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***XPC* genetic polymorphisms correlate with the response to imatinib treatment in patients with chronic-phase chronic myeloid leukemia**

By

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ABSTRACT

Chronic myeloid leukemia (CML) is driven by the BCR-ABL protein, which promotes the proliferation and viability of the leukemic cells. Moreover, BCR-ABL induces genomic instability that can contribute to the emergence of resistant clones to the ABL kinase inhibitors. It is currently unknown whether the inherited individual capability to repair DNA damage could affect the treatment results. To address this, a comprehensive analysis of single nucleotide polymorphisms (SNPs) on the nucleotide excision repair (NER) genes (*ERCC2-ERCC8*, *RPA1-RPA3*, *LIG1*, *RAD23B*, *XPA*, *XPC*) was performed in 92 chronic-phase CML patients treated with imatinib up-front. *ERCC5* and *XPC* SNPs correlated with the response to imatinib. Haplotype analysis of *XPC* showed that the wild-type haplotype (499C-939A) was associated with a better response to imatinib. **Moreover, the 5-year failure-free survival for CA carriers was significantly better than that of the non-CA carriers (98% vs 73%; P=0.02).** In the multivariate logistic model with genetic data and clinical covariates, the hemoglobin (Hb) level and the *XPC* haplotype were independently associated with the treatment response, with patients having a Hb ≤ 11 g/dl (Odds ratio [OR]= 5.0, 95% confidence interval [CI]= 1.5-16.1) or a non-CA *XPC* haplotype (OR= 4.1, 95% CI= 1.6-10.6) being at higher risk of suboptimal response/treatment failure. Our findings suggest that genetic polymorphisms in the NER pathway may influence the results to imatinib treatment in CML.

Keywords: Chronic myeloid leukemia, genetic polymorphisms, DNA repair, *XPC* gene, imatinib.

INTRODUCTION

Chronic myeloid leukemia (CML) results from the clonal expansion of pluripotent hematopoietic stem cells containing the *BCR-ABL* fusion gene. The respective BCR-ABL protein plays a central role in the initiation and maintenance of the disease, by activating a number of intracellular signal pathways that lead to increased proliferation and enhanced survival of the leukemic stem cells (1). Imatinib is a remarkably effective therapy for chronic-phase CML, permitting long-term disease control in about three fourths of patients (2). However, some patients do not respond to treatment (primary resistance) or, more often, may lose the initial response (secondary resistance) (3). The mechanisms underlying imatinib resistance in early chronic-phase are mostly unknown, since mutations in the BCR-ABL kinase domain are found in a minority of patients in this setting (4,5). Increasing rates of treatment failure are observed as the drug is given in more advanced CML, with this probably being due to the acquisition of new molecular abnormalities in the leukemic progenitors.

In this sense, a critical role of BCR-ABL in inducing genomic instability of the proliferating clone has been postulated (6). BCR-ABL increases levels of reactive oxygen species (ROS) causing oxidative DNA damage that, if imprecisely repaired, could result in *BCR-ABL* mutations and imatinib resistance (7-9). On the other hand, BCR-ABL interferes with the regular mechanisms of double strand breaks (DSB) repair (10-13). In particular, BCR-ABL regulates the nucleotide excision repair (NER), a pathway that plays an important role in the repair of DSBs and a broad range of other types of DNA lesions (14,15). Specifically, BCR-ABL interacts with the ERCC3 (XPB) protein, forming a complex that is critical for triggering the initial steps of NER (10). Recently, imatinib was shown to decrease the efficacy of NER in leukemic cells expressing BCR-ABL (16).

