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Lack of association between the *MDM2* promoter polymorphism SNP309 and clinical outcome in chronic lymphocytic leukemia

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ABSTRACT

The 309T>G polymorphism in the promoter region of the *MDM2* gene, known as SNP309, has recently been suggested as an unfavorable prognostic marker in chronic lymphocytic leukemia (CLL) although this has been questioned. To investigate this further, we analyzed the *MDM2* SNP309 genotypes in 418 CLL patients and correlated the results with established CLL prognostic factors, time to treatment and overall survival. In this Swedish cohort, no association existed between any particular *MDM2* SNP309 genotype, overall survival and time to treatment. Furthermore, no correlation was shown between the *MDM2* SNP309 genotypes and Binet stage, IGHV mutational status and recurrent genomic aberrations. In summary, this study argues against the use of the *MDM2* SNP309 as a prognostic marker in CLL.

1. Introduction

Chronic lymphocytic leukemia (CLL) is a heterogeneous disease with varying clinical outcome, where many patients have an indolent course for many years, whereas others show a more aggressive disease despite treatment. In recent years, the immunoglobulin variable heavy-chain (IGHV) gene mutational status and FISH analysis of certain genomic aberrations (11q−, +12, 13q− and 17p−) have shown to be robust prognostic markers in CLL [1–3]. To date however, the genetic factors which influence the clinical heterogeneity in this malignancy are not fully elucidated.

The murine double minute 2 (MDM2), mapped on chromosome 12q13-14, is an important regulator of the tumor suppressor protein p53 and functions by suppressing p53 transcriptional activity through binding of the p53 transactivation domain [4]. In addition, MDM2 promotes proteasome-mediated degradation of p53 [5]. Since the p53 functions are crucial for tumor suppression, excessive down regulation by MDM2 renders the cells susceptible to neoplastic lesions [6]. Furthermore, p53-independent functions of MDM2 in tumorigenesis have also been described [7], making MDM2 an important player in cancer development.

A polymorphism positioned at nucleotide 309 in the first intron region of the *MDM2* gene (SNP309, rs2279744) has been previously demonstrated to affect p53 function [8]. The study showed that the presence of the homozygous GG genotype in cell lines elevates the expression of MDM2 protein compared to those with TT genotype [8]. This was due to the increased binding affinity of the MDM2 transcriptional activator Sp1 within cell lines with GG genotype. The increased level of MDM2 in turn, is thought to cause inability to stabilize p53 in stressed cells, which may lead to insufficient DNA repair, reduced apoptosis and faster tumor formation [8]. In addition, the presence of GG genotype has also been associated with

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poor outcome in several human cancers, including breast cancer [9], renal cell carcinoma [10], Li-Fraumeni syndrome [11] and oral carcinoma [12]. Furthermore, the presence of GG genotype of the *MDM2* SNP309 has been correlated with early tumor onset among patients with Li-Fraumeni syndrome [8] and colorectal carcinoma [13].

Previous studies on the effects of the *MDM2* SNP309 on clinical outcome in CLL have shown conflicting results. The first reported study, which was performed on small cohort CLL patients (83 cases), did not reveal any effect of the different genotypes on clinical outcome [14]. A subsequent larger study, including two independent CLL cohorts (140 and 111 cases), implicated the *MDM2* SNP309 to affect outcome in CLL, where patients carrying the TG/GG genotypes had significantly shorter overall survival compared to TT carriers, while more progressive disease was indicated in patients carrying GG genotype compared to those with TT/TG genotypes [15]. In addition, the investigators demonstrated that the *MDM2* SNP309 could be applied as a prognostic factor independently of IGHV mutational status, CD38, ZAP-70 and Rai staging. However, these findings could not be verified in a large German CLL cohort (617 cases), as reported by Zenz et al. [16], as they did not observe any significant difference in time to first treatment and overall survival.

Since the relevance of the *MDM2* SNP309 as an unfavorable prognostic marker remains arguable, we here investigated the prognostic role of this SNP in our CLL cohort comprising 418 cases. We also studied the relation of the *MDM2* SNP309 to other known prognostic markers.

