Free Light Chain Assay and Cytogenetic Abnormalities for Identification of High-Risk Smoldering Multiple Myeloma

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Background

Smoldering multiple myeloma (SMM) is an asymptomatic precursor disease of multiple myeloma.

SMM is defined by excess bone marrow plasma cells and presence of a monoclonal protein without evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions).

Risk stratification incorporating cytogenetic abnormalities (CA) and readily accessible biomarkers is needed to identify high-risk smoldering multiple myeloma (SMM) patients.

Recognition of SMM patients at highest risk for rapid progression may identify candidates for early intervention strategies and clinical trial design.

Translocation (4;14) and Deletion 17p have been identified as high risk cytogenetic abnormalities.

Abnormal serum free light chain and high-risk CA at the time of SMM diagnosis could further risk stratify patients.

Methods

Retrospective analysis of 251 patients with available cytogenetics and serum free light chains in newly diagnosed SMM from 1991-2010.

Molecular cytogenetic subtype determined based on cytoplasmic FISH on bone marrow plasma cells

Serum free light chain quantification from stored serum samples at the time of SMM diagnosis

SMM defined by IMWG 2003 definition:

- Serum M-protein ≥ 3g/dL
- ≥10% bone marrow plasma cells
- No evidence of end-organ damage

Immunoglobulin FLC assay (Binding Site, U.K.) used for testing.

An ROC curve was used to determine the ability of the serum involved FLC (iFLC) to discriminate patients who progressed to symptomatic MM by 24 months

Time to progression (TTP) from date of the initial SMM diagnosis to symptomatic MM was calculated using Kaplan-Meier analysis

Stratified patients by high-risk cytogenetic abnormalities [(t(4;14) and deletion 17p)] and non-high risk CA and involved FLC >40 or iFLC <40

Results

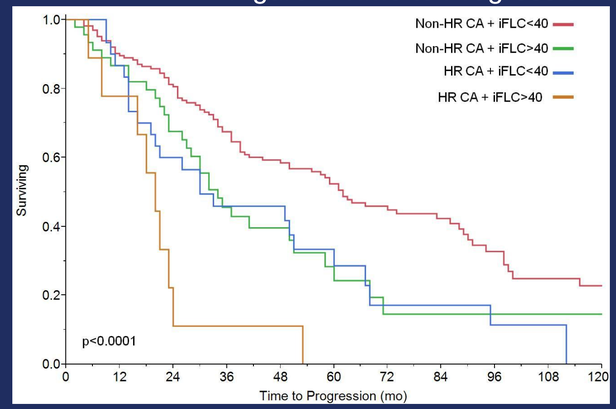
Table 1 Patient Characteristics

Variables	All (95% CI) [Range]	Non-High Risk CAs		High Risk CAs		P
		iFLC ≤40	iFLC >40	iFLC ≤40	iFLC >40	
N=	251	165	46	31	9	
Age, y	62 [30-90]	61	64	61	67	0.52
Male, %	53%	49%	48%	35%	44%	0.57
Kappa light chain, %	61%	65%	52%	67%	11%	0.004*
Serum M-spike, g/dL	2.2 (2.0-2.29)	2.2	2.1	2.5	2.6	0.12
Bone Marrow Plasma Cell, %	20% (23-26%)	19%	25%	20%	26%	0.005*
Serum Inv/Uninvol FLC ratio	13.3 (79.5-262)	6.57	93.1	11.2	100	<0.0001*
Beta-2 microglobulin	2.59 (2.81-3.97)	2.51	2.79	2.42	2.86	0.69
Albumin	3.7 (3.6-3.8)	3.8	3.8	3.7	3.7	0.54

Table 2 Cytogenetic Abnormalities

FISH abnormality	% of SMM patients
High-Risk Cytogenetic Abnormalities, % (n=)	16% (40)
t(4;14)	13% (33)
Del (17p)	3% (7)
Non-High Risk Cytogenetic Abnormalities	84% (211)
Trisomy without IgH translocation	41% (104)
IgH abnormality without trisomy	20% (50)
IgH abnormality with trisomy	4.8% (12)
Monosomy 14 without IgH translocation	1% (2)
Normal	15% (37)
Normal with incomplete sample	2.4% (6)

Figure 1 Time to Progression to MM



Risk Group	Median TTP (mo)
Non-HR CA + iFLC <40	62 (48-86)
Non-HR CA + iFLC >40	34 (26-51)
HR CA + iFLC <40	30 (19-60)
HR CA + iFLC >40	20 (5-24)

Table 3 Prognostic Variables for Progression to MM

	Univariate			Multivariate		
Variable	HR	95% CI	P	HR	95% CI	P
iFLC >40	1.9	1.3-2.8	0.0007*	1.8	1.2-2.5	0.004*
Age >65	1.8	1.3-2.4	0.001*	1.6	1.1-2.2	0.007*
BMPC % >20	2.0	1.4-2.7	0.0001*	1.7	1.3-2.4	0.0007*
M-spike >3	1.3	0.89-1.8	0.19			
β-2 microglobulin >3.5	1.7	0.72-3.8	0.21			
Albumin <3.5	1.1	0.44-2.5	0.80			

Conclusions

- Integration of the serum FLC assay and cytogenetic FISH in newly diagnosed smoldering multiple myeloma patients may facilitate recognition of SMM patients at highest risk for rapid progression
- Elevation of the involved FLC >40 in the presence of high-risk cytogenetic abnormalities [t(4;14) and deletion 17p)] revealed 89% progression at 24 months.
- Patients with high-risk cytogenetic abnormalities and elevated iFLC >40 may be candidates for early intervention strategies given their abbreviated premalignant phase.