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FCGR3A/2A polymorphisms and Diffuse Large B-cell Lymphoma outcome treated with immunochemotherapy: a meta-analysis on 1,134 patients from two prospective cohorts

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Abstract

Single nucleotide polymorphisms (SNPs) in FCγ-receptor genes *FCGR3A* (rs396991) and *FCGR2A* (rs1801274) influence the affinity of the Fc portion of anti-CD20 immunoglobulin G1 monoclonal antibody. Their roles in diffuse large B-cell lymphoma (DLBCL) treated with rituximab in combination with anthracycline-based chemotherapy remain controversial. To address this question, we genotyped *FCGR2A* and *FCGR3A* SNPs in two prospective DLBCL cohorts from Lymphoma Study Association (LYSA) trials (N=554) and Iowa/Mayo Specialized Program Of Research Excellence (SPORE) (N=580). Correlation with treatment response and hematological toxicity were assessed in LYSA. Correlation with event free survival (EFS) and overall survival (OS) was performed in both cohorts, followed by a meta-analysis to increase power. Our study shows the absence of correlation between these SNPs and treatment response. Grade 3–4 febrile neutropenia during treatment was more frequently observed in *FCGR3A* VV (39%) than VF (29%) and FF (32%) carriers (*P*=0.04). Our analysis for EFS and OS shows that

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FCGR3A was not associated with outcome. In a meta-analysis using an ordinal model, *FCGR2A* (per R allele) was associated with a better EFS (HR=0.87; 95%CI, 0.76–0.99; *P*=0.04) and OS (HR=0.86; 95%CI, 0.73–1.00; *P*=0.05) which was not altered after adjustment for the International Prognostic Index. Overall, our data demonstrate that DLBCL patients with the low affinity FCγRIIA RR had an unexpectedly better outcome than FCγRIIA H carriers. Whether rituximab efficacy is improved in FCγRIIA RR patients due a clearance reduction or other functions of FCγRIIA in DLBCL should be investigated (clinicaltrials.gov identifiers: NCT00135499, NTC00135499 NCT00140595, NCT00144807, NCT00144755, NCT01087424, NCT00301821).

Keywords

FCGR2A; *FCGR3A*; polymorphisms; immunochemotherapy; prognostic; DLBCL

Introduction

Rituximab in combination with anthracycline-based chemotherapy has improved the prognosis of diffuse large B-cell lymphoma (DLBCL) patients. Better understanding of factors that affect the response variability of rituximab remains an important therapeutic challenge [1]. Tumor burden had a prognostic impact for DLBCL patients treated with rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen and gender and weight were shown to influence outcome by affecting rituximab clearance [2,3].

Antibody-dependent cellular cytotoxicity (ADCC) is one of the major hypothesized mechanisms of action of rituximab [1]. The affinity between Fc portion of anti-CD20 monoclonal antibody and FcG receptors (FCγR) that engages ADCC can be modulated by the presence of single nucleotide polymorphisms (SNPs) in *FCGR* genes. The *FCGR3A* rs396991 SNP leading to the substitution of a valine (V) for a phenylalanine (F), confers a higher affinity to FCγRIIIA 158V for IgG1 than FCγRIIIA 158F [4]. The *FCGR2A* rs1801274 SNP modifies an amino-acid at position 131 of FCγRIIA with either a histidine (H) or an arginine (R); FCγRIIA 131H has a higher affinity than FCγRIIA 131R [4]. With rituximab in monotherapy for follicular lymphoma (FL) patients, initial studies showed that *FCGR3A* VV patients had a better response rate than *FCGR3A* F carriers [5,6]. For DLBCL patients treated with immunochemotherapy, the data on the therapeutic impact of *FCGR3A* and *FCGR2A* are unclear based on a relatively small number (51 to 263) of DLBCL patients [7–12]. A trend for a higher event-free survival (EFS) was observed for *FCGR3A* VV compared to *FCGR3A* F patients treated by R-CHOP in the RICOVER-60 trial [13]. One important observation by the authors of the latter study was that all previous studies were underpowered to observe a statistically significant difference in outcome for *FCGR3A* or *FCGR2A* genotype [13].

We analyzed the prognostic value of *FCGR2A* and *FCGR3A* in two prospective cohorts (N=554 and 580) of newly diagnosed DLBCL patients treated with anthracycline-based chemotherapy and rituximab. We performed a meta-analysis based on these 1,134 patients to increase statistical power to clarify this important therapeutic question. We performed

exploratory analyses to assess heterogeneity by sex, tumor bulk and the absolute lymphocyte count (ALC) at diagnosis, which are clinical characteristics known to affect rituximab clearance or efficacy [2,3,14].

Methods

Study population

LYSA cohort—The LNH03B program of the LYSA consisted of five prospective multicentric, controlled studies including 1,704 DLBCL patients older than 18 years of age [15–19]. Details of the treatment of 554 patients included in this study are presented in Table S1

SPORE cohort—Patients with newly diagnosed lymphoma were enrolled from 2002–2009 in the Molecular Epidemiology Resource (MER), a prospective cohort that is part of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE) [20]. Details of the treatment, which was based on routine practice, are provided in Table S1

This study was conducted in accordance with the Declaration of Helsinki. Ethics committees of Haute-Normandie (LYSA) and the SPORE study Human Subjects Institutional Review Board at Mayo Clinic and the University of Iowa approved this study. All patients provided written consent for participation. In accordance with French law, no mention of race or ethnicity was made.

