven patients was treated with interferon alpha (3MU three times per week for 24 months).

Chemotherapy protocols. CHOP and ProMACE-CytaBOM protocols were administered as previously published [15,16]. The sequential chemotherapy protocol consists of 3 cycles of CHOEP-21-like regimen (PACEBO), 1 cycle of an ifosfamide and methotrexate-based regimen (IVAM) and a priming regimen with high-dose cytosine arabinoside (HAM). The PACEBO regimen was administered as follows: doxorubicin 40 mg/m² intravenously day 1, cyclophosphamide 850 mg/m² intravenously day 1, etoposide 200 mg/m² intravenously day 1, bleomycin 10 mg/m² intravenously day 8, vincristine 1.4 mg/m² (maximum 2.0 mg) intravenously day 8 and prednisone 40 mg/m² orally days 1 to 14. The IVAM regimen consisted of ifosfamide 1500 mg/m² intravenously days 1 to 5, etoposide 150 mg/m² intravenously day 1 to 3, cytosine arabinoside 100 mg/m² intravenously day 1 to 3, methotrexate 3 g/m² intravenously day 5, mesna prophylaxis 1200 mg intravenously days 1 to 5, leucovorin rescue 25 mg/m² intravenously from day 6/7 until the plasma methotrexate level was below 0.05 μmol/l. The HAM regimen was administered as follows: cytosine arabinoside 2 g/m² twice daily intravenously days 1 and 2, mitoxantrone 10 mg/

Table 1. Patient baseline clinical characteristics (n = 102).

Median age (range)	52 years (31-84)
Sex (male-to-female ratio)	33:69 (1:2.1)
Advanced disease stage (III+IV)	89/99 (90%)
Bulky disease (>7cm)	46/81 (57%)
Bone marrow involvement	60/87 (69%)
Elevated lactate dehydrogenase level	31/102 patients (30%)
Elevated serum thymidin kinase (>15 UI/L)	35/87 (40.2%)
Elevated beta-2-micoglobuline level (>3 mg/L)	43/87 (49.4%)
Median follow-up (range)	54 months (15-159)

m2 days 2 and 3 [17]. Stem cell mobilization was performed with 12 µg/kg of filgrastim given subcutaneously twice daily. The BEAM 200 conditioning regimen dosage was standard as previously published [18].

Treatment response. The treatment responses – complete response (CR), unconfirmed complete response (uCR), partial response (PR), stable disease and progressive disease – were defined according to the International Workshop NHL Response Criteria published by Cheson et al [19]. Patients who achieved a complete response (CR) or unconfirmed complete response (CRu) plus PCR bcl-2/IgH negativity were classified as molecular CR (CRm).

Molecular analysis. A qualitative molecular evaluation of Bcl2/IgH+ cells was performed on 172 BM or PB samples obtained at time of restaging. Genotyping of FcγRIIIA polymorphism was performed on 102 BM or PB samples using a nested PCR followed by allele-specific restriction enzyme digestion as previously described [20,21]. Briefly, a 1.2 kb FcγRIIIA-specific fragment containing the polymorphic site was amplified in a 50 µL reaction volume with 1 µg of genomic DNA, 200 ng of each primer (sense primer: 5'-ATATTTACAGAATGGCACAGG-3', antisense primer: 5'-GACTTGGTACCCAGGTTGAA-3'), 200 µM of each dNTP and 1U *Taq* DNA polymerase (Promega, Madison, WI, U.S.A.). This first PCR consisted of 10 minutes at 95°C, then 35 cycles (each consisting of steps at 95°C for 1 minute, 57°C for 1.5 minutes and 72°C for 1.5 minutes), and 10 minutes at 72°C for complete extension. 1 µL of PCR product was used for further amplification of 94 bp fragment and creating an *Nla*III restriction site in FcγRIIIA-158V allele only. This second PCR used 150 ng of each sense primer: 5'-ATCAGATTCGATCCTACTTCTGCAGGGGCAT-3' and antisense primer: 5'-ACGTGCTGAGCTTGAGTGATGGTGATGTTTAC-3', 200 µM of each dNTP and 1U of *Taq* DNA polymerase. The first cycle consisted of 5 minutes at 95°C, then 35 cycles (each

