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Immunoglobulin G Fc receptor polymorphisms do not correlate with response to chemotherapy or clinical course in patients with follicular lymphoma

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Abstract

Recently, immunoglobulin G Fc receptor (FcγR) polymorphisms have been found to correlate with the clinical response to rituximab or idiotype vaccine in patients with follicular lymphoma. Two critical questions are whether the FcγR polymorphisms correlate with the clinical outcomes after chemotherapy alone in patients with follicular lymphoma and whether they can be explained by linking to underlying biology of follicular lymphoma. This is an important issue because the clinical decisions about the use of antibody therapy may be based on the FcγR polymorphisms of these patients. Here, we analyzed the FcγRIIIa 158 V/F, FcγRIIa 131 H/R, and FcγRIIb 232 I/T polymorphisms in a group of 188 patients with follicular lymphoma who were treated with chemotherapy without rituximab initially. In the current study, FcγR polymorphisms neither correlated with response rate or time to progression after induction chemotherapy, nor with time to the initial therapy or overall survival after diagnosis. Our results confirm that the correlation between FcγR polymorphisms and clinical outcome is specific to immunotherapy such as rituximab and idiotype vaccination, and not due to any effect on the underlying clinical behavior of the disease or chemotherapy response.

Keywords

Follicular lymphoma; Fc receptor

Introduction

We and others have found that Fc receptor (FcγR) polymorphisms correlated with the clinical outcomes of patients with lymphoma treated with single agent rituximab [1–3] or patients who received idiotype vaccines after induction chemotherapy [4]. These FcγR allotypes are thought to affect the ability of effector cells such as natural killer cells and macrophages to mediate antibody-dependent cellular cytotoxicity (ADCC) against antibody-coated lymphoma cells. However, this observation has been mainly limited to patients with follicular lymphoma, but was not found in patients with lymphoma with other histologies [5] or patients who were treated with other anti-lymphoma antibodies [6]. Although there is one report linking FcγRIIIa polymorphism to the clinical outcome of patients with diffuse large

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B cell lymphoma, who were treated with rituximab-CHOP [7], others have not found such correlation in patients treated with rituximab–chemotherapy combinations [8,9]. Two critical questions are whether the FcγR polymorphisms correlate with the clinical outcomes in patients with follicular lymphoma who were treated with chemotherapy alone and whether they can be explained by correlating to underlying biology of follicular lymphoma. This hypothesis is supported by a recent publication using gene expression profile of follicular lymphoma tumor biopsies to identify the importance of tumor-infiltrating immune cells, including FcγR-bearing effector cells, in predicting the survival of these patients [10]. One possibility is that a spontaneous anti-tumor immune response such as auto-antibodies against antigens from lymphoma cells found in patients regulates the behavior of lymphoma tumor cells [11]. This is an important issue because the clinical decisions about the use of antibody therapy may be based on the FcγR polymorphisms of these patients. To address this question, we analyzed the FcγR polymorphisms of 188 patients with follicular lymphoma who were treated with induction chemotherapy without rituximab and examined the possible correlation with clinical outcome in these patients.

Methods

Patient population

This retrospective study included 188 patients with follicular lymphoma, who were diagnosed and treated at Stanford Medical Center between 1974 and 2004. These patients were chosen because their tissue samples were available for FcγR polymorphism analysis. The characteristics of these patients are shown in Supplement Table 1. All patients received combination chemotherapy without rituximab as the initial therapy (Table I). This study was conducted according to an institutional review board-approved protocol and informed consent was obtained from all patients for the tissue sample use and clinical information analysis.

Determination of clinical outcomes

Three clinical outcomes were analyzed. The first was response to chemotherapy. The response rate was determined within 2 months after the last chemotherapy infusion based on physical examinations, blood counts, and radiographic studies. In general, disappearance of all measurable diseases after chemotherapy was scored as complete response (CR), tumor shrinkage of ≥50% of original size but measurable residual disease was scored as partial response (PR), and any tumor shrinkage of <50% was determined as no response. The Cheson response criteria [12] were adopted for patients treated after the year 2000. The monitoring for relapsed disease was conducted by regular follow-up after chemotherapy every 3–4 months for the first 2–3 years. Most of the patients then had semi-annual or annual follow-up.

