

Immunoglobulin G fragment C receptor polymorphisms and KRAS mutations: Are they useful biomarkers of clinical outcome in advanced colorectal cancer treated with anti-EGFR-based therapy?

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KRAS mutations have been identified as a strong predictor of resistance to anti-epidermal growth factor receptor (EGFR) therapies. Besides inhibiting the EGFR pathway, anti-EGFR monoclonal antibodies may exert antitumor effects through antibody-dependent cell-mediated cytotoxicity (ADCC). Through this mechanism, the antibody fragment C portion (Fc γ) interacts with Fc receptors (Fc γ Rs) expressed by immune effector cells. We investigated the association of Fc γ R polymorphisms and *KRAS* mutation with the clinical outcome of 104 refractory metastatic colorectal cancer (mCRC) patients treated with anti-EGFR antibodies. Fc γ R11a-H131R and Fc γ R11a-V158F polymorphisms were analyzed in genomic DNA using a 48.48 dynamic array on the BioMark system (Fluidigm, South San Francisco, CA, USA). Tumor tissues from 96 cases were screened for *KRAS* mutations. *KRAS* mutation was associated with a lower response rate (RR) ($P = 0.035$) and a shorter progression-free survival (PFS) (3 vs 7 months; $P = 0.36$). Fc γ R11a-H131R and Fc γ R11a-V158F polymorphisms did not show statistically significant associations with response, PFS, or *KRAS* status. In the logistic regression analysis, *KRAS* status ($P = 0.04$) and skin toxicity ($P = 0.03$) were associated with RR. By multivariate analysis, the clinical risk classification ($P = 0.006$) and skin toxicity ($P < 0.0001$) were found to be independent risk factors for PFS. In conclusion, the Fc γ R11a and Fc γ R11a polymorphisms are not useful as molecular markers for clinical outcome in mCRC patients. To date, the EORTC (European Organization for Research and Treatment of Cancer Classification), skin toxicity, and *KRAS* status are the only reliable biomarkers to identify patients that would benefit from anti-EGFR therapy. (*Cancer Sci* 2010; 101: 2048–2053)

Colorectal cancer is one of the most frequent causes of cancer deaths worldwide. Survival has improved in the last decade due to the development of new combinations of chemotherapy and to the recent introduction of targeted therapies.

Two anti-epidermal growth factor receptor (EGFR) antibodies (cetuximab and panitumumab) show activity in metastatic colorectal cancer (mCRC). Cetuximab, a chimeric immunoglobulin 1 (IgG1) monoclonal antibody, targeted against the extracellular domain of the EGFR, has demonstrated efficacy in chemorefractory mCRC patients.^(1,2) Recently, the phase III trial CRYSTAL conducted by Van Cutsem *et al.* showed that first-line treatment with cetuximab plus infusional fluorouracil/leucovorin plus irinotecan (FOLFIRI) reduced the risk of progression of metastatic colorectal cancer as compared with FOLFIRI alone. This study also demonstrated that the benefit of cetuximab was limited to patients with *KRAS* wild-type tumors.⁽³⁾ Panitumumab, a fully

human monoclonal IgG2 antibody that targets the EGFR, was approved as monotherapy for patients with *KRAS* wild-type tumors after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens.⁽⁴⁾

The investigation of molecular markers that could potentially predict clinical response or resistance to anti-EGFR is of high interest to avoid unnecessary drug toxicity and reduce treatment costs. *KRAS* mutation has been associated with the inefficacy of cetuximab and panitumumab^(3,5) and to date remains the most relevant biological marker of anti-EGFR resistance. However, as *KRAS* status cannot predict the clinical outcome in cases with a wild-type genotype, the search of novel markers independent of *KRAS* status is warranted. Cetuximab, and possibly panitumumab may exert anti-tumor effects by means of antibody-dependent cell-mediated cytotoxicity (ADCC). The antibody fragment C portion (Fc γ) interacts with Fc receptors (Fc γ Rs) expressed by immune effector cells.⁽⁶⁾ Polymorphisms have been described in genes coding for Fc γ R11a and in Fc γ R11a. A histidine/arginine polymorphism at position 131 for the Fc γ R11a gene and valine/phenylalanine polymorphism at position 158 for the Fc γ R11a gene have been reported to be functionally relevant in the ADCC mechanism.