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3 On the other hand, it is currently unknown whether the genomic instability of the
4 leukemic clones could be modulated by the individual capability of the patients to maintain
5 genetic integrity. In this sense, the ability of an individual to repair DNA damage is
6 genetically determined by a combination of multiple genes that may display subtle differences
7 in their activity depending on the pattern of single nucleotide polymorphisms (SNPs) (17,18).
8 In the present study, a comprehensive analysis of 14 SNPs in genes involved in the NER
9 pathway was performed in 92 early chronic-phase CML patients treated with imatinib up-
10 front, in order to assess their potential relationship with the treatment results.
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PATIENTS AND METHODS

Study subjects

The study population included a series of 92 Caucasian patients (52 males) diagnosed with *BCR-ABL*-positive CML between May 2000 and July 2007 in five Spanish Institutions. The median age at disease diagnosis was 46 years (range, 19-75), and the risk distribution according to the Sokal score was as follows: low-risk 46; intermediate-risk 33; and high-risk 13. The median haemoglobin (Hb) level at diagnosis was 125 g/l (range, 76-166), being ≤ 11 g/l in 19 cases. **Additional cytogenetic abnormalities in Ph+ cells were observed in 4 cases.** Patients received first-line therapy with imatinib 400 mg/day in early chronic phase (i.e., within the first year from CML diagnosis), and were followed for a median time of 55 months (range, 9-107). **Imatinib dose was reduced during the first year of treatment in 7 patients (8%), due to hematologic (n=4) or non-hematologic toxicity (n=3).** Disease monitoring and response to imatinib treatment were assessed by the European LeukemiaNet Recommendations (19). **At the time of data analysis, 82 patients (89%) continued on imatinib, but 20 of them had increased the dose to 600 mg/day or more.**

The study was approved by the Research Ethics Committee of the Hospital Clínico of Valencia and informed consent (according to the Declaration of Helsinki) was obtained from all patients.

Genotyping

A comprehensive analysis of SNPs in 14 genes involved in the NER pathway was performed, including those with an abundance of infrequent alleles greater than 20% in the general population. SNPs located on codifying regions (involving an aminoacid change) were preferentially selected, but SNPs located on putative regulatory regions than can modulate gene expression, mRNA stability or splicing (5'-3'UTR or near gene region >intron) were also included. The candidate genes were the following: *ERCC2 (XPD)*, *ERCC3 (XPB)*,

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3 *ERCC4 (XPF), ERCC5 (XPG), ERCC6 (CSB), ERCC8 (CKN1), RPA1, RPA2, RPA3,*
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5 *RAD23B (HR23B), LIG1, XPA and XPC (499C>T and 939A>C)* (see Table I for details).
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8 Genomic DNA was extracted from blood cells by using the DNeasy tissue kit from
9 Qiagen, (Izasa, Madrid, Spain) according to the manufacturer protocol. Genotyping analysis
10 of the 14 SNPs was performed by real-time PCR, using the TaqMan® SNP Genotyping on
11 demand Assays, which are commercially supplied by Applied Biosystems (Barcelona, Spain).
12 Assays were performed according to the manufacturer instructions. Briefly, each sample
13 reaction was composed of 2.5 µL of TaqMan Genotyping Master Mix, 0.12 uL of Taqman
14 probe assay 40X and 2.5 µl of DNA sample at 5µg/mL. Thermal cycling and detection was
15 performed in a Fast-Real time PCR system 7900HT from Applied Biosystems (Barcelona,
16 Spain). Thermal cycler conditions were: a first stage of 50°C for 2 min, second stage of 95°C
17 for 10 min and a third stage consisting on 45 cycles of 95°C for 15 sec, 60°C for 1 min.
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34 *Statistical analysis*

