ANALYSIS OF GENETIC POLYMORPHISMS AND PROGNOSTICAL SIGNIFICANCE OF CLINICAL PARAMETERS IN MYELODYSPLASTIC SYNDROME AND MULTIPLE MYELOMA

PhD thesis

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INTRODUCTION

We performed investigations in two, despite of recent treatment advances still incurable malignant hematological group of disorders, that have increasing incidence in the past decades due to the expanded life expectancy of the popuation. We conducted researches in the field of the genetic beckground of these diseases, and looked for simple, suitable prognostic factors, that can effectively guide treatment decisions.

The myelodysplastic syndrome (MDS) is a heterogenous group of clonal stem cell disorders characterized by ineffective hematopoiesis, due to excessive intramedullar apoptosis of progenitors. This apoptosis is largely cytokine mediated by paracrine as well as autocrine factors implicating both the the marrow microenviroment and the progenitors. Tumor necrosis factor-alpha (TNF-α) has a central role in this dysregulated apoptotic pathyways.

According to the WHO classification multiple myeloma (MM) is a peripheral B- cell clonal neoplasm caused by the proliferation of transformed plasma cells in the bone marrow. The proliferation of normal and malignant plasma cells is under control of a complex network of cytokines. Among the potential MM growth factors, TNF-α is a survival factor for MM cell lines, induces MM cells in the cell cycle and promotes long-term growth of malignant plasma cells. It acts either in a synergistic manner with interleukin-6 (IL-6), the major myeloma growth factor, but also may effect through a pathway independent of IL-6, having a growth-promoting effect at least equal to that of IL-6.

TNF-α is a cytokine of the tumor necrosis factor family. Through it's pro-inflammatory activity it is one of the most important mediators of the inflammation and immune regulation, but it plays prominent role in the apoptosis, proliferation, morphogenetic changes and differentiation as well. TNF-α and lymphotoxin-alpha (LT-α or LTA) belong to the same cytokine family, they have similar biological activities and bind to the same group of cellular TNF receptors. Both TNF-α and LT-α are known to play key roles in B cell growth, differentiation and maturation.

The genes coding for TNF-α and LT-α are located tandem within the class III region of the highly polymorphic major histocompatibility complex on human chromosome 6p21. The *TNF* gene is known to be in linkage disequilibrium with the gene for LT-α.

Positions of -238G>A (rs361525) and -308G>A (rs1800629) polymorphisms in the *TNF* promoter region and +252 A>G (rs909253) in the first intron of the *LTA* gene are considered to have functional significance in terms of regulating TNF-α production. The TNF -308A and the LTA +252G variant alleles are constituents of the extended ancestral haplotype (AH8.1), that is relatively frequent in Caucasian population and is known to be associated with high spontaneous TNF production.

Several lines of evidence suggest that genetic factors are involved in MM pathogenesis. In the last decade the results of the genome-wide association studies (GWAS) of MM have direct evidence for genetic predisposition been demonstrated. The first GWAS reported 3 genetic loci at 2p23.3 (rs6746082), 7p15.3 rs4487645) and 3p22.1 (rs1052501) positions that are robustly associated with MM risk. They were new genetic regions being not mentioned in connection with the pathogenesis of MM until now. Multiple replications in independent populations are very important to lend credibility to the findings of the association studies. In 2011 an international research group focusing on epidemiology, genetic and pharmacogenomics of MM, named the International Multiple Myeloma rESEarch (IMMEnSE) consortium was constituted. We have joined to this international cooperation with 139 MM patients and 104 controls representing Hungary in the study, the aim was to validate the original reported associations with a population of over 1100 case-control pairs.

Considerable heterogenity exsist in the survival outcomes and response to treatment among patients diagnosed with MM. Finding suitable prognostic factors is an issue. Numerous prognostic factors have been identified as having importance in the pre-treatment evaluation of patients, however no consensus has been achieved so far. In a previous study published in 2008, an A/M ratio, containing albumin (A) and monoclonal component (M) at diagnosis, and a created AMWBC score system containing the A/M ratio and the WBC count at diagnosis, emerged as a reliable predictor of survival duration in patients treated with conventional chemotherapy. Several novel effective agents – immunomodulatory drugs (IMiDs) and proteasome inhibitors – have been approved for myeloma treatment armamentarium in the last decade with resultant considerable improvement in outcome, hence the validation of these prognostic features in the era of novel agents is necessary.