The second outcome was the time to the initial therapy, which was defined as the time interval between the day of lymphoma diagnosis and the day of initial lymphoma therapy. The decision for administering initial therapy was made by a small group of physicians at our institute following a uniform policy [13]. The usual reason for therapy was bulky disease, acceleration of tumor growth, or developing symptoms. The final clinical outcome was the overall survival (OS), defined by the time interval between the day of lymphoma diagnosis and the day of death. All the three clinical end points analyzed in this study were determined by the information from Stanford Lymphoma Clinical Data Base.

Analysis of FcγRIIIa, FcγRIIa, and FcγRIIb polymorphism

Genomic DNA was prepared from tumor cells or peripheral blood mononuclear cells using a DNA extraction kit (QIAGEN, Valencia, CA). In 25 cases, DNA was prepared from the

serum as described [14]. Genotyping of FcγRIIIa 158 valine/phenylalanine (V/F), FcγRIIa 131 histidine/arginine (H/R), and FcγRIIb 232 isoleucine/threonine (I/T) polymorphisms was performed using TaqMan technology on an ABI Prism 7900HT Sequence Detector System (Applied Biosystems, Foster City, CA). Probe and primers were obtained from Applied Biosystems. In brief, FcγRIIIa-, FcγRIIa-, and FcγRIIb-specific primer pairs flanking the polymorphic sites were used for amplifying genomic DNA. Probes specific to FcγRIIIa 158 V, FcγRIIa 131 H, and FcγRIIb 232 T alleles were labeled with VIC at the 5′ end and nonfluorescent quencher (NFQ) at the 3′ end. Probes specific to FcγRIIIa 158 F, FcγRIIa 131 R, and FcγRIIb 232 I alleles were labeled with FAM at the 5′ end and NFQ at the 3′ end. The polymerase chain reactions (PCR) were prepared in a final volume of 5 μL, with final concentration of 1X TaqMan Universal PCR Master Mix (Applied Biosystems, Foster City, CA), 4 ng genomic DNA, primer pairs and two probes (VIC-and FAM-labeled) for individual FcγR polymorphism. The reaction mixtures were assembled at 4°C, followed by PCR consisting of 2 min 50°C UNG initiation, AmpliTaq Gold activation at 95°C for 10 min, followed by 40 cycles of 92°C for 15 s and 60°C for 1 min. Each sample was set up as duplicate. The final determination of FcγR genotypes was performed using Allelic Discrimination protocol in SDS software provided by Applied Biosystems.

Statistical analysis

The difference in response rate to induction chemotherapy was determined by two-sided Fisher exact test. The median time to progression (TTP) and difference in the progression free survival (PFS) after chemotherapy and OS were determined using Kaplan–Meier estimation (PRISM for Macintosh, GraphPad Software, San Diego, CA). Using Cox Proportional Hazard Model, an analysis including age (≥ or <60 years), follicular large cell histology at diagnosis, stage (III *vs*. IV), presence of clinical symptoms, and FcγRIIIa, FcγRIIa, and FcγRIIb genotypes was performed to identify independent prognostic variables influencing the time to the initial therapy (StatView 5.0.1, SAS, Cary, NC). An analysis including age (≥ or <60 years), follicular large cell histology at diagnosis, stage (III *vs*. IV), presence of clinical symptoms, male gender, documentation of transformation to diffuse large B cell, receiving high-dose therapy/autologous hematopoietic cell transplant, receiving rituximab-containing regimens for relapsed disease, FcγRIIIa, FcγRIIa, and FcγRIIb genotypes was performed to identify independent prognostic variables influencing the OS (StatView 5.0.1, SAS, Cary, NC).

Results

Immunoglobulin G Fc receptor polymorphism and chemotherapy response

All 188 patients were genotyped for FcγRIIIa 158 V/F, FcγRIIa 131 H/R, and FcγRIIb 232 I/T polymorphisms. For FcγR IIIa, 26 (14%) patients were 158 V/V, 76 (40%) were 158 V/F, and 86 (46%) were 158 F/F. For FcγR IIa, 42 (22%) patients were 131 H/H, 98 (53%) were 131 H/R, and 48 (25%) were 131 R/R. For FcγR IIb, 154 (82%) patients were 232 I/I, 33 (18%) were 232 I/T, and 1 (<1%) was 232 T/T. Patients with different FcγR genotypes were not different in terms of gender distribution, average age at the time of diagnosis, histology, disease stage, or fraction of patients with clinical symptoms (Supplement Table I).

