

HLA Specificities and Predisposition to the Development of Multiple Myeloma

Meral Beksac, MD; Martin Maiers, MS, PhD; Loren Gragert, BS, BA; Stephen Spellman, MBS; Smriti Shrestha, MS, MA; Mei-Jie Zhang, PhD; Angela Dispenzieri, MD; Donna E. Reece, MD; David H. Vesole, MD, PhD; and Parameswaran Hari, MD, MS

On behalf of the Plasma Cell Disorders Writing Committee, Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin, Milwaukee, WI, USA



Introduction

- ◆ HLA associations for the risk of developing Multiple Myeloma (MM) in various non-Caucasian ethnic groups have not revealed consistent results
- ◆ Several lines of evidence suggest that HLA polymorphisms may affect the risk of developing MM. These include:
 - ❖ Racial and genetic differences in cytokine polymorphisms linked to extended haplotypes
 - ❖ Association of autoimmune disorders with HLA types
 - ❖ Proximity of the HLA Class I and II genes to genes responsible for complement and cytokines
- ◆ Aim: Define HLA specificities associated with the risk of developing MM (predictive or protective) in North American Caucasian individuals

Methods (continued)

- ◆ Patients had either received a matched sibling allogeneic transplant (alloHCT) for MM reported to the CIBMTR (N=174) or had HLA typing performed and reported to the US National Marrow Donor Program (NMDP) for an unrelated donor search (N=1,629)
- ◆ HLA-A, B and DRB1 allele frequencies among patients (N=1,803) were compared to A-B-DRB1 frequencies in HLA typed healthy US Caucasian volunteers from the NMDP database (controls, N=433,838)
- ◆ Most frequent alleles among patients and controls as well as HLA haplotype frequencies estimated using the EM (expectation-maximization) algorithm were compared using Chi-square analysis with Bonferroni correction for the number of comparisons

Results

Allele/Haplotype	Frequency Controls	Frequency MM	Odds Ratio (OR)	P value (corrected)
A*02-B*44-DRB1*13	0.00620	0.00277	0.445	0.065
B*44-DRB1*13	0.01359	0.00686	0.507	0.003
A*02-B*44-DRB1*04	0.02605	0.01813	0.686	0.021
B*44	0.14552	0.12618	0.848	0.005
B*07	0.13313	0.14836	1.134	0.047
B*07-DRB1*13	0.00814	0.01397	1.714	0.007
A*02-B*07-DRB1*04	0.00367	0.00721	1.968	0.029

- ◆ B*44 was observed less frequently among the patients (a protective effect) (OR=0.848, p=0.005)
- ◆ B*07 was more common (a predisposing effect) among patients (OR=1.135, p=0.047)
- ◆ Among the top 20 two locus (HLA-A-B and HLA-B-DRB1) haplotype frequencies in either group, B*44-DRB1*13 and B*07-DRB1*13 were significant (OR=0.506 and 1.714, p=0.003 and 0.007, respectively)
- ◆ A-B-DRB1 haplotype comparisons showed significance for:
 - ❖ A*02-B*44-DRB1*04 (OR=0.686, p=0.021), (protective for MM)
 - ❖ A*02-B*07-DRB1*04 (OR=1.968, p=0.029) (predictive for MM)

Discussion

- ◆ Recognition of some MM associated antigens by HLA class I epitopes and association of some ancestral haplotypes with autoimmune disorders constitute the basis of this research

Conclusion

- ◆ Largest epidemiologic study of HLA allele frequencies and haplotype frequencies in MM
- ◆ Two alleles were identified with disparate effect on the risk of MM
- ◆ HLA-B44: a protective effect observed on the risk of MM (OR=0.85)
- ◆ HLA B*07: a predisposing effect observed on the risk of MM (OR=1.13)
- ◆ Similar predisposing and protective haplotype associations observed with A*02-B*07-DRB1*04 (OR=0.69) and A*02-B*44-DRB1*04 (OR=1.97), respectively
- ◆ The current study population was derived from a relatively young cohort of MM patients considered for AlloHCT, validation studies in other MM patient populations are warranted
- ◆ Similar studies need to be replicated in other ethnic groups to identify HLA polymorphisms that may affect the risk of MM
- ◆ Further study including major histocompatibility region SNP mapping and candidate gene testing will help elucidate the genetic basis underlying this observation

Methods

- ◆ HLA-A,-B and -DRB1 2-digit allele and haplotype frequencies in patients with MM were compared to the normal population
- ◆ 1,803 US Caucasian patients with MM were identified based on availability of HLA-A, B, DRB1 DNA-based typing or serologic typing converted to 2-digit alleles

Characteristics

	Patients	Controls
Median Age, years	49	44
Male/ Female ratio	1.86	0.74

- ◆ 62% patients were younger than 60 years and only 4% older than 70
- ◆ Reflects treatment bias limiting the use of HCT to younger patients with MM

There are no relevant conflicts of interest to disclose.