OBJECTIVES

MYELODYSPLASTIC SYNDROME

In order to gain insight into the genetic background of the disease, knowing that TNF-α has a central role in the apoptosis resulting the ineffective hematopoiesis observed in MDS, we investigated the genetic polymorphisms of the *TNF* gene with functional significance. Our hypothesis was that the high producer variant allele containing genotype frequency is higher in the MDS patients than in the controls. Our question was:

- Is there any difference between MDS patients and controls with respect to the distribution of TNF –238 and TNF –308 genotypes?

MULTIPLE MYELOMA

Investigating the genetic backgrund of MM we analysed the distribution of variant allels with higher TNF-α production either alone or their combination across in the TNF region in the form of haplotypes in MM patients and in controls, supposing that they act as markers for predisposition and may contribute to the pathogenesis of the disease. We could not find publication in the literature so far about the frequency of AH8.1 carriers in MM patients. The AH8.1 extended ancestral haplotype was determined by the coexistence of TNF −308G>A, LTA +252A>G, HSP70-2 +1267A>G and RAGE −429T>C polymorphisms. According to this we investigated:

- The distribution of the allele frequency of TNF −308G>A, LTA +252A>G, HSP70-2 +1267A>G and RAGE −429T>C polymorphisms in MM patient and in age and gender-adjusted controls

- The frequency of the carriers and non-carriers of the high producer TNF2-LTA 252G haplotype in MM patients and age and gender-adjusted controls

- The frequency of the carriers and non-carriers of the AH8.1 extended ancestral haplotype in MM patients and age and gender-adjusted controls

The first GWAS in MM reported 3 genetic loci at 2p23.3 (rs6746082), 7p15.3 (rs4487645) and 3p22.1 (rs1052501) positions that are associated with the disease risk. In a cooperative study with the international (IMMEnSE) consortium we wanted to validate the original reported associations with a population of over 1100 case-control pairs. Our question was as follows:

- Is there any difference in the genotype and allele distributions of 2p23.3 (rs6746082), 7p15.3 (rs4487645) and 3p22.1 (rs1052501) polymorphisms in MM cases and controls?

We would like to validate a previously published score system containing simple, reproducible, readily available laboratory parameters that emerged as a reliable predictor of survival duration originally in myelotoxic chemotherapy treated patient population, now testing it in patients treated with novel treatment modalities. We planned to examine:

- The prognostic role of the A/M ratio, containing albumin (A) and monoclonal component (M) at diagnosis, and a created AMWBC score system containing the A/M ratio and the WBC count at diagnosis in patients treated with IMiD or bortezomib-based novel regimens.

METHODS

PATIENTS

MYELODYSPLASTIC SYNDROME

69 MDS patients (26 males and 43 females) participated who were diagnosed before 2005 at the Semmelweis University, 3rd Department of Faculty of Medicine. 125 healthy controls (38 males and 87 females), non-related people from the Caucasian population were recruited in an outpatient department providing regular health checkup for healthy employees on a mandatory basis.

MULTIPLE MYELOMA

In the TNF-α study a total of 94 consecutive cases with MM diagnosed between 1997 and 2005 were enrolled. Eligible patients had to have symptomatic multiple myeloma. Patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma were excluded from the study. The control group consisted of 141 people matched in age and sex composition, with no hematological or oncological disease. The sampling frame for this reference group included all those registered with the participating practices in the Hungarian General Practitioners' Morbidity Sentinel Stations Program in 2001.

In the IMMEnSE consortium study 1139 MM cases from 14 groups in research and clinical institutions of 8 European countries and 1352 controls were participated, whose samples have been genotyped. From Hungary our study group contributed to the study with 139 MM patients and 104 controls. Incident cases of MM diagnosed from 1990 to 2010 were recruited. Controls were selected among the general population (Italian), blood donors (Polish, Portuguese and French) or among hospitalized subjects with different diagnoses excluding cancer (Spanish and Hungarian). All cases and controls used in this study were of Caucasian origin.