In this sample set, all patients received chemotherapy without rituximab as the initial therapy (Table I). Overall, the response rate was 95% (46% CR and 49% PR). We first compared the response rate and TTP after the induction chemotherapy according to their FcγR polymorphisms. As shown in Table II, there was no difference in the overall response rate or CR rate in patients with different FcγR genotypes. For FcγRIIIa, the estimated PFS at 2 years post-chemotherapy was 29% for 158 V/V, 38% for 158 V/F, and 40% for 158 F/F. The median TTP estimate of patients with 158 V/V was not different from that of other

patients [Figure 1(a)]. Similarly, the FcγRIIa 131 H/R polymorphism had no impact on TTP in this chemotherapy-treated patient group. The estimated 2-year PFS was 48% for 131 H/H, 37% for 131 H/R, and 29% for 131 R/R [Figure 1(b)]. Recently, a polymorphism of isoleucine and threonine at position 232 of the transmembrane domain of inhibitory FcγRIIb has been identified to affect its signaling function [15,16]. We therefore, tested whether this polymorphism has an impact on clinical outcomes. In this sample set, only one patient had 232 T/T genotype. Therefore, only 232 I/I and 232 I/T genotypes were compared. The estimated 2-year PFS was 38% for 232 I/I and 33% for 232 I/T with median TTP not different between the two groups [Figure 1(c)].

Immunoglobulin G Fc receptor polymorphism and time to initial therapy

The reason for administering the initial therapy is usually due to bulky disease, acceleration of tumor growth, or the development of symptoms. In our institute, decision was made following a uniform policy [13]. We tested whether FcγR polymorphisms were correlated with the time between diagnosis and the initial therapy. The median time to the initial therapy was not different in patients with FcγRIIIa 158 V/V, compared with patients with V/F or F/F (V/V: 4.6 months, range 0.8–92.2; V/F: 6.2 months, range 0.3–117.7; F/F: 4.5 months, range 0.2–127.7). Similarly, the FcγRIIa 131 H/R polymorphism did not affect the time to the initial therapy. The median time to the initial therapy was 4.1 (range 0.3–117.7), 6.1 (range 0.2–127.7), and 3.6 (range 0.2–110.1) months for H/H, H/R, and R/R, respectively. For FcγRIIb polymorphism, the median time to the initial therapy was not different between the I/I and I/T with 5.5 and 3.3 months for the two groups, respectively. Using Cox proportional hazard model, stage IV disease and the presence of clinical symptoms emerged as two independent predictors for shorter time to the initial therapy (Table III). In this analysis, age ≥60 had a minor impact, whereas FcγRIIIa 158 V/V, FcγRIIa 131 H/H, FcγRIIb 232 I/I genotypes and follicular large cell histology had no impact.

Immunoglobulin G Fc receptor polymorphism and overall survival

We further determined the impact on the OS after diagnosis for this group of patients. The OS at 10 years was 56% for FcγRIIIa 158 V/V, 65% for 158 V/F, and 64% for 158 F/F. The OS estimate of patients with 158 V/V was not different from that in patients with other genotypes [Figure 2(a)]. For FcγRIIa, the 10-year OS was 47% for 131 H/H, 70% for 131 H/R, and 62% for 131 R/R with OS estimate not different between different genotypes [Figure 2(b)]. For FcγRIIb, the 10-year OS was 62% for 232 I/I, and 68% for 232 I/T. The one 232 T/T patient had less than 7 years follow-up. The OS estimates were not different between 232 I/I and 232 I/T [Figure 2(c)]. Using Cox proportional hazard model, having clinical symptoms and age ≥60 years emerged as the only two independent negative predictors for OS, where-as none of the others was identified as predictor (Table IV). Although follicular lymphoma international prognostic index (FLIPI) score has been shown to correlate to OS [17], we were unable to perform such an analysis in the current study because of lack of complete information at the time of diagnosis to calculate the FLIPI score in more than 60% of the patients. The most common missing information is the lactate dehydrogenase (LDH) value at the time of diagnosis.

Discussion

The FcγR regulates FcγR-bearing immune cells following engagement by the Fc of immunoglobulin [18–20] and facilitates the clearance of immune complexes [21]. Polymorphisms of FcγRs have been found to influence the natural history of disease and efficacy of immunotherapies by affecting FcγR-bearing effector cells [1–4,22–25]. On the effector cells, FcγRIIIa (CD16) and FcγRIIa (CD32a) activate whereas FcγRIIb (CD32b)