35 The statistical tools for genotype analysis of SNPs (Hardy-Weinberg equilibrium, allele and
36 genotype distributions, and association tests) were provided by SNPStats (20). SNPStats
37 association analysis is based on binary logistic regression according to the response variable
38 (in this case, imatinib response). SNPStats provides odds ratios (OR), confidence intervals
39 (CI), and P values for multiple inheritance models (co-dominant, dominant, recessive, over-
40 dominant and log-additive). Akaike's Information Criterion (AIC) and Bayesian Information
41 Criterion (BIC) were calculated to select the best inheritance model for each specific
42 polymorphism, with the preferred model being the one with the lowest AIC/BIC value. For
43 the SNPs in the same gene, linkage disequilibrium (LD) was calculated using the SNPStats
44 application. D' is the parameter used to express LD degree. D' values of D' ranged between 0
45 and +1. D' value of 1 denoted complete LD, whereas a D' value of 0 denoted complete linkage
46 equilibrium. Haplotype association analysis for SNPs in the same gene were performed using
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3 the Haplostats statistical package (21) from R project for Statistical Computing ([www.r-](http://www.r-project.org/)
4 [project.org/](http://www.r-project.org/)).
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8 The SPSS statistical package (Version 12.0) was used to analyze, by means of binary
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10 logistic regression methods, the associations between the baseline patients' characteristics and
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12 the response to imatinib treatment. In addition to the genetic markers, the patients' age, sex,
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14 Sokal risk score, and Hb levels at CML diagnosis were added as explanatory variables in the
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16 regression analysis. In all tests, P values of less than or equal to 0.05 were considered to
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18 represent statistical significance.
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22 Transformation-free survival (TFS) was defined as the time from imatinib start to the
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24 appearance of accelerated phase (AP) or blast crisis (BC) or death, whatever the cause.
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26 Failure-free survival (FFS) was defined as the time from imatinib start to failure, including
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28 death, progression to AP/BC and the lack of achievement or the loss of a previously achieved
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30 complete hematologic response (CHR) or complete cytogenetic response (CCyR). For TFS
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32 and FFS analysis, patients were censored at the time of stem cell transplantation.
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RESULTS

At 3 months of imatinib treatment, all patients achieved a CHR; at 12 months, 91% of evaluable patients were in CCyR; at 18 months, 68% were in major molecular response (MMR). Two patients progressed to BC at 12 and 13 months of therapy, respectively. Table II depicts the frequencies of suboptimal response and failure to imatinib according to the European LeukemiaNet criteria (Baccarani *et al*, 2006). Overall, 26 (28%) and 14 (15%) patients had fulfilled at any time point during treatment the criteria for suboptimal response and failure, respectively. Among the 7 patients classified as failure in the first 18 months of treatment, four patients underwent allogeneic stem cell transplantation: two of them were in chronic phase at the time of transplantation and two had evolved to BC. By contrast, 24 of 28 patients who met the criteria of suboptimal response at 18 months or anytime earlier remained on imatinib with a stable CCyR (n=8) or MMR (n=16) at last visit. The 5-year probabilities of TFS and FFS of the whole series were of 98% and 84%, respectively.

First, we performed the association analysis between the 14 genetic polymorphisms of the NER pathway and the response to imatinib treatment. For that purpose, CML patients were categorized into two groups depending on their response to first-line therapy with imatinib: the first group comprised the 52 optimal responders, whereas the second one included 40 patients who fulfilled the European LeukemiaNet criteria for suboptimal response or treatment failure at anytime during follow-up. The results of single-SNP association tests for these comparisons are shown in Table III.

The most relevant findings in the association tests corresponded to the SNPs located in *ERCC5* (XPG) and in the exon 8 of *XPC* (499C>T). Thus, we found statistically significant differences for *ERCC5* (XPG) in a recessive model (P=0.009), with the mutant alleles in homozygosis (C/C) having an increased risk of suboptimal response/treatment failure as compared with both, the heterozygous (G/C) and the homozygous wild-type cases (G/G). In