The aim of this study was to investigate the association of the above-mentioned Fc γ R polymorphisms and *KRAS* mutation with the clinical outcome of refractory mCRC patients treated with cetuximab or panitumumab in monotherapy or in combination with chemotherapy.

Materials and Methods

Eligible patients. A total of 104 patients (66 males, 38 females; median age, 64 years) with histopathologically proven metastatic colorectal adenocarcinoma, who failed at least one prior chemotherapy regimen, were included in this study. The patients were treated from 2004 to 2009 with cetuximab or panitumumab as monotherapy or in combination with chemotherapy. Relevant clinical data (gender, age, Eastern Cooperative Oncology Group [ECOG] performance status score, etc.) were obtained from clinical records. Patients were classified according to the European Organization for Research and Treatment of Cancer (EORTC) clinical model validated by Köhne *et al.*⁽⁷⁾ Skin toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). The response to treatment was evaluated every 2 to 3 months by tomodesitometry according to the Response Evaluation Criteria in Solid

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Table 1. Baseline characteristics of metastatic colorectal cancer patients treated with anti-EGFR based therapy (n = 104)

	No.	%
Mean age, years	64	
Range	34–85	
Sex		
Female	38	36
Male	66	64
ECOG performance status score		
0–1	79	76
2	25	24
Anatomic site		
Right colon	21	20
Left colon	10	10
Sigmoid	34	33
Rectosigmoid	10	10
Rectum	28	27
No. previous lines of chemotherapy		
1	46	44
2	46	44
3	8	8
4	4	4
Clinical classification		
Low risk	30	29
Intermediate risk	49	47
High risk	25	24
Treatment		
Cetuximab + irinotecan/FOLFIRI	72/14	69/13
Cetuximab + FOLFOX/capecitabine	5/1	5/1
Panitumumab + Irinotecan	8	8
Panitumumab alone	4	4
Tumor response		
Complete response	1	1
Partial response	19	18
Stable disease	44	42
Progressive disease	35	34

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FOLFIRI, fluororacil, leucovorin and irinotecan; FOLFOX, fluororacil, leucovorin and oxaliplatin.

Tumours (RECIST)⁽⁸⁾ and classified as: (i) complete response (CR); (ii) partial response (PR); (iii) stable disease (SD); or (iv) progressive disease (PD). For the statistical analysis, the best tumor response was selected. The median follow-up time was 9.5 months (range, 0.5–44 months). All patients signed an informed consent for tissue and blood collection for the study of molecular correlates. This retrospective analysis was approved by the Institutional Ethics Committee.

KRAS mutational analysis. KRAS mutations in codon 12 and 13 were assessed on tumor DNA. Mutational analysis was

performed by PCR amplification of exon 1 of the KRAS gene following previously reported conditions.⁽⁹⁾ The purified PCR products were automatically sequenced on an ABI Prism 3130 (Applied Biosystems, Foster City, CA, USA).

FcγRIIIa-H131R and FcγRIIIa-V158F genotyping. The genomic DNA was extracted from peripheral leucocytes by the salting-out procedure.⁽¹⁰⁾ We genotyped all patient samples for the FcγRIIIa-H131R and FcγRIIIa-V158F polymorphisms using a 48.48 dynamic array on the BioMark system (Fluidigm). The sample and the TaqMan SNP Genotyping assay (Applied Biosystems) mixes were prepared following the manufacturer's recommendations. Prior to loading the mixes into the inlets, the chip was primed in the NanoFlex IFC Controller. The sample and genotyping mixes were then loaded into the inlets of the dynamic array and again placed in the IFC Controller for loading and mixing for approximately 45 min. Polymerase chain reaction (PCR) was performed on the BioMark system with an initial 2 min at 50°C and 10 min at 95°C, followed by 40 cycles of 15 s at 95°C for denaturation and 1 min at 60°C for annealing and extension. Endpoint fluorescent image data were acquired on the BioMark Real-Time PCR System and analyzed using Fluidigm SNP Genotyping Analysis software.