consisting of steps at 95°C for 1 minute, 64°C for 1 minute and 72°C for 1 minute), and 9.5 minutes at 72°C for complete extension. 10 µL of amplified DNA was digested with *Nla*III (New England Biolabs, Hitchin, UK) at 37°C for 12 hours and electrophoresed on 3% agarose gel stained with ethidium bromide. For homozygous FcγRIIIA-158F patients only one undigested band of 94 bp was detected when visualized under UV light. Homozygous FcγRIIIA-158V patients had 2 detectable bands (61 bp and 33 bp) and for heterozygous FcγRIIIA-158V/F patients three bands (94 bp, 61 bp, and 33 bp) were obtained.

Statistical analysis. Our data were analyzed using the Statistical Package for the Social Sciences (SPSS) [22]. Overall survival (OS) was defined as the time from first treatment to the date of last follow-up examination (censored) or the date of death (event) from any cause. Event free survival (EFS) was defined as the date of first treatment to the date of documented disease progression or death (event) or the date of last follow-up examination (censored). The Kaplan-Meier method [23] was used to calculate survival probabilities. The log-rank test was used to compare differences in survival times between patient subgroups. The significance level was set at a $p = 0.05$; 2-tailed tests were used in all calculations. Univariate analysis was performed using a chi square and long rank tests, multivariate analysis was performed by a multiple regression model.

Results

All 102 patients were genotyped for FcγRIIIA polymorphism: the frequencies of FcγRIIIA-VV, VF and FF were 8%, 50% and 42%, respectively. There was no significant difference in the distribution of FcγRIIIA polymorphism and age, sex, B symptoms, LDH and beta-2-m level, bulky disease, bone marrow infiltration and stage (data not shown).

Table 2. FLIPI risk groups and treatment stratification.

FLIPI risk groups (n=92)	FcγRIIIA-FF (n=40)	FcγRIIIA-VV-FV (n=52)	p=0.75
high	20/40 (50%)	24/52 (46%)	Σ=44 (100%)
intermediate	14/40 (35%)	17/52 (33%)	Σ=31 (100%)
low	6/40 (15%)	11/52 (21%)	Σ=17 (100%)
Treatment arm (n=87)	FcγRIIIA-FF (n=35)	FcγRIIIA-VV-FV (n=52)	p=0.16
CHOP	15/35 (43%)	29/52 (56%)	Σ=44 (100%)
SQ-protocol	6/35 (17%)	12/52 (23%)	Σ=18 (100%)
SQ-protocol+ASCT	14/35 (40%)	11/52 (21%)	Σ=25 (100%)
Rituximab (n=60)	FcγRIIIA-FF (n=43)	FcγRIIIA-VV-FV (n=57)	p=0.62
rituximab given	27/43 (63%)	33/57 (58%)	Σ=60 (100%)
Maintenance Tx (n=35)	FcγRIIIA-FF (n=41)	FcγRIIIA-VV-FV (n=57)	p=0.78
maintenance given	14/41 (34%)	21/57 (37%)	Σ=35 (100%)