SNP genotyping

DNA was extracted from peripheral blood. In the LYSA, *FCGR3A* (rs396991) and *FCGR2A* (rs1801274) genotyping used a complete assay containing primers, probes and TaqMan® Genotyping Master Mix from Applied Biosystems (Foster City, California, USA) on an ABI Prism 7000 Sequence Detection System (Applied Biosystems). Duplicate genotyping were performed for 10% of samples and agreement was 100%. In the SPORE, the *FCGR2A* SNP was genotyped as part of a larger project using a custom Illumina Infinium array (Illumina, San Diego, CA) and the *FCGR3A* SNP was genotyped using a custom designed pyrosequencing assay [21].

Statistical analysis

The correlation between *FCGR* genotypes and initial characteristics was assessed. Correlation between *FCGR3A* and *FCGR2A* genotype and response to treatment and toxicity (grade 3–4 anemia, grade 3–4 thrombocytopenia and grade 3–4 febrile neutropenia during treatment, at least one cycle delayed for 5 days or more) were only performed in the LYSA cohort in whom these data were prospectively collected in clinical trial setting. Tumor responses were classified based on the 1999 Cheson criteria [22]. EFS was evaluated from the date of randomization (LYSA) or the date of diagnosis (SPORE) to the date of disease progression, relapse, re-treatment or death from any cause. Overall survival was evaluated from the date of randomization (LYSA) or the date of diagnosis (SPORE) to the date of death from any cause. A Chi-square test was used to examine associations between

genotypes and patient characteristics and treatment response. Survival was estimated by the Kaplan-Meier product limit method and compared using the log-rank test. The prognostic value of each SNP was evaluated for EFS and OS in ordinal (per *FCGR3A* V and *FCGR2A* R allele) and genotypic (dominant and recessive) models, first in each cohort, and then in a meta-analysis [23].

Results

The clinical characteristics of the 554 LYSA and 580 SPORE DLBCL patients are presented in Table S2. In the LYSA, the median age was 61 years (range, 18–93), 19% had a ECOG PS 0–1, 73% had an Ann Arbor stage III–IV and 50% had an aaIPI score of 2–3. In the SPORE, the median age was 62 years (range, 18–92), 17% had an ECOG PS 0–1. Compared to the LYSA cohort, fewer SPORE patients had Ann Arbor stage III–IV (59% vs 73%) and aaIPI score 2–3 (41% vs 50%). With a median follow-up of 39 months, the 3-year EFS and OS rates were 69.3% and 75.3%, respectively in the LYSA cohort. In the SPORE cohort, with a median follow-up of 59 months, the 3-year EFS and OS rates were 66.5% and 79.8%, respectively.

Genotyping data were available on 554 LYSA and 580 SPORE patients for *FCGR2A* and 552 patients for *FCGR3A* (Table S2). The distribution of the VV, VF and FF alleles for *FCGR3A* was 15%, 46% and 39%, respectively in the LYSA and 11%, 46% and 43%, respectively in the SPORE. The HH, HR and RR allele distribution for *FCGR2A* was 28%, 49% and 23%, respectively in the LYSA and 23%, 54% and 23% in the SPORE. These distributions were consistent with Hardy-Weinberg equilibrium. There was no difference in patient characteristics according to *FCGR3A* and *FCGR2A* genotypes in the LYSA (Table S3) or in the SPORE (Table S4).

FCGR3A and *FCGR2A* and response to treatment in LYSA patients

For the *FCGR3A* SNP, complete response (CR) and unconfirmed CR (CRu) after induction therapy was observed in 50 patients (63%) with the VV allele, in 168 patients (68%) with the VF allele and in 128 patients (63%) with the FF allele (P=0.44); for *FCGR2A* SNP, CR/CRu was observed in 93 patients (62%) with the HH allele, in 171 patients (66%) with the HR allele and 82 patients (67%) with the RR allele (P=0.63). At the end of initial treatment a CR/CRu was documented for 60 (73%), 195 (76%), 158 (74%) patients with respectively *FCGR3A* VV, VF, FF genotype (P=0.85) and 113 (73%), 202 (75%), 98 (76%) *FCGR2A* HH, HR, RR carriers, respectively (P=0.88). Results were similar when analyses were restricted to the 340 and 191 patients assessable for response treated by R-CHOP and R-ACVBP in induction therapy, respectively (data not shown).