inhibits activation. Previously, we and others have found that Fc*γ*RIIIa 158 V/V and Fc*γ*RIIa 131 H/H genotypes independently correlate with response to rituximab in patients with follicular lymphoma [1,2]. We also identified Fc*γ*RIIIa 158 V/V genotype as a predictor for longer TTP after idiotype vaccination following induction chemotherapy [4,34]. It is believed that these two favorable Fc*γ*R genotypes affect the efficacy of ADCC due to higher affinity to the Fc of therapeutic antibodies (such as rituximab and anti-idiotype antibodies induced by vaccination). However, the correlation between Fc*γ*R polymorphisms and rituximab response has only been observed in patients with follicular lymphoma or Waldenstrom macroglobulinemia [3] but not in patients with chronic lymphocytic leukemia (CLL) [5]. The reason for this discrepancy is unknown. One possibility is that rituximab mediates its anti-tumor effect *via* different mechanisms in different lymphomas. This notion has been supported by the evidence of active complement-mediated cytotoxicity and apoptosis in patients with CLL after rituximab infusion [26–28]. The other possibility is that Fc*γ*R polymorphisms correlate with the differences in the underlying biology of the lymphoma cells among patients with follicular lymphoma, which is not specific to antibody therapy.

Several reports have associated tumor-infiltrating immune cells with the clinical outcomes including survival of patients with follicular lymphoma [10,29,30]. Therefore, the Fc*γ*R polymorphism may affect the natural course of patients with follicular lymphoma by affecting the function of Fc*γ*R-bearing immune cells. In the current report, we found no impact of Fc*γ*R polymorphisms on the time to initial therapy or OS. Patients with follicular lymphoma usually do not need therapy at diagnosis and only require therapy when the tumors become bulky, fast growing, or when patients experience symptoms. The ‘need for therapy’ is subjective and very much in the ‘eye of the beholder’. Although all patients with follicular lymphoma in our institute were accessed by a small group of physicians who follow a policy that has been published previously [13], this end point may still be a difficult one to draw conclusion due to the variability between different physicians. In addition, the number of patients in the current study is still relatively small (n = 188) because of the limitation of tissue availability.

The three Fc*γ*R polymorphisms did not have an impact on the OS. Consistent with the previous notion, the OS was negatively affected by the presence of clinical symptoms and age ≥60 years (Table IV). This finding is in accordance with a recent report showing no association between Fc*γ*RIIIa polymorphism and OS in 194 patients with non-Hodgkin lymphoma with different histologies, which includes patients with follicular lymphoma [31]. However, almost all of the patients in the current study have received a variety of treatments, including chemotherapy, immunotherapy, bone marrow transplantation, and radiotherapy over their lifetime. The OS of these patients may be affected not just by the natural course of their underlying disease but also largely by their response to individual treatment. To this end, we found no impact of Fc*γ*R polymorphisms on the response rate to chemotherapy or TTP after induction chemotherapy (Table III, Figure 1). Although rituximab–chemotherapy combination has become a standard therapy for B cell lymphoma, whether rituximab eliminates tumor cells with ADCC when it is used in combination remains to be answered.

To support the role of ADCC, there is now evidence linking Fc*γ*RIIIa polymorphism to the clinical outcome of patients with diffuse large B cell lymphoma who were treated with rituximab–chemotherapy combination [7]. However, other studies showed no such association [8,9]. Our current results further confirm that our previous observation of the association between Fc*γ*RIIIa and Fc*γ*RIIa polymorphisms and clinical outcome of rituximab-treated and vaccinated-patients is specific to immunotherapy manipulation. Consistent with this notion, the association between these two Fc*γ*R polymorphisms and

response to therapy was also observed with other therapeutic antibodies including anti-HER2/Neu and anti-epidermal growth factor receptor antibodies [32,33].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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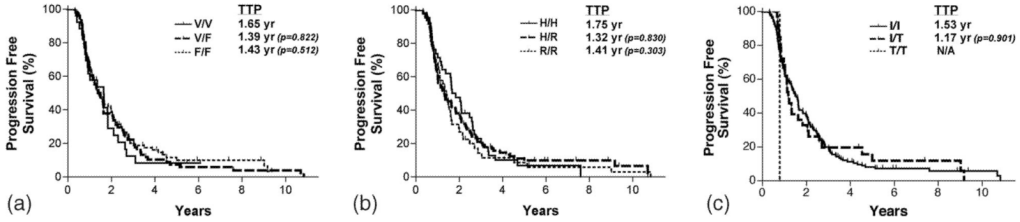

Figure 1.

Progression free survival after chemotherapy by FcγR polymorphism. Progression free survival curves were plotted by FcγRIIIa 158 V/F (a), FcγRIIa 131 H/R (b), and FcγRIIb 232 I/T (c) genotype. TTP, median time to progression.