As a quality control, normal, heterozygous and homozygous sequenced samples were included on every array for each genotype.

Statistical analysis. The differences between categorical variables were measured by the χ^2 -test. Logistic regression was used as a multivariate method to ascertain which variables independently predicted response after adjustment for other relevant clinical variables. The Kaplan–Meier estimates and log-rank tests were used in the univariate analysis of progression-free survival (PFS). Progression-free survival (PFS) was calculated from the beginning of treatment until progression of the neoplasia or death. The Cox regression model was used for multivariate analyses of PFS. Results were considered statistically significant when *P*-values were < 0.05.

Results

A total of 104 Caucasian patients were studied. Clinical data are shown in Table 1. Overall, 92 patients (88%) were treated with cetuximab plus chemotherapy and 12 patients (12%) were treated with panitumumab alone or in combination with irinotecan. One patient had CR, 19 had PR (18%), 44 had SD (42%), and 35 progressed (34%). Five patients were not evaluated. The median PFS was 4 months (range, 0.5–30 months) and median overall survival was 9.5 months (range, 0.5–44 months).

Clinical parameters and outcomes. There were significant differences in the clinical response when patients were grouped in accordance with the clinical classification (EORTC model). While 21% of the low-risk patients achieved a CR/PR, only 4%

Table 2. Clinical classification (EORTC model) and outcome of mCRC patients treated with anti-EGFR-based therapy

	Clinical classification						<i>P</i> -value
	Low risk		Intermediate risk		High risk		
N	28		46		25		
Response	No.	%	No.	%	No.	%	
CR/PR	6	21	14	30	1	4	<0.0001*
SD	18	64	19	41	6	24	
PD	4	14	13	28	18	72	
Median PFS (months)	8		7		2		<0.0001†
95% CI	6.1–9.8		4.1–9.8		1–2.9		

*Fisher's exact test; †log-rank test. CI, confidence interval; CR, complete response; EGFR, epidermal growth factor receptor; EORTC, European Organization for Research and Treatment of Cancer; mCRC, metastatic colorectal cancer; PFS, progression-free survival; PR, partial response; SD, stable disease.

of high risk patients presented a PR. In a similar way, 14% of low risk patients had a progressive disease compared to 72% of high risk patients ($P < 0.0001$). Accordingly, a longer median PFS was observed in low risk patients compared with high risk patients (8 months [95% confidence interval, CI, 6.1–9.9] vs 2 months [95% CI, 1–2.9] $P < 0.0001$) (Table 2). Overall survival also differed in accordance with the clinical classification (13 months in low- and intermediate-risk patients [95% CI, 7.3–18.6 months] vs 5 months in high-risk patients [95% CI, 3.2–6.7 months]; $P < 0.0001$).

Grade 2 or 3 skin rash was observed in 68 patients (65%). Skin rash severity was significantly associated with clinical response; 19 patients (29%) with severe skin toxicity responded to treatment versus only two patients (6%) with grade 0 or 1 of skin toxicity ($P < 0.009$). Skin rash severity was associated with a better PFS ($P < 0.0001$; Fig. 1a) and OS ($P < 0.006$; Fig. 1b).

