A Proposed Biphasic Approach Based on Analysis of Genetic Alteration in Newly Diagnosed Plasma Cell Myeloma Patients

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Background/Purpose: Plasma cell myeloma (PCM) is a hematological neoplasm arising from clonal plasma cells due to acquired genetic alterations especially in advanced age. It is relatively common accounting for an approximately 1% of all malignancies and 15% of all hematological neoplasms with a slightly male predominance. The initial prognostication and monitoring of the disease progression can be obtained by identification of plasma cell genetic abnormalities. In previous studies, analysis of newly diagnosed patients with PCM revealed a genetic abnormality rate in about 20-30% and 50-60% by convictional karyotyping and fluorescence in situ hybridization (FISH), respectively. More recent studies showed a substantial improvement in detection power when a modernistic molecular cytogenetic technique used. Furthermore, neoteric reports displayed a racial difference in genetic alteration among PCM patients. This retrospective study evaluated the molecular cytogenetic aberrations at our institution in a cohort of newly diagnosed patients with comparison to internationally published data.

Methodology: All adult bone marrow reports done between 2012 and 2015 were reviewed to identified the newly diagnosed PCM patients. The total number of newly diagnosed patients is 103 patients in the study period. However, 90 patients had a completed molecular cytogenetic study in our institute. The molecular cytogenetic study used FISH interphase technique examining at least 200 cells from bone marrow aspiration sample by two different skillful clinical cytogeneticists. The current validated PCM-FISH panel included five different probes; trisomy 12q15, deletion 13q14/13q34, deletion 17p13.1, translocation (11;14) and translocation (4;14).

Results: Ninety newly diagnosed PCM patients with a median age of 55.5 years (Range: 25-87 years) and 12% of all patients 40 years. Fifty-three patients were male and 37 were female with male to female ratio of 1.4. Moreover, 72 (80%) in-house and 18 (20%) referral cases were investigated. The FISH-panel detected genetic abnormalities in 66 (73%) of analyzed bone marrow samples with an average of 2.2 abnormalities per positive sample. The hyperdiploidy/trisomy, hypodiploidy/monosomy and immunoglobulin heavy chain (IGH) rearrangement were detected in 40 (44%), 30 (33%) and 19 (21%) cases, respectively, with 15 (17%) cases showing mixing abnormalities (table1). Trisomy of chromosome (Ch) 11 was positive in 39 (43%) cases and monosomy of Ch 13 was detected in 30 (33%)cases. Moreover, deletion of Ch 17 was reported in 8 (9%) of all investigated samples (table 2). Classical karyotype study was done in only 13 samples that revealed 62%, 23% and 15% as negative and positive results and failure rate. However, all the negative result cases by karyotyping showed at least one abnormality by FISH method. Other diagnostic laboratory investigations were also incorporated in this study (table 3).

Conclusion: This is the first reported molecular genetic study using FISH method from Saudi Arabia for newly diagnosed PCM patients showing an early age of onset and a significant difference of genetic abnormality comparing with international reports, namely IGH rearrangements. These observations support a recently published data demonstrated racial differences in PCM characteristics. Furthermore, this study was valuable in implementing a new biphasic PCM-panel approach including two phases; screening and comprehensive (figure 1).

Figure 1: The proposed algorithm for genetic evaluation of newly diagnosed plasma cell myeloma patients (the screening phase including; 1P deletion/ 1q AMP, MDM2 Ch 12, 13q14/13q34 deletion, IgH breakapart and 17p (P53) deletion, the comprehensive phase as followed: additional numerical panel including; 7/8/9 centromere, 3/11/15 centromere and 5q31/5p15.2 probe and the specific IGH partner panel including; IgH/FGFR3 dual Fusion, IgH/CCND1 dual Fusion and IgH/MAF dual Fusion).

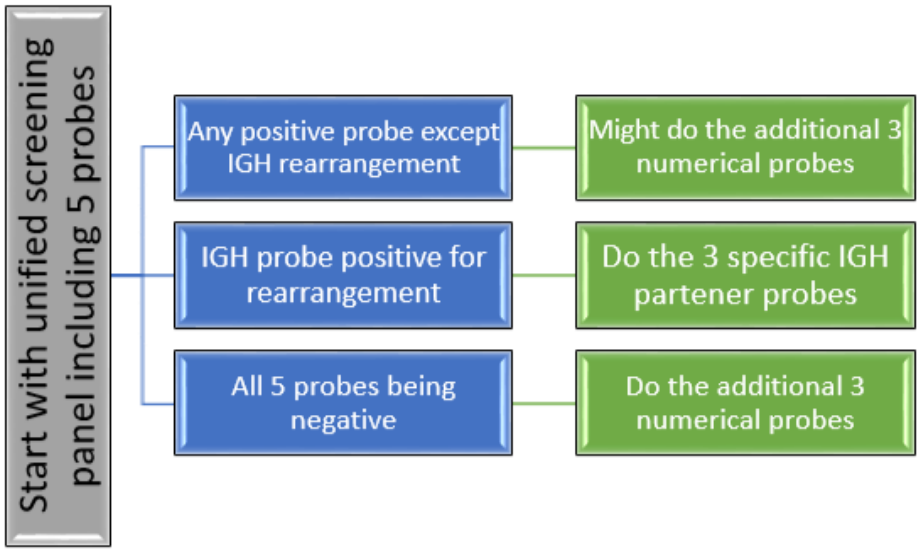

Table 2: Comparison between KFSH&RC study including 90 PCM patients and Mayo Clinic published data included 484 cases (PCM patient with poor prognosis genetic abnormality showed better outcome when a detection of additional trisomy abnormality seen).

FISH abnormality	Frequency in KFSHRC, n (%)	Trisomy present in KFSHRC, n (%)	Frequency in Mayo	Trisomy present in Mayo
All Abnormalities	66 (73%)	N/A	469 (97%)	N/A
Any IGH rearrangements	19 (21%)	7 (37%)	220 (46%)	74 (34%)
IGH/CCND1 fusion, t(11;14)	11 (12%)	3 (27%)	86 (18%)	12 (14%)
IGH/FGFR3 fusion, t(4;14)	4 (4.4%)	2 (50%)	47 (10%)	19 (40%)
Other IGH rearrangements	4 (4.4%)	2 (50%)	87 (18%)	43 (49%)
Any trisomy	40 (44%)	N/A	275 (57%)	N/A
Trisomy 11				
Trisomy alone				
Monosomy				
Monosomy 13				
Del 17/P53				
Normal Result				

Table 3: Initial investigation results for the 90 newly diagnosed PCM patients.

Test Name	No. of Tested samples	Positive/Increased	Negative/Normal	Failed/Decreased	Not Done
Karyotype	13	3	8	2	77
	NA	23%	62%	15%	NA
FISH	90	66	24	0	0
	NA	73%	26%	0	NA
CD56	82	68	13	1	8
	NA	83%	16%	1%	NA
Bence Jones protein	47	37	10	0	43
	NA	79%	21%	0	NA
Protein Serum Level	72	35	17	20	18
	NA	49%	23%	28%	NA
Beta2-microglobin	72	69	3	0	18
	NA	96%	4%	0%	NA
Ig Type	IgG	49	Free	11	18
		68%		15%	NA
	IgA	8	IgM	3	NA
		11%		4%	NA
	IgD	2	IgG + IgA	1	NA
		3%		1.40%	NA
Ig Light Chain	Kappa	58	Lambda	26	6
		69%		31%	NA