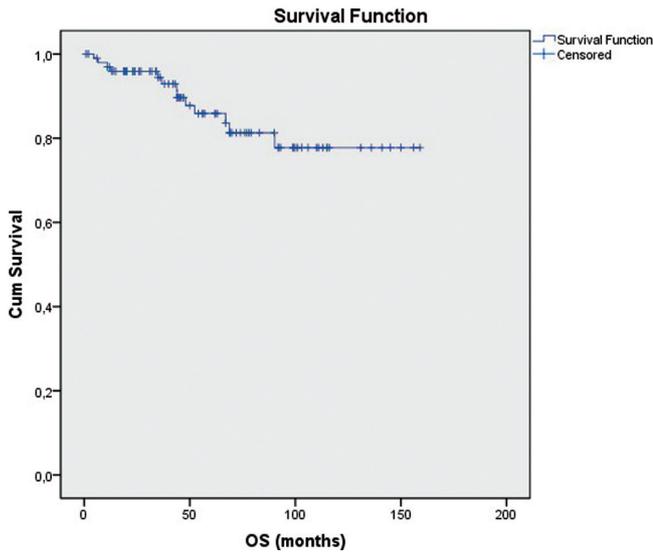


Figure 1. Overall survival (OS), all patients.

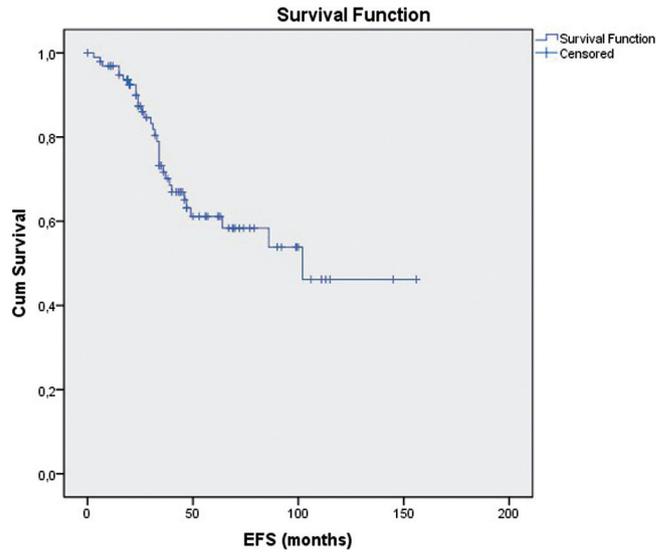


Figure 2. Event free survival (EFS), all patients.