EFS and OS according to *FCGR3A* and *FCGR2A* genotypes

The 3-year EFS rates for patients with *FCGR3A* VV, VF and FF were not significantly different in LYSA (P=0.59) (Figure 1A) or the SPORE (P=0.93) cohort (Figure 1B). We also did not observe any difference for OS for this SNP in LYSA (P=0.19) (Figure 2A) and in the SPORE (P=0.47) (Figure 2B). The 3-year EFS between HH, HR and RR carriers of *FCGR2A* SNP was not significantly different in LYSA (P=0.21) (Figure 1C) or in the

SPORE (*P*=0.15) (Figure 1D). However, we observed a trend of higher 3-year EFS rates for *FCGR2A* RR patients compared to FCGR2A H carriers in LYSA (75.4% [67.9%–83.6%] vs 67.4% [62.9%–72.2%], *P*=0.08) and in the SPORE (72.4% [65.1%–80.6%] vs 64.8% [60.3%–69.5%], *P*=0.06). Similarly, the OS was not significantly different between the three *FCGR2A* genotypes in LYSA (*P*=0.11) (Figure 2C) or in the SPORE (*P*=0.24) (Figure 2D), but we observed a better OS in LYSA (81.5% [74.7%–89%] vs 73.4% [69.1%–77.9%], *P*=0.04) and a trend in the SPORE (85.9% [80.2%–92%] vs 78% [74.2%–82%], *P*=0.10) for *FCGR2A* RR compared to *FCGR2A* H patients.

In a meta-analysis of the results for *FCGR3A* (N=1,134 patients), there was no association for EFS (hazard ratio [HR]=1.04; 95%CI, 0.90–1.19; *P*=0.61) or OS (HR=0.98; 95%CI, 0.83–1.15; *P*=0.78) using an ordinal (per allele) model (Table 1). We also did not observe any difference of outcome between patients who carried the high-affinity FCγRIIIA VV genotype compared to patients with the low affinity FCγRIIIA F allele (genotypic model) (Table S5). For *FCGR2A*, the combined analysis showed that this SNP (per allele) was associated with EFS using an ordinal model (HR=0.87; 95%CI, 0.79–0.99; *P*=0.04) and OS (HR=0.86; 95%CI, 0.73–1.00; *P*=0.05) (Table 2). These results retained significance after aaIPI adjustment for EFS (HR=0.85; 95%CI, 0.74–0.97; *P*=0.02) and for OS (HR=0.83; 95%CI, 0.71–0.97; *P*=0.02). While we did not observe any difference of outcome between the high affinity genotype (FCγRIIA HH) and the low affinity allele (FCγRIIA R) (genotypic model) (Table S6), we observed in the meta-analysis better prognosis of *FCGR2A* RR compared to *FCGR2A* H for EFS (HR=0.71; 95%CI, 0.56–0.91; *P*=0.01) and OS (HR=0.68; 95%CI, 0.51–0.91; *P*=0.01) (Table 3), which remained after aaIPI adjustment for both EFS (HR=0.70; 95%CI, 0.55–0.89; *P*=0.006) and OS (HR=0.83; 95%CI, 0.71–0.97; *P*=0.02).

Association of *FCGR3A* and *FCGR2A* with clinical characteristics

Sex—In LYSA, males with the *FCGR3A* VV genotype compared to *FCGR3A* F carriers had a poorer OS (HR=1.86; 95%CI, 1.09–3.19; *P*=0.02), but this result was not significant after aaIPI adjustment and was not confirmed in the SPORE (Table S5). In the meta-analysis, the beneficial effect on EFS of *FCGR2A* RR compared to *FCGR2A* H showed the same trend among men (HR=0.71; 95%CI, 0.51–0.99; *P*=0.05) and women (HR=0.75; 95%CI, 0.52–1.10; *P*=0.14). These results were also observed for OS among men (HR=0.63; 95%CI, 0.42–0.95; *P*=0.03) and women (HR=0.75; 95%CI, 0.48–1.17; *P*=0.20) (Table 3).

ALC—We hypothesized that *FCGR* polymorphisms could display a distinct role in patients with low or high lymphocyte counts. Among patients with a low ALC ($<1.0 \times 10^9$/L), there was no association of the *FCGR3A* SNP with either EFS or OS (Table 1 and Table S5). For patients with a high ALC ($\geq 1.0 \times 10^9$/L), those with *FCGR3A* VV genotype had a worse EFS (HR=1.60; 95%CI, 0.94–2.73; *P*=0.08) and OS (HR=2.10; 95%CI, 1.17–3.78; *P*=0.01) compared to *FCGR3A* F carriers in LYSA; however, we could not confirm the results in the SPORE cohort. In contrast, the *FCGR2A* RR was associated with a better EFS (HR=0.60; 0.40–0.89; *P*=0.01) and OS (HR=0.56; 0.34–0.90; *P*=0.02) for patients with a high ALC in the meta-analysis (Table 3), and these results remained significant after aaIPI adjustment for EFS (HR=0.57; 95%CI, 0.38–0.85; *P*=0.01) and OS (HR=0.55; 95%CI, 0.33–0.88; *P*=0.01).

For patients with low ALC, the benefit effect of *FCGR2A* RR was weaker and not statistically significant for EFS (HR=0.83; 95%CI, 0.59–1.19; *P*=0.31) and OS (HR=0.78; 95%CI, 0.51–1.19; *P*=0.25).

Bulky disease—We assessed whether the *FCGR3A* and *FCGR2A* SNPs influenced the prognosis of patients with or without a bulky disease, as defined by the presence of a mass>10cm. We did not observe any association for the *FCGR3A* (Table 1 and Table S5) or the *FCGR2A* (Tables 2–3) SNPs when stratified on bulky disease.