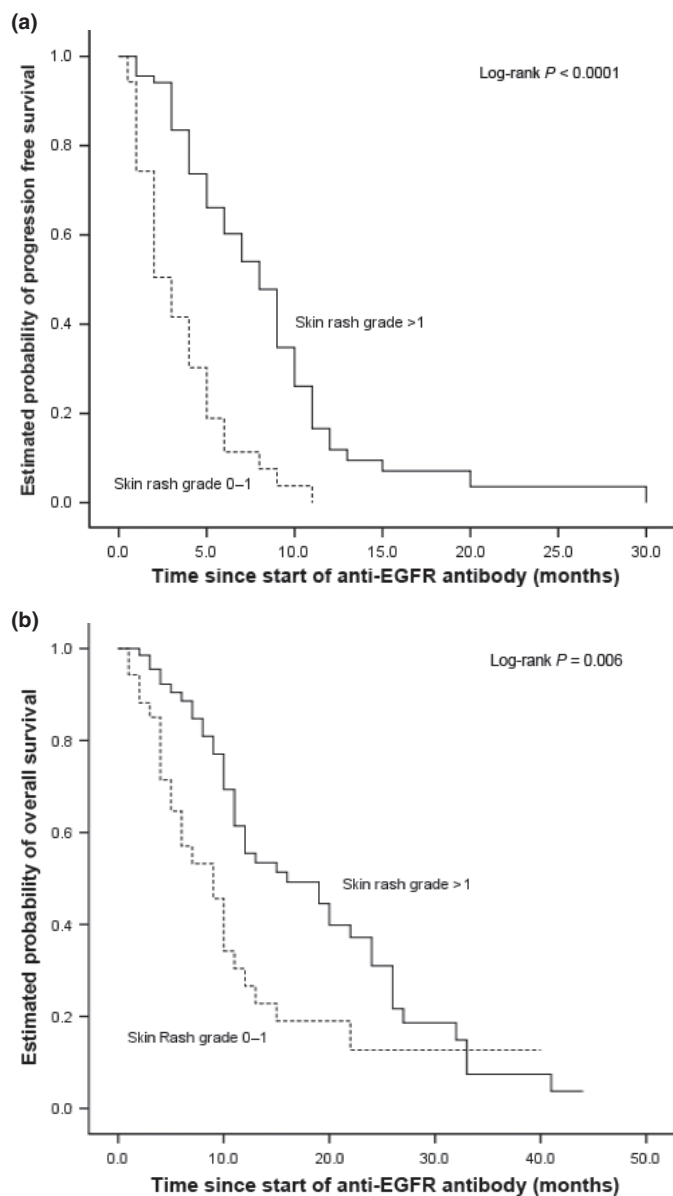


Fig. 1. (a) Kaplan–Meier curve for progression-free survival and skin toxicity in metastatic colorectal cancer (mCRC) patients treated with anti-epidermal growth factor receptor (EGFR) therapy. (b) Kaplan–Meier curve for overall survival and skin toxicity in mCRC patients treated with anti-EGFR therapy.

Genetic determinants and outcomes. Table 3 shows the frequencies of the two polymorphisms in the *FcγRIIa* and *FcγRIIIa* genes and *KRAS* mutation status. Frequencies of the polymorphisms studied were similar to those reported previously in a Caucasian population. There was no linkage disequilibrium between the *FcγRIIa* and *FcγRIIIa* polymorphisms in our group of patients ($r^2 = 0.02$). *KRAS* status was evaluated in 96 cases and a mutation was detected in the tumor of 22 patients (21%). Epidermal growth factor receptor (EGFR) expression status obtained by immunohistochemistry was negative in 44% of cases, <10% in 12%, 10–30% in 18%, and >30% in 5%. No relation was observed between EGFR expression and response. There was no concordance between the *FcγRIIa* and *FcγRIIIa* polymorphisms and EGFR status, excluding the involvement of this parameter in the ADCC activity.

KRAS mutation was associated with a lower response rate: only one out of 22 patients with this mutation responded. Nineteen out of 69 nonmutated patients were responders (4.5% vs 27.5%; $P = 0.035$). Patients without *KRAS* mutation showed a trend to longer median PFS compared to mutated patients (7 vs 3 months; $P = 0.36$) (Table 4).

No statistically significant differences were observed in response to treatment or PFS based on the *FcγRIIa-H131R* polymorphism. Neither did we observe a significant association when considering this polymorphism together with the *KRAS* status. However, patients with *FcγRIIa-131R/R* and wild-type *KRAS* showed a better response rate than those with the H/H or H/R genotype (53% vs 22% and 19% respectively; $P = 0.1$) (Table 5).

Similarly, no statistically significant difference was observed for tumor response based on *FcγRIIIa-V158F* polymorphism, regardless of *KRAS* status (Table 6).