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3 contrast, the dominant model was more discriminative for *XPC499* ($P=0.02$), with the T
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5 mutant alleles in homozygosis or heterozygosis (T/T, C/T) being associated with an increased
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7 likelihood of achieving suboptimal response/treatment failure as compared with the CC
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9 homozygotic wild-type cases ($P=0.02$; OR=2.6, 95% CI= 1.1-6.2). Another SNP of *XPC*,
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11 located in exon 16 (939A>C), was marginally associated with the treatment results. Since
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13 both SNPs were in the same gene, we calculated the LD for this pair (*XPC499/939*), which
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15 confirmed that they were fully linked ($D'=0.94$), as previously reported (22). Then, we
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17 performed a haplotype association analysis for this pair of SNPs, as depicted in Table IV. Of
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19 note, the frequency of the double mutant haplotype (499T-939C) was very low (less than 1%).
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21 Therefore, only three haplotypes (corresponding to three protein variants) were considered for
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23 determination of OR and p values: the 499C939A wild-type haplotype (CA); the 499T939A
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25 haplotype, which is a variant with a single mutation in the 499 position (TA); and the 499C-
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27 939C haplotype, in which a single mutation is located in the 939 position (CC). The observed
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29 frequencies of these haplotypes in healthy donors were 31%, 29.5%, and 39.5% for the CA,
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31 TA, CC variants, respectively (data not shown). As elicited in Table IV, the CA haplotype
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33 was more prevalent in the group of patients with an optimal response to imatinib ($P=0.005$,
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35 39% versus 18%), whereas the CC and TA haplotypes were similarly distributed among
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37 patients with or without an optimal response. Thus, any combination of single mutant
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39 haplotypes taking the wild-type CA variant as the reference group correlated with a higher
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41 risk of suboptimal response/treatment failure ($P_{\text{global}}=0.03$; OR 2.3, 95% CI= 1.1-4.9 and
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43 OR= 2.5, 95% CI= 1.15-5.3, for the CC and TA variants, respectively). **In addition, the 5-year**
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45 **FFS for CA carriers was significantly better than that of the non-CA carriers (98% vs 73%;**
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47 **$P=0.02$), as shown in Figure I.**

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58 **An additional association test analysis was performed** considering each haplotype as
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60 an allele, with the individual *XPC* genotype being the combination of pairs of haplotypes
(Table V). Of note, the frequency of individuals with one or two copies of the CA haplotype

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3 (61%) was more than two-fold higher among the optimal responders to imatinib than among
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5 those with suboptimal response or treatment failure (27.5%). The best statistical model to
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7 describe such differences was a dominant one, in which the CA carriers (either in
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9 homozygosis or heterozygosis) had a 4-fold lower risk to attain a suboptimal response or
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11 failure to imatinib than the non-CA carriers (P=0.001, OR=0.24, 95% CI= 0.10-0.58). A
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13 futher logaritmic regression analysis considering all haplotype combinations found that the
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15 one composed by single mutant haplotypes (TA/CC) was more prevalent among the bad
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17 responders than among the optimal responders (45% versus 15%, P=0.002, OR= 4.5, 95%
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19 CI= 1.7-12).

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24 Finally, the patient's clinical characteristics (patients' age, sex, Sokal risk score, Hb
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26 levels at CML diagnosis) were correlated with the response to imatinib. At univariate
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28 analysis, the only factors that were significantly associated with the treatment response were
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30 the Hb level at baseline (> 11 g/dl versus ≤ 11 g/dl)(P= 0.01) and the Sokal risk score (low
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32 versus intermediate/high)(P= 0.03). Next, a binary logistic-regression analysis was performed
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34 entering these two clinical variables together with the genetic data in order to identify the best
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36 model to predict the response to imatinib. Thus, the Hb level (P= 0.007) and the XPC
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38 haplotype (P= 0.004) were independently associated with the treatment response, with
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40 patients with Hb level ≤ 11 g/dl (OR= 5.0, 95% CI= 1.5-16.1) and the non-CA haplotype
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42 carriers (OR: 4.1, 95% CI=1.6-10.6) having a higher risk of suboptimal response/treatment
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44 failure.
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DISCUSSION

Increasing evidence has been reported in recent years supporting a crucial role of the BCR-ABL protein in the genomic instability of the proliferating clone in CML (1,6). According to such data, BCR-ABL is not only essential for CML initiation and maintenance, but should also be considered critical for the progression of the disease, since it may induce direct DNA damage by ROS (7,8), as well as compromise the fidelity of DNA repair (9-12). As a consequence, the accumulation of additional molecular abnormalities in the leukemic cells could eventually lead to resistance to the ABL kinase inhibitors and disease progression. However, there is a lack of information regarding the role of the individual inherited factors that may modulate the genomic instability of the CML cells. In this sense, the association observed in the current study between the genetic variants of the NER pathway and the response to imatinib treatment in CML is noteworthy.

