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Title: Race-Based Differences in Routine Cytogenetic Profiles of Patients with Multiple Myeloma

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Multiple myeloma (MM) is an haematological malignancy for which there is no cure with standard therapy (Howlader, *et al* 2014). Black patients have an incidence of MM that is twice that of white patients (Avet-Loiseau, *et al* 2010, Jagannath, *et al* 2007, Pineda-Roman, *et al* 2008, Sagaster, *et al* 2007). Despite the increased incidence, black patients with MM experience better overall survival (Howlader, *et al* 2014). Cytogenetics represent an important factor in MM prognostication (Corre and Avet-Loiseau 2011). Deletion of chromosome 13q, detected by routine karyotype analysis, or t(4; 14), detected by fluorescent in situ hybridization (FISH), have been associated with poorer treatment response rates and thus poorer prognosis (Avet-Loiseau, *et al* 2010, Jagannath, *et al* 2007, Pineda-Roman, *et al* 2008, Sagaster, *et al* 2007). Newer MM treatments, such as bortezomib and lenalidomide, appear to be effective in patients with high and low risk cytogenetics (Barlogie, *et al* 2008, Reece, *et al* 2009). Despite efficacy in both cytogenetic profiles, survival improvements associated with bortezomib and lenalidomide may disproportionately benefit white patients, suggesting race-based cytogenetic differences (Kumar, *et al* 2008). Little is known about how racial differences in cytogenetics may influence MM prognosis.

To identify racial differences in common MM-associated chromosomal abnormalities, we examined routine cytogenetic results in a retrospective cohort study of patients from the United States Veterans Health administration (VHA). A cohort of 5,202 patients diagnosed with MM between 1 October 1998 and 31 December 2009 was identified using the VHA central cancer registry. Patients were identified with International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes 9732/3, 9731/3 and 9734/3 (MM and plasmacytoma). Among these patients, we identified a sub-cohort of 1,256 patients who had common procedural terminology (CPT) codes 88271-8275, 88291, 88299, 88365, 83896, 88237, 88261-88264, 88280, 88283 and 88285, indicating that routine cytogenetic testing had been performed. Further examination of the electronic records of this sub-cohort provided results of karyotype analysis in 828 patients.

Fifteen patients from racial groups other than black or white were excluded, leading to a final cohort of 813 patients; of whom 228 were black and 585 were white (Fig 1).

Additional data regarding date of birth, date of diagnosis, date of death, comorbidities, weight and height at time of diagnosis were obtained from VHA administrative datasets. The Romano comorbidity index was calculated using International Classification of Disease (ICD)-9 codes (Romano et al, 1993). Body Mass Index was calculated using weight and height at time of diagnosis using the standard formula: weight in kilograms divided by height in metres squared.

Chi-Square test and Fisher's exact test was used to assess for race-based differences in the following cytogenetic abnormalities: del(13q), hypodiploidy, hyperdiploidy and translocations involving the immunoglobulin heavy-chain (chromosome 14). Cox Proportional Hazard model was used to estimate association between race and survival while adjusting for age. A two-tailed α significance level of 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Among the 813 patients, normal cytogenetic profiles, isolated Y chromosome deletion, or no mitotic activity were observed in 704 (87%). Only four chromosome 14 translocations were observed on routine cytogenetics; no statistical conclusions could be drawn. Hyperdiploidy was noted in 13/228 (5.7%) black and 45/585 (7.7%) white patients ($p=0.32$). Del(13q) was detected in 8/228 (3.5%) black patients and 21/585 (3.6%) white patients ($p=0.96$). Hypodiploidy was noted in 4/228 (1.8%) black and 12/585 (2.0%) white patients ($p=1.00$). There was no difference in age-adjusted survival based on race (Hazard ratio [HR], 0.90; 95% confidence interval [CI] 0.72-1.14). Consistent with other studies, black patients in this cohort were significantly younger than white patients (mean age 62.2 vs. 66.6, respectively, $p<0.0001$) (Howlader, *et al* 2014). Despite having a younger mean age, black patients in our cohort had a significantly higher mean Charlson score than white patients (Table I).