In the AMWBC score retrospective analysis records of 103 consecutive patients in whom multiple myeloma was newly diagnosed between January 1996 and July 2006 were reviewed. Patients were diagnosed, followed, and treated at the Semmelweis University 3rd Department of Faculty of Medicine. Patients were excluded if they had any other clonal plasma cell disorders like MGUS, SMM or amyloidosis. In case of light chain disease and nonsecretory myeloma the A/M ratio cannot be interpreted, therefore these patients were not enrolled either. So as to have more homogenous patients group regarding the survival, transplanted patients and those, who had a concomitant other malignant disease were excluded as well. From the total of the 103 patients 47 were given only conventional therapy and 56 persons were treated with non-myelotoxic novel treatment modalities - thalidomide, bortezomib - alone or in combination with conventional agents.

LABORATORY METHODS

The TNF -238G>A (rs361525), TNF -308 G>A (rs1800629) SNPs and the HSP70-2 +1267A>G (rs1061581) as well as the RAGE -429 T>C (rs1800625) SNPs were analyzed using restriction fragment length polymorphism (RFLP) technique at the Research Laboratory of the Semmelweis University 3rd Department of Faculty of Medicine.

Genotyping of LTA 252A>G (rs909253) polymorphism was carried out by PCR-RFLP in the laboratory of the Department of Medical Genetics and Child Development Faculty of Medicine, University of Pécs.

In the IMMEnSE study the analysis of the 7p15.3 (rs4487645), 3p22.1 (rs1052501) and 2p23.3 (rs6746082) polymorphisms were performed in the laboratory of the German Cancer Research Centre in Heidelberg. With the exception of the Danish controls, genotyping was carried out using TaqMan (ABI, Applied Biosystems, Foster City, CA, USA) technology, according to the protocol specified by the manufacturers. PCR plates were read on an ABI PRISM 7900HT instrument (Applied Biosystems). Genotyping for Danish controls was performed with Human Hap 550 Infinium II Chip and Human 610-Quad Chip (Illumina, San Diego CA, USA) in the context of previously published GWASs and made available for this analysis.

RESULTS

MYELODYSPLASTIC SYNDROME

Distribution of the genotype variants of TNF -238G>A (rs361525) and TNF -308G>A (rs1800629) polymorphisms in MDS patients and controls

The distribution of the TNF -308 GG, GA and AA genotypes was almost the same in the two populations. However, there was a slight difference in the frequencies of the TNF -238 genotype variants, but it did not reached the statistical significance *(Table 1).* The distribution of the -308 alleles in the control group correspond to the previously published data of the Hungarian population.

Table 1. The distribution of the two analyzed TNF gene polymorphism in MDS patients and in the control group

	GG	GA	AA	
TNF -308				
MDS (n=69)	50(72%)	17(25%)	2(2,9%)	p=0,91
Control (n=125)	87(69%)	34(27%)	4(3%)	
TNF -238				
MDS (n=69)	62(91%)	6(8,8%)	0(0%)	p=0,0815
Control (n=125)	121(96,8%)	4(3,2%)	0(0%)	

A: adenin G: guanin
The appropriate genotypes are given in numbers and the percentage in parentheses.
For statistical analyses Fisher's exact test was applied.

MULTIPLE MYELOMA

TNF -308G>A (rs1800629), LTA +252A>G (rs909253), HSP70-2 +1267A>G (rs1061581), RAGE -429T>C (rs1800625) polymorphisms variants and their haplotypes in MM patients and controls

Frequency of the TNF -308A (TNF2) variant allele was significantly (p=0,027) lower in the gruop of patients (9,6 %) then in the control group (21,3 %). By contrast we did not find significant differences between the two groups in the frequency of the other SNPs tested. When the frequency of the carriers and non-carriers of the TNF2-LTA 252G haplotype was compared between patients (9,6 %) and controls (20,6 %), a significantly lower frequency (p=0,041) was found in the MM patinets. By contrast, the frequency of the AH8.1 carriers was about the same in both groups.

Next, in order to check if the results obtained with univariate analysis can be repeated by multivariate analysis as well, we compared the allele and haplotype frequencies in patient and control groups by age- and gender-adjusted multiple logistic regression. Both the carrier state of the TNF2 variant allele and the TNF2-LTA 252G haplotype was associated with significant, more than two times decreased odds to belong to the MM group, while no such relationship was found with the other alleles tested for the carrier state of AH8.1 *(Table 2)*.