2. Materials and methods

2.1. Patients and materials

A total of 418 Swedish CLL patients were included in the current study; 175 patients from Uppsala University Hospital, Uppsala, Karolinska University Hospital, Stockholm and Umeå University Hospital, Umeå and 243 CLL patients from the Swedish part of a population-based case–control study called SCALE (Scandinavian Lymphoma Etiology) [17]. Tumor material was obtained predominantly from peripheral blood (340 cases) and bone marrow (48 cases). In addition, tumor samples were also collected from lymph nodes (26 cases) and spleen (4 cases). Samples displayed the typical CLL immunophenotype ($CD5^+/CD19^+/CD23^+$) and met the diagnostic criteria presented by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) [18]. Informed consent was obtained according to the Declaration of Helsinki and ethical approval by the local ethical review committee.

Survival data was available on all 418 patients, with a median follow-up time of 111 months (quartile range, 60–162 months), while data on time to treatment was available for 287 patients. Binet data was available for 306 patients, with 222 patients classified as Binet stage A, 58 as stage B and 26 as stage C.

2.2. Analysis of the MDM2 SNP309 polymorphism

Genomic DNA was extracted from frozen tumor cells as previously described [19]. DNA was whole-genome amplified according to the manufacturer's protocol (GenomiPhi DNA Amplification, GE Healthcare, Uppsala, Sweden). Identification of the *MDM2* SNP309 genotype was performed using the PCR-restriction fragment length polymorphism (RFLP) method as previously described by Hirata et al. [10], with slight modifications. Briefly, PCR amplification was performed in a 25 μl reaction volume consisting of 100 ng of whole-genome amplified DNA, 800 mM dNTP, 1 unit of Hotstar *Taq* polymerase (Qiagen GmBH, Hilden, Germany), and 2 mM of each forward (5′-CTGCCCACTGAACCGGC-3′) and reverse primers (5′-GAGGTCTCCGCGGGAGTTC-3′). The amplification program comprised of 10 min of denaturing at 95 °C, followed by 30 cycles of 30 s at 95 °C, 30 s at 57 °C and 1 min at 72 °C, with a final step at 72 °C for 7 min. For RFLP analysis, the PCR product was *MSPA1*1 (New England Biolabs GmbH, Frankfurt am Main, Germany) digested, according to the manufacturer's protocol and visualized on 2% agarose gel. A homozygous TT genotype was verified by a 145 bp long fragment. The heterozygous TG genotype produced three fragments (145 bp, 99 bp and 46 bp in size), while the homozygous GG genotype demonstrated two fragments (99 bp and 46 bp).

To verify that the whole-genome amplification process had not caused any false genotyping results, we subjected original genomic DNA from 20 randomly selected samples to the similar genotyping process as mentioned above. We could not detect any differences in genotypes between genomic and whole-genome amplified DNA.

2.3. Assessment of IGHV gene mutational status

The IGHV gene mutational status was assessed by PCR amplification with IGHV gene family-specific primers, followed by sequence analysis as previously described [20,21]. Sequences were submitted to IMGT/V-QUEST [22,23] and GenBank/IgBlast to determine the IGHV identity. The IGHV gene was considered mutated when the identity to the corresponding germline gene was less than 98%.

2.4. Analysis of recurrent genomic aberrations

Cytogenetic screening for recurrent genomic aberrations was performed on 150 patients samples using a commercial CLL FISH probe panel (VYSIS, Downers Grove, IL, USA) to detect del(17)(p13), +12, del(11)(q22), and del(13)(q14). At least 200 interphase nuclei were analyzed for each probe and tumor sample. The cutoff of an aberration was set at >10%. In addition, 130 CLL samples were analyzed using high-resolution Affymetrix 250K SNP-arrays from which we extracted data on known recurrent genomic aberrations, as described in a previous study [24].

2.5. Statistical analysis

All statistical analyses were carried out using Statistica version 8 (Stat Soft, US). Fisher's exact test or *Chi-square* (χ^2) test were employed to determine the significance of differences in genotype usage between patient groups. Comparison of median age at diagnosis between patients with different genotypes was carried out using the Kruskal–Wallis test. Overall survival time was measured from the date of diagnosis to either the last follow-up date (defined as censored) or death. Time to treatment was evaluated by the time interval from the diagnostic date until date of initial treatment. The Kaplan–Meier analysis was performed to construct survival curves for overall survival and time to treatment. Differences in median time to treatment and overall survival between groups were evaluated using the log-rank test.

Univariate Cox proportional hazards model was applied to evaluate the possible association between single risk factors (i.e. sex, age at diagnosis, Binet stage, *MDM2* SNP309 genotype, IGHV mutational status, and genomic aberrations) with overall survival. Variables found to be statistically significant ($p < 0.05$) in the univariate analysis were subsequently included in a multivariate Cox proportional hazards model to evaluate the relationship between the variables.