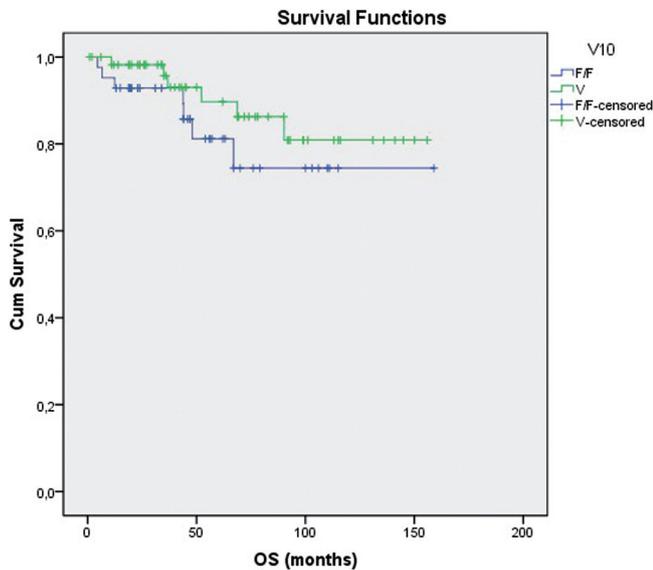


Figure 3. Overall survival (OS), FcγRIIIA-FF vs FcγRIIIA-VV-FV, log rank p=0.55

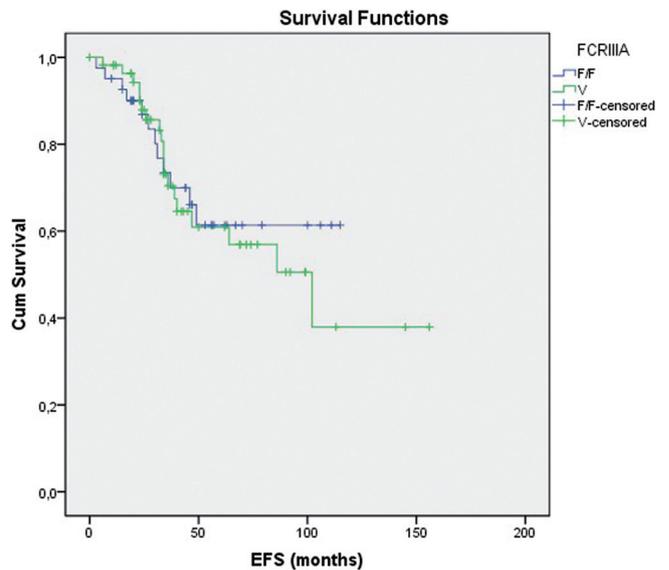


Figure 4. Event free survival (EFS) FcγRIIIA-FF vs FcγRIIIA-VV-FV, log rank p=0.3

The FLIPI score distribution was not different in F/F patients as compared to V/F+V/V carriers (chi-square, P=0.7). The treatment modalities (treatment arm or rituximab administration) had the same distribution in V/V+V/F vs F/F patients (chi-square, P=0.38 and P=0.52, respectively) (Table 2). Complete remission rates were similar irrespective of the different FcγRs variants: 76.8% for FcγRIIIA-VF/VV and 86.0% for FcγRIIIA-FF (p=ns). The molecular remission rates were almost identical in both groups: 66.7% for FcγRIIIA-VF/VV and 67.5% for FcγRIIIA-FF (p=ns).

After median follow up 54 months (range 15-159) the OS of all patients is 81% (95% CI 0.73-0.90) in 5 years (Figure 1). Event-free survival (EFS) at 5 years reached 58% (95% CI 0.47-0.70) (Figure 2). The 5-year OS of the patients with FcγRIIIA-FF was 72% compared to 81% in patients bearing the combined FcγRIIIA-VF/VV (p=ns) (Figure 3). The 5-year EFS of patients with FcγRIIIA-FF was 63% (last event in 49 months) compared to 55% in patients bearing the combined FcγRIIIA-VF/VV (p=ns) (Figure 4). During observation period lymphoma relapsed in 17 patients (median time to relapse 40.8

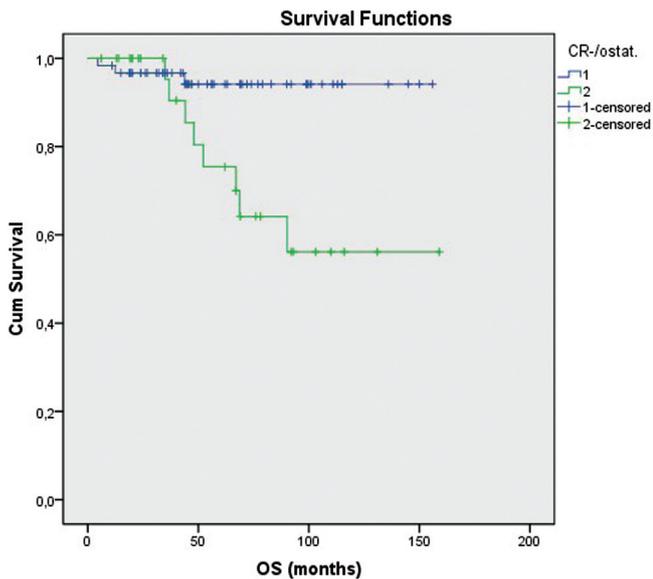


Figure 5. Overall survival (OS) – effect of molecular remission. Upper line: patients who achieved molecular CR, bottom line: patients who did NOT achieved molecular CR, log rank $p=0.002$