ERCC5 (also known as XPG) is a single-stranded structure-specific DNA endonuclease involved in DNA excision repair that acts as a cofactor for a DNA glycosylase that removes oxidized pyrimidines from DNA. The *ERCC5 XPG* Asp1104His polymorphism has been associated with chromosomal translocations in certain subtypes of sarcomas (23). In the present study, an association between this polymorphism and the response to imatinib treatment was noted, with patients harboring the mutant homozygous genotype (C/C) showing an increased risk of achieving suboptimal response or treatment failure. However, since the homozygously mutated genotype is very infrequent (about 3% in general population), it should not play a significant role in the overall results.

A more interesting finding in our study was the correlation between the *XPC* haplotypes, including the SNPs in exons 8 and 16, and the response to imatinib. These two polymorphisms involve changes in protein sequence (22,24) and have been associated with the risk of developing several cancers (25-27). Moreover, experimental data (28,29) suggest

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3 that both the TA and the CC haplotypes result in protein variants that are less active in DNA
4 repair than the CA wild-type. We found that the CA wild-type haplotype was associated with
5 a favorable response to imatinib, since patients who carried one or two copies of such
6 haplotype had a 4-fold lower risk of achieving suboptimal response or failure to imatinib than
7 the remainders. By contrast, the combination of single mutant haplotypes in heterozygosity
8 (TA/CC) correlated with the worst outcome.
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17 An interesting question is how the *XPC* haplotype variants can influence the response
18 to imatinib treatment. It has been reported that overexpression of BCR-ABL increases the rate
19 of DNA DSBs through the generation of ROS. If mutant variants of *XPC* are less active in
20 DNA repair than the wild-type, then the efficacy of NER in patients lacking a copy of the CA
21 haplotype would be diminished in a circumstance (increase of ROS) where it is strongly
22 needed. As a consequence, the higher genomic instability might facilitate the accumulation of
23 mutations and chromosomal aberrations in the CML cells, conferring them additional
24 proliferative advantages by BCR-ABL independent mechanisms that could eventually
25 promote imatinib resistance. Of note, 3 of the 4 patients developing ABL kinase domain
26 mutations in our study were non-CA carriers. However, the relatively small size of the series
27 precluded the detection of significant differences in the occurrence of genetic aberrations
28 according to the *XPC* genotypes.
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46 In summary, a strong association between the *XPC* haplotypes (SNPs in positions 499
47 and 939 of the *XPC* protein) and the response to imatinib in early chronic-phase CML was
48 observed. The homozygous wild-type CA seems a protective haplotype, being
49 overrepresented in optimal responders, whereas heterozygous carriers of TA/CC haplotype
50 were particularly prone to achieve less favorable responses to imatinib. We postulate that such
51 differences in the treatment response could be related to subtle variations in the interaction
52 between BCR-ABL and the NER proteins, which can affect the genomic instability of the
53 leukemic cells by interfering with DNA repair. However, further studies are needed to
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validate our results in larger number of patients, including the analysis of genetic polymorphisms in other pathways of DNA repair.

For Peer Review

LEGEND FOR THE FIGURE I

Failure-free survival in 92 early chronic-phase CML patients treated with imatinib according to the *XPC* genetic variants.

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AUTHORSHIP CONTRIBUTIONS

VMG and JCHB designed the research and wrote the manuscript; VMG performed the research; FC revised the manuscript; FC, JM, AAL, AS, MM and JCHB managed the patients and provided the genetic material for the study; MCo, MCa and IM supervised the molecular monitoring of the patients.