Table 2. Frequency of carriers of the TNF -308A allele, LTA 252G allele, HSP70-2 +1267G allele, RAGE -429C allele, the TNF -308-LTA 252G haplotype as well as the 8.1 ancestral haplotype among patients with MM and age-matched control subjects as well as odds ratio of the carriers vs. non-carriers for MM (calculated by age- and gender-adjusted multiple logistic regression analysis)

Genotype	Number (frequency) of the variant allele or haplotype		Odds ratio (95%CI)	p value
	Patient group (n=94)	Control group (n=141)		
TNF-308 G>A	9 (9,6%)	30 (21,3%)	0,402 (0,179-0,902)	**0,027**
LTA +252 A>G	43 (45,9%)	72 (51,1%)	1,134 (0,668-1,923)	0,642
HSP70-2 1267 A>G	60 (63,5%)	76 (53,8%)	1,269 (0,852-1,889)	0,242
RAGE-429 T>C	25 (26,1%)	43 (30,8%)	0,894 (0,517-1,547)	0,690
TNF-308A-LTA 252G haplotype	9 (9,6%)	29 (20,6%)	0,429 (0,191-0,965)	**0,041**
8.1 ancestral haplotype	5 (9,45%)	11 (7,7%)	0,855 (0,267-2,740)	0,792

Regarding the subgroup analysis, since we found significant (p=0,026) interaction between the age and the TNF-308A (TNF2) variant allele for the difference between the MM patient and control groups, we studied if the same association between the risk of myeloma and TNF2 carrier frequency stands for both the relatively young and elderly subjects. We divided the subjects according to the median age of the control group (≥69 years, <69 years). Frequency of the TNF2 carriers was lower in the younger than in the older subgroup (6,9 % and 13,3 %, respectively). Carriers of the TNF2 allele had almost 5 times decreased odds to develop MM in the younger patients (<69 years of age), while in the group of ≥69 years old subjects no significant association between the carrier state of the TNF2 allele and the odds of multiple myeloma was calculated *(Table 3).*

Table 3. Odds ratio of the carriers of TNF -308A (TNF2) variant allele, carriers vs. non-carriers for MM (calculated by gender-adjusted multiple logistic regression analysis) divided according to age

Age group	Age at diagnosis, years, median (interquartile range)	TNF2 carrier/all subjects (%)		Odds ratio (95% CI)	p value
		Patients	Controls		
≤69 years	53,0 (45,0-60,0)	3/49 (6,9)	17/68 (25,0)	0,203 (0,056-0,742)	**0,016**
>69 years	69,0 (66,0-72,5)	6/45 (13,3)	13/73 (17,8)	0,809 (0,272-1,409)	0,7000

Similar, but even higher age-dependent difference was found when carrier state of the TNF2-LTA 252G haplotype was considered (gender-adjusted odds ratios for the younger and older subgroups were 0,196 (0,054-0,711, p=0,013) and 0,710 (0,249–2,025, p = 0,522), respectively).

We also divided the study group by gender. Negative association between the TNF2 allele and multiple myeloma was detected only in females, where the carrier state of this allele was associated with a four times lower risk. By contrast, in males no significant association was found *(Table 4)*.

Table 4. Odds ratio of the carriers of TNF -308A (TNF2) variant allele, carriers vs. non-carriers for MM (calculated by gender-adjusted multiple logistic regression analysis) divided according to gender

Gender	TNF2 carriers/all subjects (%)		Odds ratio (95% CI)	p value
	Patients	Controls		
Males	5/28 (17,9)	13/60 (21,7)	0,76 (0,24-2,47)	0,650
Females	4/66 (6,1)	17/81(21,0)	0,24 (0,08-0,76)	**0,015**

A 7p15.3 (rs4487645), 3p22.1 (rs1052501) és 2p23.3 (rs6746082) polymorphisms in MM patients and control subjects

The strongest association was shown by rs4487645 at 7p15.3, with an almost 1,4-fold increased risk for the C allele (odds ratio [OR] = 1,37, 95% confidence interval [CI]: 1,21–1,56, p = 0,0000000796). The second strongest association was observed for the A allele of the rs6746082 at 2p23.3 (OR = 1,22, 95%CI: 1,05–1,41, p = 0,0080), while a non-significant association with the OR going in the same direction reported previously was found for the rs1052501 at 3p22.1 (OR = 1,12, 95%CI: 0,98–1,30, p = 0,098) *(Table 5)*.