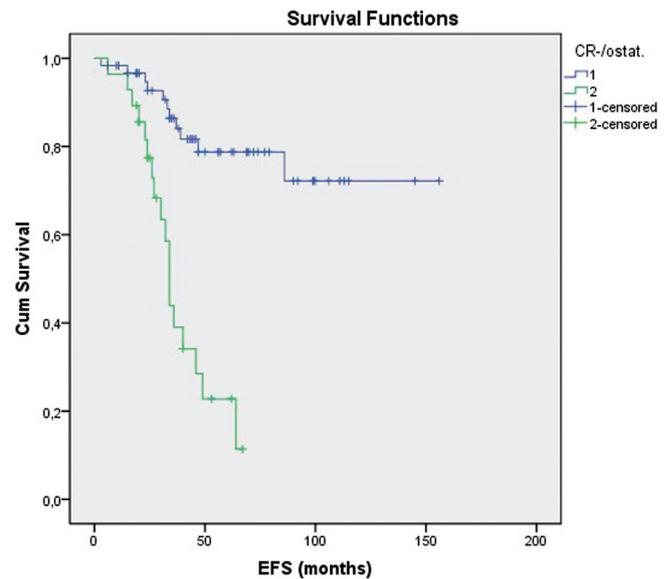


Figure 6. Event free survival (EFS) – effect of molecular remission. Upper line: patients who achieved molecular CR, bottom line: patients who did NOT achieved molecular CR, log rank $p<0.001$.

months, range 20.4-102.3 months). There was no difference in cumulative relapse-hazard curves between FcγRIIIA-FF and FcγRIIIA-VV-FV carriers (log rank $p=0.21$).

Subanalysis of the patients treated with rituximab in first line showed no difference in OS (log rank $p=0.99$) and EFS (log rank $p=0.35$) between FcγRIIIA groups. Similarly, there was no significant difference in OS (log rank $p=0.39$) and EFS (log rank $p=0.85$) in rituximab naïve group. We confirmed much better clinical outcome associated with clearance of the bcl-2/IgH+ cells (molecular CR). Patients who achieved molecular CR after first line therapy have longer 5-year OS (63% vs 92%, $p=0.002$) and 5-year EFS (12% vs 74%, $p<0.001$) than patients without molecular CR (Figure 5,6). Patients who received maintenance treatment have longer 5-year EFS (46% vs 75%, $p=0.005$) and 5-year OS (76% vs 100%, $p=0.003$) than patients who did not (Figure 7). Subanalysis of the 35 patients receiving maintenance treatment showed no significant difference in EFS curves between FcγRIIIA subgroups (log rank $p=0.11$). Despite it all five events were observed in FcγRIIIA-VV-VF carriers.

Multivariate analysis. The effects of multiple factors on EFS and OS were analyzed using logistic regression. The following variables were evaluated: age, sex, serum LDH level, bulky disease, rituximab application, autologous stem cell transplant, maintenance treatment application, beta-2-m level, molecular remission and FcγRIIIA (VF/VV vs FF) genotypes. The only prognostic factor for OS was age above 60 years (hazard ratio 5.158; 95% CI 1.65-16.17; $p=0.005$). Two factors independently predict EFS: non-achievement of molecular remission (hazard ratio 4.189; 95% CI 1.75-10.0; $p=0.001$) and maintenance treatment application (hazard ratio 0.33; 95% CI 0.11-0.99; $p=0.048$).