CONFLICT OF INTEREST DISCLOSURES

All authors declare no competing financial interests.

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For Peer Review

Table I. Summary of the candidate gene single nucleotide polymorphisms (SNPs)

| Gene | SNP ID | Alleles A/B ¹ | Sequence position ² | Codon-change | Aminoacid-change | Taqman Assay |
|----------------|-----------|--------------------------|--------------------------------|--------------------------|------------------|---------------|
| ERCC2 (XPD) | rs13181 | A/C (T/G) | exon 23 (751) | <u>A</u> AG/ <u>C</u> AG | Lys/Gln | C_3145033_10 |
| ERCC3 (XPB) | rs4662717 | C/T (G/A) | near gene 3' | - | - | C_1441179_10 |
| ERCC4 (XPF) | rs3136155 | C/T | intron 8 | - | - | C_26942939_10 |
| ERCC5 (XPG) | rs17655 | G/C | exon 4 (1104) | <u>G</u> AT/ <u>C</u> AT | Asp/His | C_1891743_10 |
| ERCC6 (CSB) | rs3793784 | C/G (G/C) | near gene 5' | - | - | C_27502098_10 |
| ERCC8 (CKN1) | rs3117 | T/C (A/G) | UTR-3 | - | - | C_1153140_10 |
| RPA1 | rs2287321 | T/C (A/G) | intron 4 | - | - | C_1387367_1_ |
| RPA2 | rs7356 | A/G (T/C) | UTR-3 | - | - | C_2989640_10 |
| RPA3 | rs6945447 | G/A | near gene 3' | - | - | C_2634666_10 |
| LIG1 | rs251692 | C/T (G/A) | UTR-3 | - | - | C_2426556_10 |
| RAD23B (HR23B) | rs2147072 | A/G | intron 1 | - | - | C_16136777_10 |
| XPA | rs2808668 | T/C | intron 2 | - | - | C_9312100_20 |
| XPC499 | rs2228000 | C/T (G/A) | exon 8 (499) | <u>G</u> CG/ <u>G</u> TG | Ala/Val | C_16018061_10 |
| XPC939 | rs2228001 | A/C (T/G) | exon 16 (939) | <u>A</u> AG/ <u>C</u> AG | Lys/Gln | C_234284_1 |

¹Nucleotide variants in codifying sequence or in forward strand: A (frequent allele)/ B (unfrequent allele). When Taqman assay is designed for reverse strand, nucleotide variants on reverse strand are indicated in brackets.

²When the SNP is located in an exon, the aminoacid change position on protein sequence is indicated in brackets.

Table II. Classification of 92 early chronic-phase CML patients treated with imatinib according to the European LeukemiaNet criteria¹.

| Months of therapy | Evaluable patients (n) | Suboptimal Response (n) | Failure (n) | Disease progression (n) | Imatinib discontinuation (n) |
|-------------------|------------------------|-------------------------|-------------|-------------------------|------------------------------|
| 3 | 92 | 0 | 0 | | 0 |
| 6 | 90 | 1 | 2 | | 1 |
| 12 | 90 | 4 | 4 | Blast crisis (2) | 3 |
| 18 | 88 | 25 | 3 | | 0 |
| Follow-up | | 2 | 5 | | 6 ² |

¹Patients could be ascribed to the same or different categories during follow-up whenever they continued on imatinib treatment.