Table 3. Frequencies of genetic determinants

	No.	%
KRAS status		
Wild type	74	71
Mutated	22	21
Non-assessable	8	8
FcγRIIa polymorphism		
H/H	27	26
H/R	54	52
R/R	23	22
FcγRIIIa polymorphism		
V/V	16	15
V/F	41	39
F/F	47	45

F, phenylalanine allele; FcγR, fragment c γ receptor; H, histidine allele; R, arginine allele; V, valine allele.

Table 4. KRAS status and outcome of mCRC patients treated with anti-EGFR-based therapy

	KRAS status				P-value
	Wild type		Mutated		
<i>n</i>	69		22		
Response	No.	%	No.	%	
CR/PR	19	27.5	1	4.5	0.035*
SD/PD	50	72.5	21	95.5	
Median PFS (months)	7		3		0.36†
95% CI	5–8.9		1.2–4.7		

*Fisher's exact test; †log-rank test. CI, confidence interval; CR, complete response; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 5. Outcome of patients treated with anti-EGFR-based therapy according to FcγRIIIa polymorphism and KRAS mutations

Whole group	FcγRIIIa						P-value
	H/H		H/R		R/R		
Response	No.	%	No.	%	No.	%	
CR/PR	4	17	8	15	9	41	0.13*
SD	9	37	26	49	8	36	
PD	11	46	19	36	5	23	
Median PFS (months)	4		6		6		0.61†
95% CI	2.9–5		3.4–8.5		3.6–8.3		
wt KRAS							
Response	No.	%	No.	%	No.	%	
CR/PR	4	22	7	19	8	53	0.1*
SD	6	33	18	50	5	33	
PD	8	44	11	31	2	13	
Median PFS (months)	5		7		7		0.7†
95% CI	3.5–6.5		4.2–9.7		5.5–8.4		
mut KRAS							
Response	No.	%	No.	%	No.	%	
CR/PR	–	–	1	7	–	–	1.0*
SD	2	50	7	47	2	67	
PD	2	50	6	47	1	33	
Median PFS (months)	3		3		6		0.7†
95% CI	0.6–5.9		0.7–5.2		0–12.4		

*Fisher's exact test; †log-rank test. CI, confidence interval; CR, complete response; EGFR, epidermal growth factor receptor; FcγR, fragment c γ receptor; H, histidine allele; mut, mutated; PFS, progression-free survival; PR, partial response; R, arginine allele; SD, stable disease; wt, wild-type.

Combining the *FcγRIIIa-H131R* and *FcγRIIIa* polymorphisms we established a favorable genotype (patients homozygous 131 R/R and/or 158 F/F) and a non-favorable genotype (patients homozygous 131 H/H and/or 158 V/V). No significant difference was observed for tumor response and PFS between these genotype subsets (Table 7).

A logistic regression analysis indicated that *KRAS* status (odds ratio [OR] = 0.11; 95% CI, 0.01–0.93; *P* = 0.04) and skin toxicity (OR = 2.52; 95% CI, 1.09–5.85; *P* = 0.03) were the only independent predictive factors for response.

A multivariate Cox regression model that included baseline characteristics showed that the clinical risk classification (HR: 0.24; 95% CI, 0.08–0.66; *P* = 0.006) and skin toxicity (HR: 0.5; 95% CI, 0.37–0.67; *P* < 0.0001) were independent risk factors for PFS. Skin rash showed a trend to a better OS (HR: 0.73; 95% CI, 0.53–1; *P* = 0.052). *FcγRIIIa-H131R* and *FcγRIIIa-V158F* polymorphisms were not shown to be independent predictors of PFS and OS.

Discussion

Although *KRAS* status has been identified as the most relevant molecular marker of non-response to anti-EGFR monoclonal antibodies,^(11–13) not all wild-type patients respond. Furthermore, some mutant patients experience long-term disease control,^(12,14,15) suggesting that *KRAS* mutation is not the only genetic alteration conferring resistance to cetuximab.