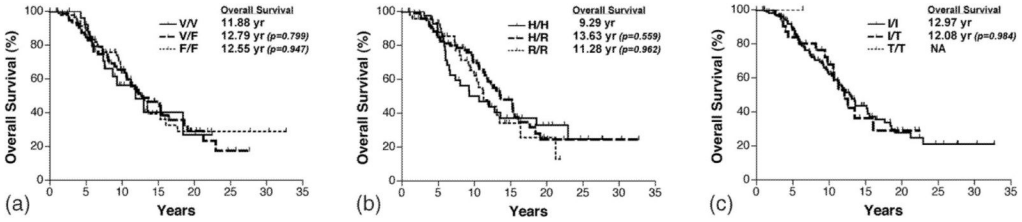

Figure 2.

Kaplan–Meier estimates of overall survival by FcγR polymorphisms. Overall survival curves were plotted by FcγRIIIa 158 V/F (a), FcγRIIa 131 H/R (b), and FcγRIIb 232 I/T (c) genotype. OS, median overall survival after diagnosis.

Table I

Induction chemotherapy.

	***n* = 188**
Induction chemotherapy	
Ch (P)	34
CVP	99
CVP/F	7
CVP/CHOP	16
CHOP	16
CEPP	3
CMOPP	6
MACOP-B	2
Other	5
Response to chemotherapy	
CR	86
PR	93
NR/PD	9

Ch, chlorambucil; P, prednisone; CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; F, fludarabine; CEPP, cyclophosphamide, etoposide, procarbazine, prednisone; CMOPP, cyclophosphamide, mechlorethamine, vincristine, prednisone, procarbazine; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; CR, complete response/complete response unconfirmed; PR, partial response; NR/PD, no response/progressive disease.

Table II

Clinical response to chemotherapy according to their Fc*γ* receptor polymorphism.

	FcγRIIIa			
	V/V	**V/F**	**F/F**	***p****
CR	12/26	35/76	39/86	
Objective response†	23/26 (88%)	72/76 (95%)	84/86 (98%)	*0.125*
	FcγRIIa			
	H/H	H/R	R/R	
CR	26/42	43/98	17/48	
Objective response	42/42 (100%)	94/98 (96%)	43/48 (90%)	*0.062*
	FcγRIIb			
	I/I	I/T	T/T	
CR	68/154	18/33	0/1	
Objective response	146/154 (95%)	32/33 (97%)	1/1 (100%)	*0.849*

*Objective response includes PR, partial response and CR, complete response/complete response unconfirmed.

†All *p* values are two-sided Fisher's exact test.

Table III

Prognostic factors for time to first treatment: Cox proportional hazard model.

	Relative benefit*	CI	p†
158 V/V	1.05	0.68–1.63	*0.812*
131 H/H	0.99	0.69–1.41	*0.948*
232 I/I	1.30	0.88–1.92	*0.191*
Stage IV	0.52	0.37–0.73	*0.0002*
Clinical symptoms‡	0.37	0.23–0.60	*<0.0001*
Age ≥60	0.60	0.38–0.95	*0.030*
Follicular Large	1.07	0.57–2.01	*0.835*

*Relative benefit: to have longer freedom from treatment from diagnosis, CI: 95% confidence intervals.

†All *p* values are two-sided and considered to be statistically significant for $p < 0.05$.

‡Clinical symptoms: fever, night sweats, weight loss.

Table IV

Prognostic factors for overall survival: Cox proportional hazard model.

	Relative benefit*	CI	*p*†
158 V/V	1.03	0.55–1.93	*0.935*
131 H/H	0.73	0.44–1.21	*0.223*
232 I/I	1.28	0.72–2.29	*0.397*
Stage IV	0.70	0.43–1.14	*0.149*
Clinical symptoms‡	0.50	0.25–0.99	*0.049*
Age ≥60	0.40	0.21–0.75	*0.004*
Male gender	1.08	0.69–1.70	*0.728*
Bone marrow transplant	0.89	0.51–1.54	*0.667*
Follicular large	0.88	0.21–1.04	*0.062*
Transformation	0.87	0.50–1.49	*0.609*
Rituximab	1.46	0.90–2.36	*0.123*

*Relative benefit: to have longer freedom from death from diagnosis. CI: 95% confidence intervals.

†All *p* values are two-sided and considered to be statistically significant for $p < 0.05$.

‡Clinical symptoms: fever, night sweats, weight loss.