R-CHOP patients

In LYSA and SPORE, 351 and 511 patients were treated by R-CHOP regimen, respectively. There was no association of the *FCGR3A* with either EFS or OS (Table 1 and Table S5). For *FCGR2A*, the meta-analysis of the ordinal model showed a suggestive trend for EFS (HR=0.88; 95%CI, 0.75–1.02; *P*=0.09) and OS (HR=0.85; 95%CI, 0.72–1.01; *P*=0.07) (Table 2). Compared to *FCGR2A* H carriers, *FCGR2A* RR patients had superior EFS (HR=0.75; 95%CI, 0.58–0.98; *P*=0.04) and OS (HR=0.69; 95%CI, 0.51–0.95; *P*=0.02) (Table 3), including after aaIPI adjustment for EFS (HR=0.73; 95%CI, 0.56–0.95; *P*=0.02) and OS (HR=0.67; 95%CI, 0.49–0.92; *P*=0.01). The results were similar when excluding the 60 patients treated with R-low-dose-CHOP.

Hematological toxicities during treatment

Previous reports showed that the degree of neutropenia could be influenced by the *FCGR3A* SNP for patients treated with rituximab monotherapy after autologous stem cell transplantation [24] or in combination with chemotherapy [8,25]. We observed that LYSA patients with *FCGR3A* VV genotype (N=32, 39%) were more likely to have at least one febrile neutropenia (grade 3–4) during treatment than *FCGR3A* VF (N=75, 29%) and *FCGR3A* FF (N=69, 32%) genotypes (*P*=0.04). The *FCGR2A* SNP was not associated with the rate of febrile neutropenia. Neither SNP was associated with anemia, thrombocytopenia, or the number of cycles applied with a delay ≥ 5 days.

Discussion

Eight smaller series (51 to 263 DLBCL patients), likely underpowered [13], reported weak and not statistically significant correlations between these two *FCGR* SNPs and prognosis after immunochemotherapy [7–12]. We performed a meta-analysis of two large and independent cohorts to overcome this limitation.

We found no association for the *FCGR3A* SNP with EFS or OS in DLBCL patients treated by rituximab and anthracycline-based chemotherapy, confirming five previous smaller studies [7,8,10–12]. The prognostic effect of the *FCGR3A* SNP has mainly been observed in FL patients treated by single agent rituximab in retrospective studies [5,6,14], although these results were not confirmed prospectively [26]. One explanation for the lack of prognostic value of *FCGR3A* SNP in the context of immunochemotherapy is that the association between chemotherapy and rituximab is deleterious for ADCC effectors. Another hypothesis is that the rituximab dose (375mg/m^2) used in the immunochemotherapy schedule abrogated

the rituximab activity modulation of *FCGR3A* SNP, which was only observed at low concentration (<0.01 μg/mL) in an *in vitro* study [27]. Our data are consistent with results from FL and chronic lymphocytic leukemia in which *FCGR3A* had no prognostic impact when patients were treated by immunochemotherapy [28,29]. With respect to hematological toxicity, *FCGR3A* VV patients had more frequent grade 3–4 neutropenia during immunochemotherapy, which is consistent with previous reports [8,25].

Our results for the *FCGR2A* SNP were unexpected, given that we observed that the low-affinity FCγRIIA 131RR genotype had a modest but significantly better outcome than the high-affinity FCγRIIA 131H carriers. In DLBCL, most studies have not observed any prognostic effect of the *FCGR2A* SNP for patients treated with immunochemotherapy [7,9,10,12,13]. An increase susceptibility to systemic lupus erythematous had been described for *FCGR2A* RR carriers in relation with a reduced ability of FCγRII 131RR to clear immune complexes leading to their increased depositions in tissues [31]. With anti-tumor necrosis factor-α monoclonal antibodies, patients with rheumatoid arthritis who carry FCγRII 131RR genotype had a better clinical response with a reduced clearance of infliximab in the circulation [32]. One hypothesis could be that FCγRII 131RR carriers have a reduced clearance of rituximab that increases anti-CD20 availability. Unfortunately, no rituximab dosage was available in our series to explore this hypothesis. In the study of Muller et al. assessing the rituximab clearance in DLBCL, they observed that after completion of immunochemotherapy, rituximab remained detectable in patient sera up to 9 months (median 1.1μg/mL, range 0–2.8) [3]. Whether *FCGR2A* SNP is able to modulate residual rituximab clearance after initial treatment should be investigated with the hypothesis being that *FCGR2A* RR compared to *FCGR2A* H patients retain higher rituximab serum levels that could be active on residual disease. We also observed this trend for *FCGR2A* SNP in FL patients included in PRIMA study [29]. After induction immunochemotherapy, among FL patients randomized in the observational arm, *FCGR2A* RR patients had a non-significant but clear trend for a better 3-year PFS (62.5%) compared to *FCGR2A* HR (52.7%) and *FCGR2A* HH (54.4%) carriers (P=0.26) but in the rituximab maintenance arm, the PFS curves of the three *FCGR2A* genotypes were all superimposed. One hypothesis is that the addition of rituximab every 2 months for 2 years abolished the effect of FCγRIIA 131RR observed after initial treatment in the observational arm.