This is the largest investigation of racial disparities in MM cytogenetics to date. Contrary to our *a priori* hypothesis, we did not find a significant difference in metaphase cytogenetics between black and white patients. While previously published papers (Corre and Avet-Loiseau 2011, Howlader, *et al* 2014, Kumar, *et al* 2008) alluded to a better prognosis for black patients, based on our data this change is not attributable to racial differences in metaphase cytogenetics.

According to the literature, hyperdiploidy and del(13q) have the highest rates of abnormal karyotype detection, which our data supports; however, at a lower frequency than previously observed (Corre and Avet-Loiseau 2011). Despite their younger age, black patients had a higher mean co-morbidity score, which would increase the risk of death due to causes other than MM.

The strengths of this study include drawing data from the largest health system in the United States, providing the best available statistical power as well as detailed patient information. A major limitation of this study was the lack of FISH results in most patients. The low frequency of cytogenetic abnormalities is attributable to the historic use of routine cytogenetics instead of FISH testing in the VHA. Our study population was predominately male, which is similar to national data (Howlader, *et al* 2014); as a consequence, these findings may not be generalizable to women.

In conclusion, we found no significant racial differences in metaphase cytogenetics among a large cohort of MM patients. Further research into how race might influence genetic differences in plasma cell malignancies will require comparison of FISH testing or genomic sequencing results. Alternatively, it is possible that there are no major race-based differences in the malignant plasma cells and that those racial differences in MM incidence are driven by differences in environmental exposures or molecular abnormalities in tissues other than the malignant plasma cells.

Author contributions

Brandon Blue, Katuscia O'Brian, Arun Ganti, Kristen Sanfilippo and Jason Gumbel performed the research. Brandon Blue and Kenneth Carson designed the research study. Kenneth Carson contributed essential reagents or tools. Suhong Luo, Brandon Blue and Kenneth Carson analysed the data. Brandon Blue, Katuscia O'Brian, Kenneth Carson, Kristen M. Sanfilippo, Suhong Luo and Arun Ganti wrote the paper and approved final version.

Competing interests

The authors have no competing interests to disclose.

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Table I: Basic Demographics of United States veterans with Multiple Myeloma with routine cytogenetic testing within the Veterans Health administration system, by race ($n= 813$)

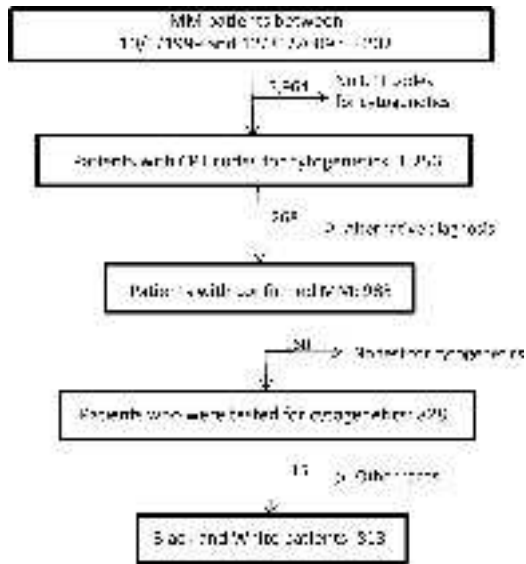
Demographic clinical characteristics	Overall	Race		P-value
		White	Black	

	N=813	(n=585)	(n=228)	
Age (mean years)	65.3	66.6	62.2	<0.0001†
Male (%)	97.8	98.5	96.1	0.0360*
Body mass index (%)				
<18.5	1.1	0.9	1.8	
18.5 - <25	23.7	22.6	26.8	
25 - <30	36.3	35.9	37.3	
≥30	26.2	27.2	23.7	
Unknown	12.7	13.5	10.5	0.1018§
Comorbidities (mean Charlson score)	2.8	2.6	3.1	0.0366†
Diagnosis year (median)	2006	2006	2007	0.0466‡

* Chi-square test; † Anova test; § Cochran-Mantel-Haenszel (Row Mean Score) test; ‡ Wilcoxon Two-Sample Test

Figure 1: CONSORT Diagram

MM, multiple myeloma; CPT, common procedural terminology



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