3. Results

3.1. MDM2 SNP309 genotype distribution

Out of 418 CLL cases included in the study, 44.2% (185 cases) showed the TT genotype of the *MDM2* SNP309, whereas 45.5% (190 cases) displayed a heterozygous genotype and 10.3% (43 cases) were found to carry the GG genotype. There was no difference in median age at diagnosis for patients with the TT, TG and GG genotypes (64, 65 and 64 years, respectively). The *MDM2* SNP309 genotype distribution in our cohort was in accordance with the Hardy–Weinberg equilibrium and was comparable to recently published studies [15,16].

3.2. SNP309 genotype and prognosis

Comparison of overall survival between patients with the different *MDM2 SNP309* genotypes revealed no significant difference (Fig. 1). The median survival was 112 months (range, 60–161 months), 111 months (range, 61–157 months) and 90 months (range, 46–142 months) for patients with the SNP309 TT, TG and GG genotypes, respectively. Furthermore, Kaplan–Meier analysis of time to treatment did not reveal any significant difference between patients with TT, TG and GG genotypes (Fig. 2). The median time to treatment for patients with SNP309 TT, TG and GG genotypes were 25 months (range, 6–107 months), 70 months (range, 5–132 months) and 20 months (range, 4–74 months), respectively.

The *MDM2* SNP309 genotypes were then grouped into T+ alleles (combining the T/T and T/G genotypes into one group) and alleles encompassing the GG genotype. Analysis of time to treatment between the dichotomized groups failed to indicate any significant difference between the two groups ($p = 0.167$, data not shown). In addition, overall survival analysis showed no significant difference between dichotomized groups ($p = 0.263$, data not shown). When

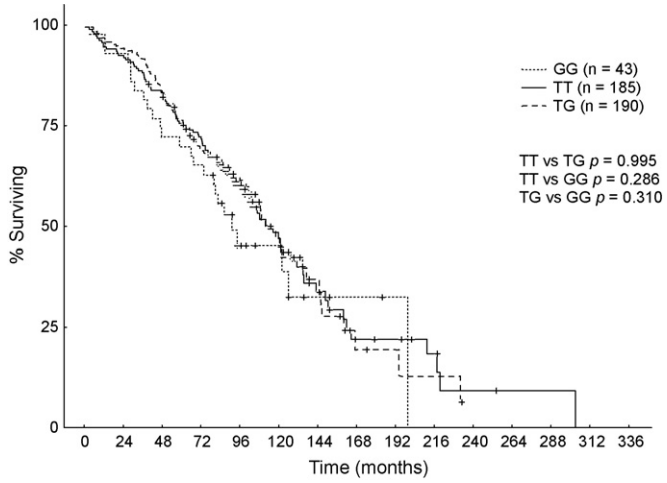

Fig. 1. Overall survival for CLL patients according to the *MDM2* SNP309 polymorphism status. No significant difference was indicated by log-rank test between the genotypes indicated.

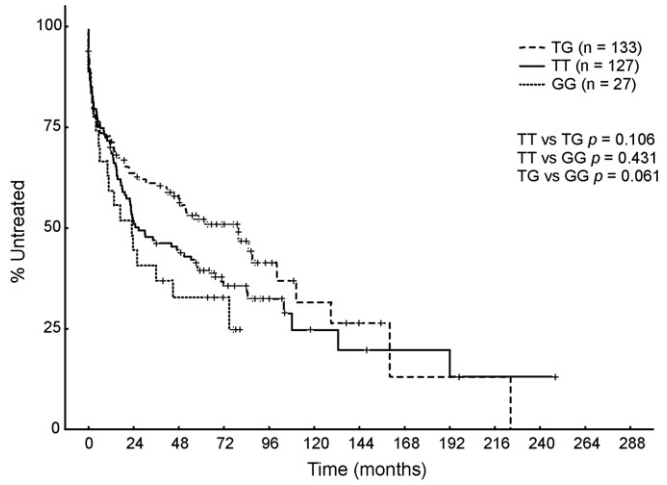

Fig. 2. Time to treatment analysis for CLL patients according to the *MDM2* SNP309 polymorphism status. No significant difference was indicated by log-rank test between any of the genotypes indicated.

studying Binet stage A patients only, no differences were observed in overall survival or time to treatment in patients with different MDM2 SNP309 genotypes (data not shown).