FCγRIIA is the receptor of the C-reactive protein (CRP) and FCγRIIA 131RR has a better affinity with CRP than FCγRIIA 131H [33]. In pneumococcal diseases, patients with FCγRIIA 131RR have a higher affinity for CRP and an increase of proinflammatory cytokine response [34]. A study found a protective effect of FCγRIIA 131RR for patients with invasive pneumococcal diseases with lower hospital mortality [35]. It would be interesting to investigate whether FCγRIIA modulates inflammatory response in DLBCL. A role in lymphoma pathogenesis cannot be excluded, as the *FCGR2A* SNP has been implicated in lymphoma susceptibility [36].

While sex and tumor burden could affect rituximab clearance and efficacy in DLBCL [2,3], we did not observe any significant associations in analyses stratified by sex or by tumor burden, although power was lower for these analyses. We observed that the better prognosis of *FCGR2A* RR seemed more pronounced in high compared to low ALC patients. It would

be interesting to have a larger patient sample size to investigate if *FCGR2A* RR patients with higher immune effectors have a better benefit of rituximab treatment compared to *FCGR2A* H patients.

One limitation of our study is that patients were not treated homogeneously. In the LYSA trials two types of induction treatment (R-CHOP and R-ACVBP) and different consolidation therapies were used. Patients in the SPORE lacked a controlled treatment trial setting, but both cohorts were very similar from clinical, genotype frequency and outcomes perspectives. We did not perform any correction test in our statistical analysis: the primary objective of the study was to test previously reported effect of *FCGR3A* and *FCGR2A* SNPs in two large prospective DLBCL cohorts and perform a meta-analysis to gain statistical power. Our results for the subgroup analyses should be viewed as exploratory.

In conclusion, in these two large prospective cohorts, we observed no association of the *FCGR3A* rs396991 SNP and DLBCL outcome. Somewhat unexpectedly, the *FCGR2A* rs1801274 SNP influenced DLBCL outcome. While the effect was relatively weak, it suggests a re-evaluation of the relation of FCγRIIA and rituximab clearance and its impact on DLBCL pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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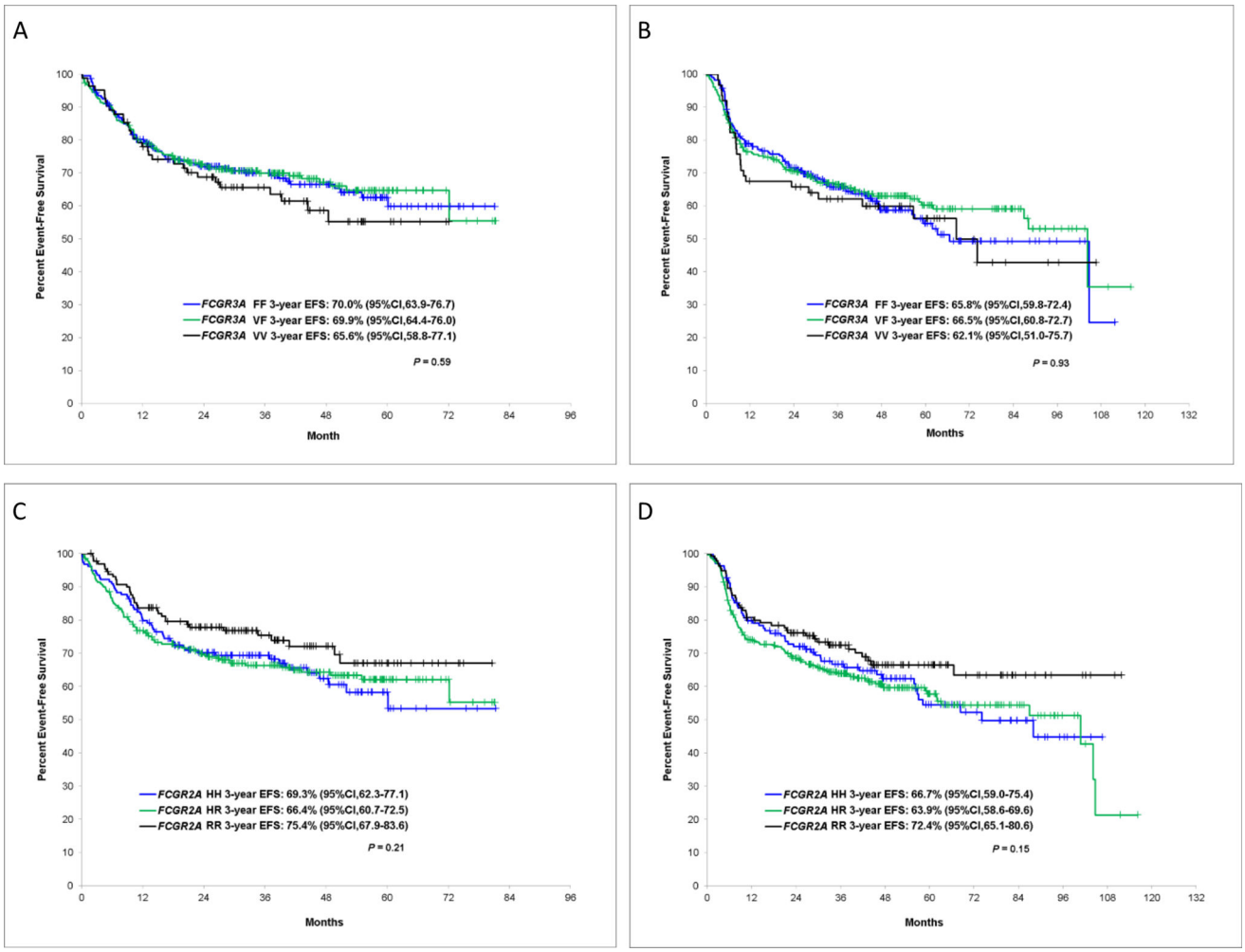

Figure 1.