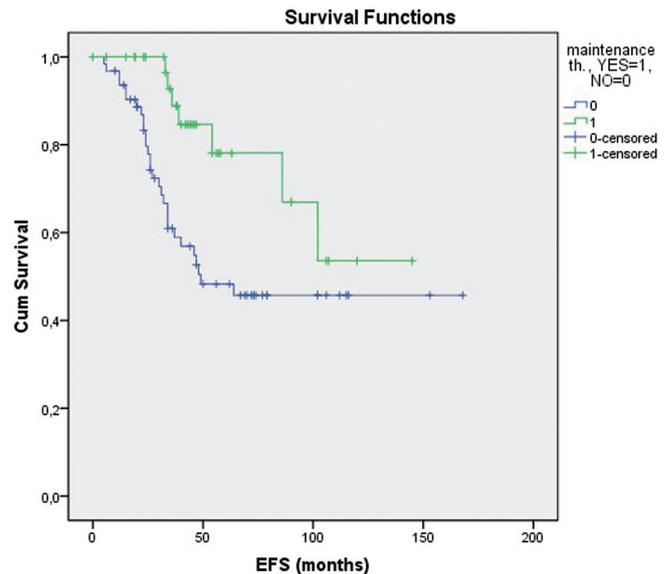


Figure 7. Maintenance treatment – effect on EFS. Upper line: patients who received maintenance treatment, bottom line: patients who did NOT received maintenance treatment, log rank $p=0,005$.

Discussion

Our study demonstrate, that FcγR variants did not influence treatment response quality or survival in FL patients. This fact may be caused by more factors. Patient population enrolled in our study share many unfavourable features: almost half of patients had high risk FLIPI score, more than

half had bulky disease and 90% of patients had advanced clinical stage. This was reasons for application of more intensive treatment strategies including high dose therapy and stem cell transplant. Risk-adapted intensive therapy can probably overcome negative prognostic impact of low-affinity FcγR variants. Most important factors influenced prognosis in our study were achievement of molecular CR and long term disease control (maintenance treatment application). Molecular CR was achieved independently on FcγR status, and similarly low affinity FcγR variant did not modify effectivity of maintenance treatment.

These results are in good correlation with previously published data of FL patients treated with R-CHOP [12] or chemotherapy alone [24]. There is only one large trial [13], which independently demonstrated survival advantage of FcγRIIIA-VV-FV genotype over FcγRIIIA-FF in FL patients treated with chemoimmunotherapy. Two different monoclonal antibodies were used in this study: rituximab (45%) and I-131 tositumomab (55%). It is not obvious whether survival advantage of high affinity allele was caused by rituximab or by radioimmunotherapy (I-131 tositumomab). The situation is less obvious in patients with Diffuse Large B-cell Lymphoma (DLBCL). Kim and co-workers published positive correlation between FcγRIIIA-VV genotype and response in patients with DLBCL treated with R-CHOP [25]. Similarly, Zhang and colleagues found FcγRIIIA-VV or VF genotype to be superior to FF genotype in term of long term survival of B-cell lymphoma patients [26]. This benefit was not confirmed by prospective trials. Large randomized trial RICOVER-60 showed no impact of FcγRIIIA genotype on treatment outcome in elderly population with DLBCL. FcγRIIIA genotype does not influence both in chemotherapy and immunochemotherapy arm (27). Surprisingly, Mitrovic and colleagues found FcγRIIIA-VV genotype to be negative predictive factor for treatment response after R-CHOP. Patients with high affinity FcγRIIIA-VV genotype have lower CR rate comparing to F carriers (40% vs. 83%, $p=0.01$) [28].

Different results of this studies may be, at least in a part, explained by the differences in studied populations. Asian population have high proportion of V/V phenotype, European patients in RICOVER-60 were elderly and part of them was treated with dose dense CHOP.

FcγRIIIA play important role in mechanism of action when is rituximab used as single agent. Our and other studies support the hypothesis, that ADCC and phagocytose mediated by FcγRIIIA are not most relevant processes in killing lymphoma cells when the antibody is combined with chemotherapy.

Understanding to complex network of immune mechanisms of destruction of the lymphoma cells is necessary in development of new monoclonal antibodies [29-31]. Inherited cytokines gene polymorphisms were found to modify overall prognosis in patients with FL and probably may also modify efficacy anticancer therapy and of new biologic drugs in particular patients [32,33]. Host immunogenetics is promising

class of prognostic factors and should be taken into account in future lymphoma trials [34].

In conclusion, although FcγRIIIA-VV genotype is prerequisite for more efficient clinical response in FL patients treated with rituximab alone, this study demonstrate that in population treated with risk-adapted chemotherapy with or without rituximab lose FcγR genotype its predictive importance.

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