Table 5. Association of genetic loci at 7p15.3 (rs4487645), 3p22.1 (rs1052501) and 2p23.3 (rs6746082) with MM risk in the IMMEnSE population

SNP	Cases (%)	Controls (%)	OR	95%CI	p value
rs4487645 (7p15.3)					
A/A	67 (6,3)	139 (10,4)	1	–	–
A/C	423 (39,8)	598 (44,9)	1,47	1,07–2,02	**0,017**
C/C	572 (53,9)	595 (44,7)	1,99	1,45–2,73	**0,00000173**
A	557 (26,2)	876 (32,9)	1	–	–
C	1567 (73,8)	1788 (67,1)	1,37	1,21–1,56	**0,0000000796**
rs6746082 (2p23.3)					
C/C	35 (3,3)	61 (4,6)	1	–	–
A/C	304 (28,7)	425 (31,8)	1,21	0,78–1,89	0,392
A/A	721 (68,0)	849 (63,6)	1,48	0,96–2,27	0,074
C	374 (17,6)	547 (20,5)	1	–	–
A	1746 (82,4)	2123 (79,5)	1,22	1,05–1,41	**0,008**
rs1052501 (3p22.1)					
A/A	655 (61,5)	870 (65,7)	1	–	–
A/G	371 (34,9)	399 (30,1)	1,25	1,05–1,49	**0,011**
G/G	38 (3,6)	56 (4,2)	0,93	0,60–1,42	0,726
A	1681 (79,0)	2139 (80,7)	1	–	–
G	447 (21,0)	511 (19,3)	1,12	0,98–1,30	0,098

A: adenin G: guanin C: citozin
The appropriate genotypes/alleles are given in numbers and the percentage in parentheses.

Albumin / M protein (A/M) ratio and the AMWBC score system as a predictor of survival in newly diagnosed MM patients

The pre-treatment A/M ratio, WBC count *(Table 6.)* and the AMWBC score *(Table 7.)* were determined in all cases, and correlated to the survival.

Table 6. The correlation of the pre-treatment A/M ratio and WBC count with the prognosis

A/M	< 1	poor prognosis
WBC	< 4.5 G/l	poor prognosis

Table 7. AMWBC prognostic score index calculation

Score	0	1
A/M	≥ 1	< 1
WBC	≥ 4.5 G/l	< 4.5 G/l

0 score: good prognosis
1 score: intermediate prognosis
2 score: poor prognosis

Our results, in agreement with the original study, show that those patients who had A/M < 1 at diagnosis have significantly poorer prognosis either at the 2 years (p=0,006) and at the 5 years (p=0,005) survival endpoint as well *(Figure 1)* in the total of 103 patients.

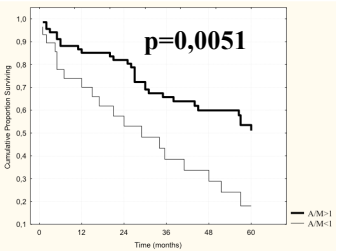

Figure 1. A/M ratio and survival in all MM patients at 5 years endpoint p=0,0051 (n=103)

In the 56 patients treated with the novel therapy significant difference was observed at the 2 years endpoint (p=0,015) and a near significant difference at the 5 years survival endpoint (p=0,07) *(Figure 2 and 3)*.

p = 0,015

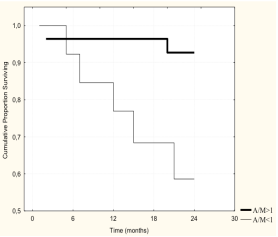

Figure 2. A/M ratio and survival in MM patients treated with novel agents at 2 years endpoint p=0,015 (n=56)

p = 0,07

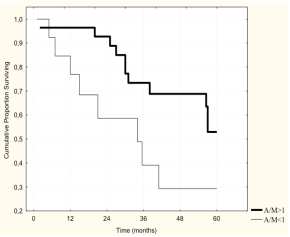

Figure 3. A/M ratio and survival in MM patients treated with novel agents at 5 years endpoint p=0,07 (n=56)

In our present study there was no significant correlation between the initial lower WBC count and the survival time, neither in the total of 103 patients, and nor in the group of 56 patients who received novel therapy (data not shown). When the patients were selected according to the AMWBC score system, we found a near significant statistical difference at the 5 years survival period (data shown in the group of 56 patients treated with novel therapy [p = 0,056]), and according to our present findings we consider, that this result is attributable particularly to the A/M ratio *(Figure 4)*.