Event free survival according to *FCGR3A* and *FCGR2A* alleles in LYSA and the SPORE cohorts. *FCGR3A* in LYSA (A) and in the SPORE (B), *FCGR2A* in LYSA (C) and in the SPORE (D)

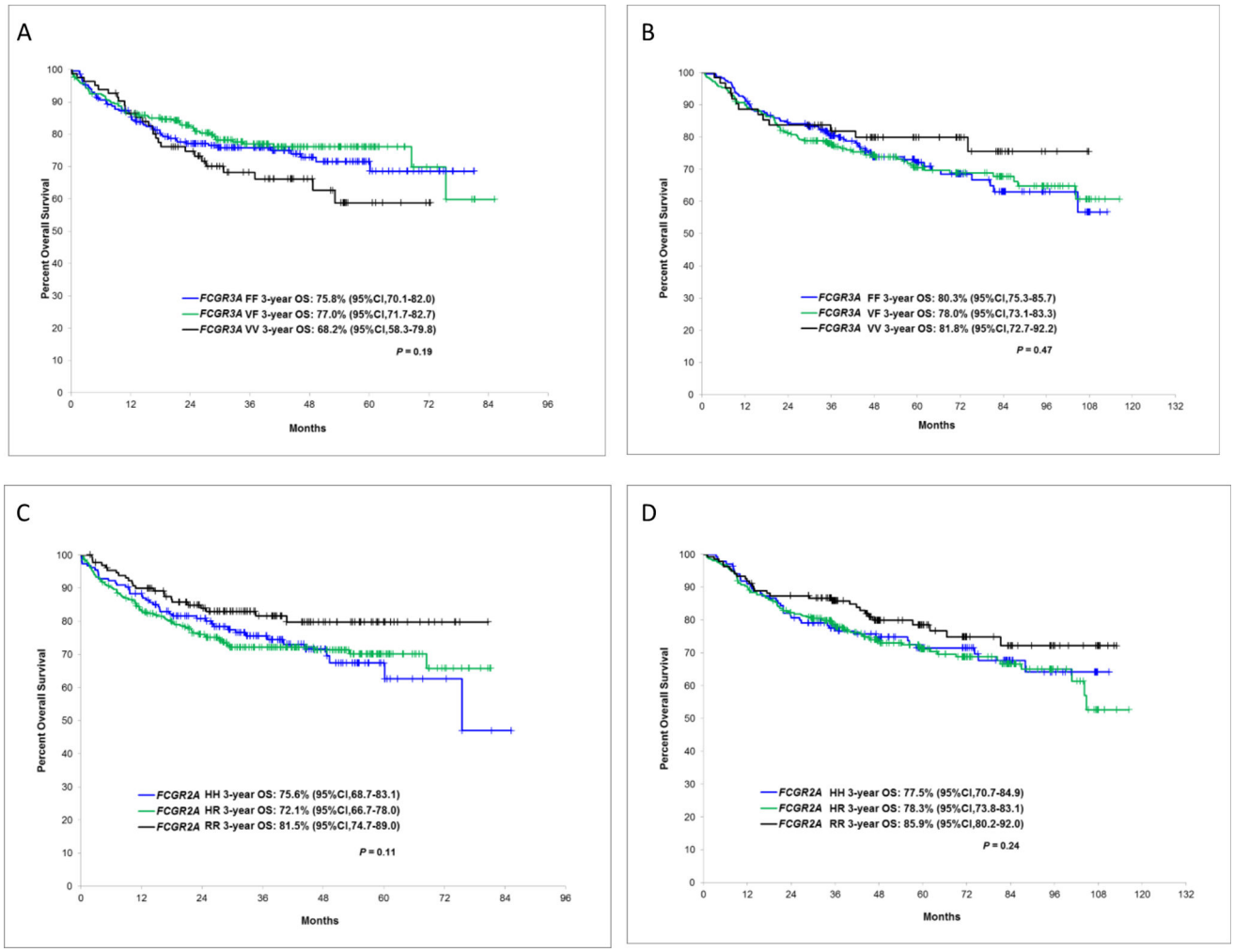

Figure 2.