In addition to their EGFR antagonist function, cetuximab and possibly panitumumab have a functional fragment C portion with potential therapeutic properties. This fragment C portion can bind to the IgG fragment C receptor (FcγR) which is located on cytotoxic cells (natural killer lymphocytes or macrophages) and allows antitumor activity via ADCC.⁽¹⁶⁾

In an *in vitro* study, Parren *et al.* found the first evidence supporting the role of the FcγR coding genes in the ADCC mecha-

Table 6. Outcome of patients treated with anti-EGFR-based therapy according to FcγRIIIa polymorphism and KRAS mutations

Whole group	FcγRIIIa						P-value
	V/V		V/F		F/F		
Response	No.	%	No.	%	No.	%	
CR/PR	4	27	7	18	10	22	0.5*
SD	4	27	16	42	23	50	
PD	7	46	15	40	13	28	
Median PFS (months)	4		5		7		0.5†
95% CI	2.8–5.1		3.9–6		4.3–9.6		
wt KRAS							
Response	No.	%	No.	%	No.	%	
CR/PR	4	33	6	25	9	27	0.6*
SD	3	25	10	42	16	48	
PD	5	42	8	33	8	24	
Median PFS (months)	4		8		7		0.3†
95% CI	1.1–6.8		4.2–11.7		4.9–9.1		
mut KRAS							
Response	No.	%	No.	%	No.	%	
CR/PR	–	–	1	9	–	–	0.3*
SD	–	–	4	36	7	70	
PD	1	100	6	55	3	30	
Median PFS (months)	2		3		6		0.3†
95% CI			0.8–5.1		0–13.7		

*Fisher's exact test; †log-rank test. CI, confidence interval; CR, complete response; EGFR, epidermal growth factor receptor; F, phenylalanine allele; FcγR, fragment c γ receptor; mut, mutated; PFS, progression-free survival; PR, partial response; SD, stable disease; V, valine allele; wt, wild-type.

Table 7. Outcome of patients treated with anti-EGFR-based therapy according to the combination of FcγRIIIa and FcγRIIIa polymorphisms

	FcγR combined				P-value
	H/H and/or V/V		R and F		
Response	No.	%	No.	%	
CR/PR	8	22	13	21	0.5*
SD	13	36	30	48	
PD	15	42	20	32	
Median PFS (months)	5		7		0.27†
95% CI	3.9–6.1		4.6–9.4		
	R/R and/or F/F		H and V		
Response	No.	%	No.	%	
CR/PR	13	25	8	17	0.17*
SD	25	48	18	38	
PD	14	27	21	45	
Median PFS (months)	7		5		0.9†
95% CI	5.4–8.6		3.8–6.2		

*Fisher's exact test; †log-rank test. CI, confidence interval; CR, complete response; EGFR, epidermal growth factor receptor; F, phenylalanine allele; FcγR, fragment c γ receptor; PFS, progression-free survival; PR, partial response; SD, stable disease; V, valine allele.

nism. On studying the *FcγRIIIa* gene, they showed that the 131H allele had a higher binding efficiency for human IgG2 antibodies than the 131R allele.⁽¹⁷⁾

Pharmacogenetic studies have recently reported controversial results regarding the involvement of two genetic polymorphisms (H131R and V158F) located at the extracellular ligand-binding

domain of two receptors (*FcγRIIa* and *FcγRIIIa*, respectively) in immune cells. Here we discuss only the pharmacogenetic results obtained in colorectal cancer patients treated with anti EGFR antibodies.

Zhang *et al.* studied 39 mCRC treated with single-agent cetuximab.⁽⁶⁾ The two mentioned FcγR gene polymorphisms were associated with clinical outcome. Patients with the *FcγRIIa-131H* allele had a longer PFS than patients with the *FcγRIIa-131R* allele. Combined analysis of these two polymorphisms showed that patients with the favorable genotypes (*FcγRIIa*, any histidine allele, and *FcγRIIIa*, any phenylalanine allele) showed a median PFS of 3.7 months (95% CI, 2.4–4.4 months), whereas patients with any two unfavorable genotypes (*FcγRIIa* arginine/arginine or valine/valine) had a PFS of 1.1 months (95% CI, 1.0–1.4 months; $P = 0.04$; long-rank test). These authors increased the sample to a total of 130 patients, all of whom were part of a phase II open-label multicenter clinical trial (IMC 0144) with cetuximab. This broad study of North American patients analyzed genetic markers in different genes, and the previous associations of the *FcγRIIa-FcγRIIIa* polymorphisms with clinical outcomes could not be replicated.⁽¹⁸⁾