²Two of the these patients discontinued imatinib due to late toxicity

Table III. Single-SNP association analysis with the response to imatinib therapy

| Gene | Genotype | Optimal responders N (%) | Suboptimal/ Failures N (%) | Best model ¹ | OR (CI95%) | p |
|-------------------|----------|-----------------------------|----------------------------------|-------------------------|-------------------------|---------------|
| ERCC2 (XPD) | A/A | 17 (32.7%) | 15 (38.5%) | Dominant | 0.78 (0.33-1.85) | 0.57 |
| | A/C-C/C | 35 (67.3%) | 24 (61.5%) | | | |
| ERCC3 (XPB) | C/C-T/T | 23 (46%) | 21 (55.3%) | Overdominant | 0.69 (0.30-1.61) | 0.39 |
| | C/T | 27 (54%) | 17 (44.7%) | | | |
| ERCC4 (XPF) | C/C-C/T | 42 (82.3%) | 36 (92.3%) | Recessive | 0.39 (0.10-1.55) | 0.16 |
| | T/T | 9 (17.6%) | 3 (7.7%) | | | |
| ERCC5 (XPG) | G/G-G/C | 50 (100%) | 36 (90%) | Recessive | NA (0.00-NA) | 0.0095 |
| | C/C | 0 (0%) | 4 (10%) | | | |
| ERCC6 (CSB) | G/G-C/C | 31 (60.8%) | 15 (40.5%) | Overdominant | 2.27 (0.96-5.39) | 0.06 |
| | G/C | 20 (39.2%) | 22 (59.5%) | | | |
| ERCC8 (CKN1) | T/T-T/C | 47 (94%) | 32 (82%) | Recessive | 3.43 (0.82-14.25) | 0.076 |
| | C/C | 3 (6%) | 7 (17.9%) | | | |
| RPA1 | T/T-T/C | 40 (76.9%) | 35 (89.7%) | Recessive | 0.38 (0.11-1.29) | 0.1 |
| | C/C | 12 (23.1%) | 4 (10.3%) | | | |
| RPA2 | A/A | 23 (46.9%) | 16 (43.2%) | Dominant | 1.16 (0.49-2.74) | 0.73 |
| | A/G-G/G | 26 (53.1%) | 21 (56.8%) | | | |
| RPA3 | G/G-G/A | 45 (86.5%) | 32 (82%) | Recessive | 1.41 (0.45-4.40) | 0.53 |
| | A/A | 7 (13.5%) | 7 (17.9%) | | | |
| LIG1 | C/C-T/T | 26 (50%) | 26 (66.7%) | Overdominant | 0.50 (0.21-1.18) | 0.11 |
| | C/T | 26 (50%) | 13 (33.3%) | | | |
| RAD23B (HR23B) | A/A-A/G | 39 (78%) | 33 (84.6%) | Recessive | 0.64 (0.22-1.93) | 0.43 |
| | G/G | 11 (22%) | 6 (15.4%) | | | |
| XPA | T/T-C/T | 48 (96%) | 33 (86.8%) | Recessive | 3.64 (0.67-19.88) | 0.12 |
| | C/C | 2 (4%) | 5 (13.2%) | | | |
| XPC499 | C/C | 29 (55.8%) | 13 (32.5%) | Dominant | 2.62 (1.11-6.18) | 0.025 |
| | C/T-T/T | 23 (44.2%) | 27 (67.5%) | | | |
| XPC939 | A/A | 23 (44.2%) | 11 (27.5%) | Dominant | 2.09 (0.86-5.06) | 0.097 |
| | A/C-C/C | 29 (55.8%) | 29 (72.5%) | | | |

Abbreviations: OR, odds ratio; CI, confidence interval, NA, not applicable.

¹Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) were calculated to select the best inheritance model for each specific polymorphism. The preferred model was the one with the lowest AIC/BIC value.

Table IV. XPC haplotypes and the response to imatinib treatment

| ESTIMATION OF HAPLOTYPE FREQUENCIES | | | | | | HAPLOTYPE ASSOCIATION ANALYSIS ¹ | | | | | |
|---|---------|-------|------------------|----------------|--------------|---|-------------|----------------------------|---------|----------------------------|---------|
| | | | | | | Haplo base CA ² | | Haplo base CC ³ | | Haplo base TA ⁴ | |
| XPC 499 | XPC 939 | Total | Optimal response | Subopt/failure | P | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| C | A | 0.30 | 0.39 | 0.18 | 0.005 | 1.00 | NA | 0.40 (0.18 - 0.86) | 0.02 | 0.38 (0.18 - 0.81) | 0.01 |
| C | C | 0.37 | 0.34 | 0.42 | 0.22 | 2.30 (1.07 - 4.93) | 0.03 | 1.00 | NA | 0.92 (0.45 - 1.91) | 0.83 |
| T | A | 0.32 | 0.28 | 0.38 | 0.13 | 2.46 (1.15 - 5.27) | 0.02 | 1.01 (0.48-2.13) | 0.97 | 1.00 | NA |
| T | C | 0.008 | 0 | 0.02 | NA | - | - | - | - | - | - |
| Global haplotype association p-value = 0.03 | | | | | | | | | | | |