3.3. *MDM2 SNP309 genotype and relation to IGHV mutational status, Binet stage and genomic aberrations*

In line with earlier reports [1,3], overall survival and time to treatment analysis on the current cohort of CLL confirmed unmutated IGHV genes, Binet stages B and C as well as presence of 17p deletion, 11q deletion and trisomy 12 as prognostic markers predicting poor clinical outcome (Table 2).

On the other hand, the *MDM2* SNP309 genotype distribution showed no significant difference in relation to Binet stage, IGHV mutation status and presence of recurrent genomic aberrations, except for trisomy 12 (Table 1). In addition, we did not observe any influence of the *MDM2* SNP309 genotype on overall survival and time to treatment according to IGHV mutational status, Binet stage and type of genomic aberration subgroups (data not shown).

We next performed a Cox proportional hazards regression analysis to identify independent prognostic indicator for overall survival. In univariate analysis, age at diagnosis, gender, Binet stage, IGHV mutational status and genomic aberrations significantly influenced overall survival (Table 3), and in multivariate analysis, all factors except gender remained significant (Table 3).The SNP309 showed no significant association with prognosis when analyzed in univariate analysis and was subsequently not included in multivariate analysis.

4. Discussion

The relevance of the MDM2 SNP309 genotype as a prognostic marker in CLL has been suggested in recent findings by Gryshchenko et al. [15]. These authors showed that the *MDM2* SNP309 G allele correlated to inferior disease outcome, where CLL patients with the GG genotype had shorter overall survival and time to treatment. In addition, based on regression analysis between the SNP309 genotypes and other prognostic markers, e.g. IGHV mutational status, CD38, ZAP-70 expression and Rai stage, the investigators identified *MDM2* SNP309 as an independent marker for prediction of treatment-free survival in CLL. They also observed that the effect of *MDM2* SNP309 on progression, at least partly depended on the

Table 1
Clinical data of the current cohort of CLL cases genotyped for the MDM2 SNP309 polymorphism.

Variable	All patients	TT	TG	GG	*p* value*
No. of patients (%)	418	185 (44.2%)	190 (45.5%)	43 (10.3%)	
Median age at diagnosis (years)		64	65	64	NS[a]
Binet stage	306				
A	222 (72.5%)	101 (45.5%)	96 (43.2%)	25 (11.3%)	NS
B	58 (19.0%)	29 (50.0%)	22 (37.9%)	7 (12.1%)	NS
C	26 (8.5%)	11 (42.3%)	11 (42.3%)	4 (15.4%)	NS
IGHV mutation status	409				
Mutated IGHV gene	239 (58.4%)	106 (44.4%)	114 (47.7%)	19 (7.9%)	NS
Unmutated IGHV gene	170 (41.6%)	77 (45.3%)	69 (40.6%)	24 (14.1%)	NS
Genomic aberrations	280				
No aberration	65 (23.3%)	19 (29.2%)	35 (53.8%)	11 (16.9%)	NS
13q deletion	128 (45.7%)	63 (49.2%)	56 (43.8%)	9 (7.0%)	NS
11q deletion	40 (14.3%)	16 (40.0%)	20 (50.0%)	4 (10.0%)	NS
17p deletion	20 (7.1%)	8 (40.0%)	9 (45.0%)	3 (15.0%)	NS
Trisomy 12	27 (9.6%)	14 (51.8%)	9 (33.3%)[b]	4 (14.8%)	0.02

* Comparisons were made against the total number of the CLL patients for each genotype.
NS = not significant between groups by either the χ^2 test or the Fisher's exact test.
[a] NS: not significant between groups by Kruskal–Wallis test.
[b] Due to the limitations of genotyping methods, TTG and TGG genotypes were not distinguishable.

Table 2
Overall survival and time to treatment data of the current cohort of CLL cases according to Binet stage, IGHV mutation status and recurrent genomic aberrations.