Graziano *et al.* investigated possible associations between genetic variants in genes that could influence cetuximab-related pathways and clinical outcomes in 110 mCRC European patients. They were treated with cetuximab–irinotecan salvage therapy. No statistically significant associations between the *FcγRIIa-FcγRIIIa* polymorphisms and patients outcome were reported.⁽¹⁹⁾

More recently, other authors evaluated the association of *FcγRIIa* and *FcγRIIIa* polymorphisms and KRAS mutation with the outcome of irinotecan-refractory mCRC patients ($n = 69$) treated with cetuximab plus irinotecan. Those patients with *FcγRIIa-131H/H* and/or *FcγRIIIa-158V/V* had a longer PFS than 131R and 158F carriers (5.5 vs 3.0 months; $P = 0.005$). The difference remained significant for mutated-KRAS patients. Multivariate analysis showed that KRAS mutation and FcγR combined status were independent risk factors for PFS.⁽¹⁵⁾

The present study confirmed the prognostic clinical model proposed by Köhne *et al.* based on four baseline clinical parameters: performance status, level of white blood cell count, alkaline phosphatase, and number of involved tumor sites.⁽⁷⁾ As our results showed a very poor outcome in the high-risk group of patients, the use of a monoclonal antibody treatment should not be considered for this population. Our study also confirmed that the presence and severity of skin rash was associated with improved clinical efficacy, as previously reported by other authors.^(1,20,21) However, it should be pointed out that skin toxicity cannot be considered a clinically useful baseline feature

to preselect those patients who would benefit from anti-EGFR therapies.

As reported in previous publications, the presence of a KRAS mutation in tumor DNA was highly associated with a poor response.⁽³⁾ In our series only one out of 22 mutated patients responded, while 19 out of 69 wild-type cases achieved a clinical response. In addition, patients with a wild-type KRAS status had a longer PFS (7 vs 3 months; $P = 0.36$). The low frequency of KRAS mutations in our group of patients was due to the fact that patients were treated with anti-EGFR therapies, without taking KRAS status into consideration until 2008. Since then, only wild-type KRAS patients have been treated with anti EGFR monoclonal antibodies.

In our study, as in those previously reported with a high number of patients,^(18,19) FcγR polymorphisms did not show any significant association with response to anti-EGFR therapy, and no significant effect was detected in the PFS in relation with these polymorphisms, whatever the KRAS status.

The present study has its limitations. First, most patients analyzed were treated with chemotherapy plus anti-EGFR monoclonal antibodies, while the ideal scenario to analyze the ADCC mechanism would be to include patients treated with anti-EGFR in monotherapy. Second, like other authors, we examined only two polymorphisms in only two genes involved in the ADCC mechanism. The results regarding the involvement of the FcγR polymorphisms in the efficacy of anti-EGFR are controversial. Differences in patients' characteristics, study design, therapeutic protocols, and even in the distribution of genotypes in the different patient groups might, in part, explain the discrepancies. The role of ADCC in anti-EGFR efficacy is, therefore, yet to be thoroughly investigated.

To the best of our knowledge, this is the first study to show that the clinical risk EORTC classification is a prognostic marker – independently of the skin toxicity and of the KRAS status – in mCRC patients treated with chemotherapy and monoclonal antibodies. Our findings allow us to conclude that the *FcγRIIa* and *FcγRIIIa* polymorphisms are not useful as molecular markers for clinical outcome in mCRC patients. Markers of poor prognosis other than KRAS mutation, such as v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation, phosphatidylinositol 3-kinase, catalytic, alpha polypeptide (PIK3CA) mutation, and phosphatase and tensin homolog (PTEN) loss, should be investigated as a next step.

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