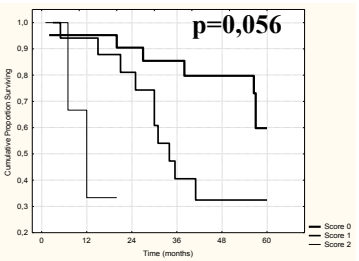

Figure 4. Survival at 5 years endpoint according to the AMWBC score in patients treated with novel agents p = 0,056 (n=56)

CONCLUSIONS

The aim of our research was to investigate the genetic background of two common malignant hematological disorders: the myelodysplastic syndrome and the multiple myeloma, and in case of myeloma we analysed the prognostic value of some simple laboratory parameters. The answers to our questions defined in the objetives are as follows:

MYELODYSPLASTIC SYNDROME

1. Analysing the genetic polymorphisms of the *TNF* genes with functional significance we did not find any difference between MDS patients and controls with respect to the distribution of TNF –238 and TNF –308 genotypes. In our work we could not support that the investigated genetic polymorphisms of the *TNF* gene act as markers for predisposition of MDS.
2. The distribution of the –308 alleles in the control population corresponds to the previously published data from the Hungarian population.

MULTIPLE MYELOMA

3. Frequency of the variant TNF2 allele was significantly ($p = 0.027$) lower in the group of MM patients than in the age and gender-adjusted control group.
4. The frequency of the carriers of the high producer TNF2-LTA 252G haplotype were significantly lower ($p = 0.041$) in MM patients than in age and gender-adjusted controls.
5. In order to check if the results obtained with univariate analysis can be repeated by multivariate analysis as well, we compared the allele and haplotype frequencies in MM patient and control groups by age- and gender-adjusted multiple logistic regression. Both the carrier state of the TNF2 allele and the TNF2-LTA 252G haplotype was associated with a significant, more than two times decreased odds to belong to the multiple

myeloma group, while no such relationship was found with the other alleles tested or for the carrier state of AH8.1 extended ancestral haplotype. Our present findings indicate that carriers of the TNF2 allele or those of the TNF2-LTA 252G haplotype have a decreased risk for multiple myeloma.

The difference was, however, restricted to the females, as well as the relatively young (<69 years) subjects. Since both rare alleles can be considered as high producers that are associated with a more pronounced ability to mount TNF-alpha or lymphotoxin-alpha for different stimuli, it seems that high production of these cytokines in patients as compared to controls does not facilitate development of MM but even may have a protective effect. Due to the low case numbers this result should be confirmed.

6. We did not find significant differences between the MM patients and control groups in the frequency of LTA +252A>G (rs909253), HSP70-2 +1267A>G (rs1061581), RAGE -429T>C (rs1800625) polymorphisms and the AH8.1 extended ancestral haplotype tested.
7. Very strong association was shown by rs4487645 at 7p15.3, with an almost 1,4-fold increased MM risk for the C allele. This polymorphism site is in connection with a region that encodes a MYC-interacting protein and these findings strongly point towards a crucial role of the MYC pathway in MM onset.
8. Strong association was observed for the A allele of the rs6746082 at 2p23.3 with a 1,22-fold MM risk. This association annotates a gene, DNA (cytosine-5)- methyltransferase 3 alpha (DNMT3A) that encodes a DNA methyltransferase. It is highly expressed gene in MM- regulating cytokines and it can focus the attention on the epigenetic regulation.
9. Patients with A/M<1 at diagnosis have significantly poorer prognosis, while A/M >1 refers on longer survival. It could be confirmed in case of patients treated with novel therapies. A/M is useful to separate the poor prognostic group of patients who requires more aggressive therapy, it can be recommended completed with genetic tests for predicting prognosis of MM patients.

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