Variable	Overall survival					Time to treatment				
	Valid, *N*	Median (months)	Interquartile ranges (months)		*p* value	Valid, *N*	Median (months)	Interquartile ranges (months)		*p* value
			25%	75%				25%	75%	
Binet stage	306					241				
A	222	142	84	209		175	79	21	140	
B	58	72	41	92		45	2	1	11	
C	26	47	35	90	<.001[a]	21	0	0	4	<.001[a]
IGHV mutational status	409					282				
Mutated IGHV gene	239	146	105	210		170	102	17	163	
Unmutated IGHV gene	170	70	42	101	<.001	112	14	2	35	<.001
Genomic aberrations	280					226				
No aberration	65	129	92	177		51	Not achieved	15	Not achieved	
13q deletion	128	121	99	220		104	91	19	149	
11q deletion	40	71	46	111		33	4	1	40	
17p deletion	20	58	31	120		15	5	1	45	
Trisomy 12	27	77	49	109	<.001[b]	23	16	1	39	<.001[b]

[a] Log-rank test was made to compare between Binet stage A against combined stages B and C.
[b] Log-rank test was performed to compare between patients with either 11q deletion, 17p deletion or trisomy 12 against those with 13q deletion or no genomic aberration.

Table 3
Cox regression analysis of overall survival.

Variable	Comparison	Valid, *N*	Univariate analysis			Multivariate analysis		
			HR	95% CI	*p* value	HR	95% CI	*p* value
Age at diagnosis	≤65 vs. >65 years old	418	1.77	1.34–2.34	<0.0001	2.10	1.38–3.19	0.0005
Gender	Female vs. male	418	1.47	1.08–1.98	0.01	1.62	0.99–2.67	0.054
Binet stage	A vs. B + C	307	3.67	2.64–5.11	<0.0001	3.39	2.19–5.22	<0.0001
IGHV mutational status	Mutated vs. unmutated	409	3.73	2.81–4.95	<0.0001	3.20	1.89–5.40	<0.0001
Genomic aberration	Normal + del(13q) vs. del(17p) + del(11q) + trisomy 12	280	3.04	2.13–4.34	<0.0001	2.32	1.45–3.71	0.0004
MDM2 SNP309	TT/TG vs. GG	418	1.27	0.84–1.94	0.2	Not included		
	TT vs. GG/TG	418	1.05	0.80–1.38	0.7			

Abbreviations: HR, hazard ratio; CI, confidence interval.

p53 status in a gene-dosage fashion, since both TG and GG genotypes correlated significantly with reduced treatment-free survival in patients with monoallelic loss of 17p. Furthermore, the presence of the G allele was shown to increase the MDM2 protein expression levels in CLL cells [15].

However, no significant difference was observed in time to treatment or overall survival among patients with the different genotypes in the present study. Thus, we found no support for an influence of *MDM2* SNP309 on clinical outcome in CLL patients. Likewise, no correlation was apparent between the different *MDM2* SNP309 genotypes and Binet stage, IGHV mutation status or genomic aberrations. It was noted that the distribution of SNP309 genotypes were significantly different in patients with trisomy 12. However, the relevance of this finding, if any, is unknown. Moreover, we addressed whether the *MDM2* SNP309 correlates with CLL age at diagnosis, since such observations were reported in other types of cancers [8,13]. Comparison of age at diagnosis between patients with different *MDM2* SNP309 did not reveal any significant difference.

In line with our findings, Zenz et al. [16] have also been unable to detect any influence of the *MDM2* SNP309 on either overall survival or disease progression. Additionally, no correlation was found between the polymorphism and either Binet stage or other molecular prognostic factors in CLL, such as genomic aberrations and IGHV mutational status. Furthermore, the authors also argued against the postulated effect of the *MDM2* SNP309 on the expression of MDM2 protein itself, since no significant difference in *MDM2* mRNA levels based on the SNP309 genotype was found [16].

In conclusion, the *MDM2* SNP309 does not appear to influence the clinical course in CLL and should not be considered as a new prognostic marker for outcome prediction. In recent years, a number of SNPs have been suggested as useful prognostic markers in CLL. The presence of certain SNPs within the *BAX* [25], *P2X7* [26], *GNAS1* [27] and *BCL2* [28] genes have been associated to disease progression and inferior survival for the patients. However, none of these potential SNPs have been confirmed in subsequent investigations by other groups [19,29–32]. Thus, it is important that any potential SNP should be verified by large independent cohorts and independent research centers.

Conflict of interest

The authors report no potential conflicts of interest.

Authorship and disclosures

MAK performed research, analyzed data and wrote the paper; MM and NZ analyzed data and wrote the paper; NC, RG, MJ and JJ provided associated phenotypic and molecular data; EK, AÅ, JL and GJ provided clinical data, BG and MM provided samples and associated data, RR supervised the research and wrote the paper.

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