Overall survival according to *FCGR3A* and *FCGR2A* alleles in LYSA and the SPORE cohorts. *FCGR3A* in LYSA (A) and in the SPORE (B), *FCGR2A* in LYSA (C) and in the SPORE (D)

Table 1

Association of *FCGR3A* rs396991 V allele (ordinal or per allele model) with event-free and overall survival

	EFS						OS					
	LYSA		SPORE		Meta-analysis		LYSA		SPORE		Meta-analysis	
Population	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***
All	1.07 (0.87, 1.32)	0.52	1.01 (0.82, 1.23)	0.93	1.04 (0.90, 1.19)	0.61	1.10 (0.86, 1.39)	0.45	0.91 (0.72, 1.16)	0.45	0.98 (0.83, 1.15)	0.78
R-CHOP*	1.07 (0.85, 1.34)	0.57	1.00 (0.81, 1.24)	0.99	1.03 (0.88, 1.21)	0.68	1.17 (0.91, 1.50)	0.23	0.91 (0.70, 1.18)	0.47	1.03 (0.86, 1.24)	0.72
R-CHOP	1.07 (0.84, 1.35)	0.60	1.01 (0.82, 1.23)	0.93	1.03 (0.89, 1.20)	0.69	1.10 (0.84, 1.44)	0.51	0.91 (0.72, 1.16)	0.45	0.99 (0.83, 1.19)	0.91
Bulky	1.13 (0.76, 1.69)	0.54	1.14 (0.69, 1.89)	0.61	1.13 (0.83, 1.55)	0.43	1.14 (0.73, 1.77)	0.56	0.89 (0.51, 1.54)	0.68	1.04 (0.73, 1.46)	0.84
Non bulky	1.05 (0.82, 1.35)	0.70	0.99 (0.79, 1.24)	0.93	1.02 (0.86, 1.20)	0.85	1.08 (0.81, 1.44)	0.58	0.91 (0.69, 1.19)	0.47	0.99 (0.81, 1.20)	0.88
Male	1.25 (0.94, 1.66)	0.12	0.95 (0.73, 1.25)	0.73	1.08 (0.89, 1.32)	0.41	1.37 (1.00, 1.88)	0.05	0.82 (0.59, 1.13)	0.22	1.06 (0.85, 1.34)	0.59
Female	0.88 (0.64, 1.21)	0.43	1.09 (0.80, 1.49)	0.57	0.98 (0.79, 1.23)	0.89	0.82 (0.56, 1.19)	0.29	1.06 (0.73, 1.52)	0.77	0.93 (0.72, 1.21)	0.60
Low ALC	0.86 (0.63, 1.17)	0.33	1.17 (0.87, 1.57)	0.30	1.01 (0.81, 1.25)	0.95	0.90 (0.64, 1.26)	0.54	1.11 (0.78, 1.59)	0.56	0.99 (0.78, 1.27)	0.96
High ALC	1.40 (1.03, 1.91)	0.03	0.80 (0.59, 1.09)	0.16	1.06 (0.85, 1.32)	0.59	1.53 (1.06, 2.20)	0.02	0.69 (0.47, 0.99)	0.05	1.03 (0.79, 1.33)	0.85

Hazard Ratio (HR) is per V allele (ordinal model, modeled as 0, 1, or 2). A HR>1 corresponds to deleterious effect for event-free survival (EFS) or overall survival (OS) of the V allele; HR<1 correspond to protective effect.

EFS: event-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; R-CHOP: rituximab, cyclophosphamide, vincristine and prednisone; ALC: absolute lymphocyte count. Low and high absolute lymphocyte count (ALC) are defined by ALC< and ≥1.0×10^9/L.

*R-CHOP regimen including 60 patients older than 80 years old treated with R-low-dose-CHOP

Table 2

Association of *FCGR2A* rs1801274 R allele (ordinal or per allele model) with event-free and overall survival

	EFS						OS					
	LYSA		SPORE		Meta-analysis		LYSA		SPORE		Meta-analysis	
Population	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***
All	0.86 (0.70, 1.05)	0.15	0.88 (0.73, 1.07)	0.20	0.87 (0.76, 0.99)	0.04	0.82 (0.65, 1.04)	0.10	0.88 (0.70, 1.10)	0.25	0.86 (0.73, 1.00)	0.05
R-CHOP*	0.88 (0.71, 1.10)	0.27	0.87 (0.71, 1.07)	0.19	0.88 (0.75, 1.02)	0.09	0.81 (0.63, 1.04)	0.10	0.89 (0.70, 1.13)	0.34	0.85 (0.72, 1.01)	0.07
R-CHOP	0.85 (0.67, 1.06)	0.15	0.88 (0.73, 1.07)	0.20	0.87 (0.75, 1.00)	0.05	0.78 (0.60, 1.02)	0.06	0.88 (0.70, 1.10)	0.25	0.84 (0.70, 0.99)	0.04
Bulky	0.85 (0.58, 1.26)	0.42	1.18 (0.76, 1.83)	0.46	0.98 (0.73, 1.31)	0.90	0.72 (0.46, 1.12)	0.14	1.29 (0.76, 2.20)	0.34	0.91 (0.65, 1.28)	0.60
Non bulky	0.87 (0.69, 1.11)	0.27	0.84 (0.68, 1.04)	0.10	0.85 (0.73, 1.00)	0.05	0.88 (0.67, 1.16)	0.37	0.82 (0.64, 1.06)	0.13	0.85 (0.71, 1.02)	0.09
Male	0.80 (0.62, 1.04)	0.10	0.90 (0.70, 1.16)	0.41	0.85 (0.71, 1.02)	0.08	0.74 (0.55, 1.00)	0.05	0.87 (0.64, 1.17)	0.35	0.80 (0.65, 0.99)	0.04
Female	0.94 (0.69, 1.30)	0.73	0.89 (0.66, 1.18)	0.41	0.91 (0.74, 1.13)	0.40	0.97 (0.67, 1.42)	0.89	0.90 (0.64, 1.27)	0.57	0.93 (0.73, 1.20)	0.60
Low ALC	0.91 (0.68, 1.23)	0.55	0.87 (0.65, 1.16)	0.33	0.89 (0.72, 1.09)	0.27	0.88 (0.63, 1.22)	0.43	0.85 (0.60, 1.21)	0.36	0.86 (0.68, 1.10)	0.23
High ALC	0.79 (0.59, 1.07)	0.13	0.91 (0.68, 1.20)	0.49	0.85 (0.69, 1.04)	0.12	0.75 (0.52, 1.07)	0.12	0.89 (0.63, 1.24)	0.48	0.82 (0.64, 1.05)	0.11