Abbreviations: OR, odds ratio; CI, confidence interval; NA: not applicable.

¹As three haplotypes (CA, CC and TA) were quite abundant and the wild-type CA was not the most frequent haplotype, we used as base haplotype for OR calculations not only the wild-type CA² but also CC³ and TA⁴.

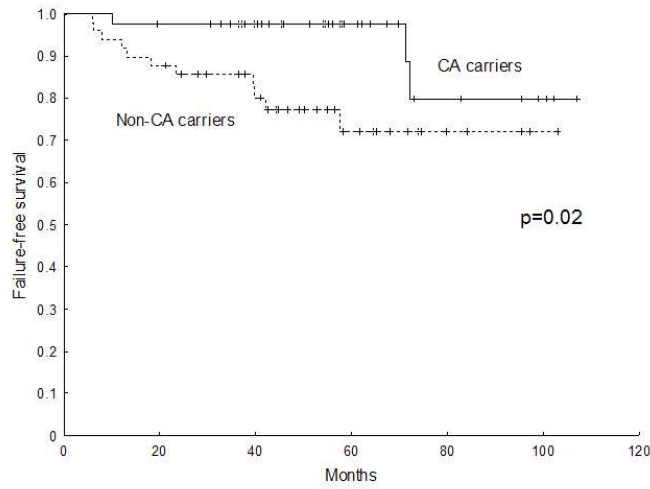
Table V. Impact of the CA haplotype on the response to imatinib treatment

| Model | XPC Genotype ¹ | Optimal response N (%) | Subopt./failure N (%) | OR (95% CI) | P-value | AIC ² | BIC ³ |
|--------------|---------------------------|------------------------|-----------------------|-------------------------|--------------|------------------|------------------|
| Codominant | X/X | 20 (38.5%) | 29 (72.5%) | 1.00 | 0.004 | 121.2 | 128.7 |
| | CA/X | 23 (44.2%) | 8 (20%) | 0.24 (0.09-0.64) | | | |
| | CA/CA | 9 (17.3%) | 3 (7.5%) | 0.23 (0.06-0.96) | | | |
| Dominant | X/X | 20 (38.5%) | 29 (72.5%) | 1.00 | 0.001 | 119.2 | 124.2 |
| | CA/X-CA/CA | 32 (61.5%) | 11 (27.5%) | 0.24 (0.10-0.58) | | | |
| Recessive | X/X-CA/X | 43 (82.7%) | 37 (92.5%) | 1.00 | 0.16 | 127.9 | 133 |
| | CA/CA | 9 (17.3%) | 3 (7.5%) | 0.39 (0.10-1.54) | | | |
| Overdominant | X/X-CA/CA | 29 (55.8%) | 32 (80%) | 1.00 | 0.013 | 123.8 | 128.9 |
| | CA/X | 23 (44.2%) | 8 (20%) | 0.32 (0.12-0.81) | | | |
| Log-additive | --- | --- | --- | 0.37 (0.19-0.74) | 0.002 | 120.7 | 125.8 |

Abbreviations: OR, odds ratio; CI, confidence interval.

¹X= non-CA haplotype (CC or TA); ²Akaike's Information Criterion; ³Bayesian Information Criterion.

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Failure-free survival in 92 early chronic-phase CML patients treated with imatinib according to the XPC genetic variants.
254x190mm (96 x 96 DPI)

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