Hazard Ratio (HR) is per R allele (ordinal model, modeled as 0, 1, or 2). A HR>1 corresponds to deleterious effect for event-free survival (EFS) or overall survival (OS) of the R allele; HR<1 correspond to protective effect

EFS: event-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; R-CHOP: rituximab, cyclophosphamide, vincristine and prednisone; ALC: absolute lymphocyte count. Low and high absolute lymphocyte count (ALC) are defined by ALC< and ≥1.0 × 10^9/L.

*R-CHOP regimen including 60 patients older than 80 years old treated with R-low-dose-CHOP

Table 3

Association of low-affinity FCγRIIA RR versus high-affinity FCγRIIA H with event-free and overall survival

	EFS						OS					
	LYSA		SPORE		Meta-analysis		LYSA		SPORE		Meta-analysis	
Population	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***
All	0.71 (0.49, 1.04)	0.08	0.72 (0.52, 1.01)	0.06	0.71 (0.56, 0.91)	0.01	0.62 (0.40, 0.98)	0.04	0.71 (0.48, 1.07)	0.10	0.68 (0.51, 0.91)	0.01
R-CHOP*	0.75 (0.50, 1.12)	0.16	0.76 (0.53, 1.08)	0.12	0.75 (0.58, 0.98)	0.04	0.60 (0.37, 0.98)	0.04	0.77 (0.51, 1.16)	0.21	0.69 (0.51, 0.95)	0.02
R-CHOP	0.75 (0.50, 1.14)	0.18	0.72 (0.52, 1.01)	0.06	0.74 (0.57, 0.95)	0.02	0.64 (0.39, 1.06)	0.09	0.71 (0.48, 1.07)	0.10	0.69 (0.50, 0.94)	0.02
Bulky	0.49 (0.22, 1.09)	0.08	0.71 (0.30, 1.70)	0.44	0.58 (0.32, 1.05)	0.07	0.24 (0.07, 0.77)	0.02	1.19 (0.49, 2.89)	0.71	0.66 (0.32, 1.34)	0.25
Non bulky	0.82 (0.54, 1.25)	0.35	0.75 (0.52, 1.07)	0.11	0.78 (0.59, 1.02)	0.07	0.83 (0.51, 1.35)	0.45	0.67 (0.43, 1.06)	0.09	0.74 (0.53, 1.03)	0.08
Male	0.65 (0.39, 1.07)	0.09	0.77 (0.49, 1.20)	0.25	0.71 (0.51, 0.99)	0.05	0.57 (0.31, 1.03)	0.06	0.69 (0.40, 1.21)	0.19	0.63 (0.42, 0.95)	0.03
Female	0.81 (0.46, 1.41)	0.45	0.71 (0.43, 1.18)	0.19	0.75 (0.52, 1.10)	0.14	0.72 (0.36, 1.42)	0.34	0.77 (0.43, 1.40)	0.40	0.75 (0.48, 1.17)	0.20
Low ALC	0.88 (0.52, 1.49)	0.63	0.80 (0.50, 1.29)	0.36	0.83 (0.59, 1.19)	0.31	0.74 (0.40, 1.37)	0.34	0.82 (0.47, 1.46)	0.51	0.78 (0.51, 1.19)	0.25
High ALC	0.55 (0.30, 1.00)	0.05	0.63 (0.37, 1.08)	0.09	0.60 (0.40, 0.89)	0.01	0.49 (0.23, 1.03)	0.06	0.61 (0.32, 1.16)	0.13	0.56 (0.34, 0.90)	0.02

With a genotypic model, the prognostic effect of the low-affinity receptor FCγRIIA RR was compared to the high-affinity receptor FCγRIIA H (HH or HR). A hazard ratio (HR)>1 corresponds to deleterious effect for event-free survival (EFS) or overall survival (OS) of FCγRIIA RR; a HR<1 correspond to protective effect.

EFS: event-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; R-CHOP: rituximab, cyclophosphamide, vincristine and prednisone; ALC: absolute lymphocyte count. Low and high absolute lymphocyte count (ALC) are defined by ALC< and ≥1.0 × 10^9/L.

*R-CHOP regimen including 60 patients older than 80 years old treated with R-low-dose-CHOP