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Monoclonal Gammopathies & Multiple Myeloma

IS THERE A PROGNOSTIC AND DIAGNOSTIC ROLE OF MYC REARRANGEMENTS IN MULTIPLE MYELOMA AT DIAGNOSIS BY FISH? DESCRIPTION OF 3 CLINICAL CASES

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Introduction: Prognosis and response to treatment in Multiple Myeloma (MM) patients are profoundly influenced by genetic and cytogenetic alterations, either primary and secondary. The gold standard in clinical practice to detect these alterations is represented by fluorescence in situ hybridization (FISH) on purified or enriched plasma cells. Current guidelines recommend routine use of FISH to identify the following key high-risk prognostic markers: t(4;14), t(14;16), t(14;20), del(17p), gain(1q) and/or del(1p). In this context, aberrations involving the MYC family oncogenes [C-MYC (8q24) and, to a lesser extent, N-MYC (2p24)], are crucial progression events but are not currently evaluated in the clinical routine.

Methods:

Conventional cytogenetic analysis was done using G-banding (GTG) on whole bone marrow cells. FISH was performed on isolated PC initially with standard probes from MM panel, followed by the MYC probe after evidence of karyopypic alterations involving MYC loci.

Results: The clinical and therapeutic results in three patients with MYC rearrangements at the conventional cytogenetic analysis followed by FISH confirmation with specific MYC probes are reported. Clinical data of the three patients are reported in the Table. Conventional cytogenetic analysis revealed C-MYC rearrangements in two cases (pt 1 and 2) and N-MYC rearrangement in one case (pt 3). These rearrangements were confirmed by FISH. From a prognostic point of view, according to the International Scoring System (ISS) classification one out three patients (pt 1) was at low-risk, while according to the Revised ISS (R-ISS) all three patients were at intermediate risk. All three patients were treated frontline with standard VTD scheme: pt 1 achieved a very good partial response (VGPR) but relapsed after 36 months and became resistant thereafter, pt 2 achieved a VGPR but had an early relapse and became resistant after a 2nd short partial response, pt 3 remained always in stable disease during three different lines of therapy with subsequent progression.

Conclusions: Cytogenetic risk assessment is essential to identify high-risk abnormalities. While C-MYC and N-MYC play a key role among the genes involved in progression in about 15% of patients with MM and are associated with an unfavorable outcome, their evaluation is not considered in the standard FISH analysis and in the standard high-risk classification: as a consequence, their role is underestimated in the current clinical practice. Our three cases highlight the bad prognosis of patients carrying MYC alterations: it should be emphasized that these alterations would have not reported if only the conventional FISH panel on plasma cells had been used. Therefore, the inclusion of MYC rearrangements in the FISH panel is essential for a comprehensive and timely risk assessment in MM, reducing the proportion of patients with the so called “functional high-risk”.

Table – Clincal features and treatment response in the three MYC rearranged patients

	Patient 1	Patient 2	Patient 3
Gender/Age (years)	M/66.0	F/69.3	F/65.3
Previous MGUS (Y/N)	N	Y	N
Hb (g/dl)/Creatinine (mg/dl)	11.0/1.07	7.7/0.96	9.3/15.4
Type of component	K (not secreting)	IgGk	ƛ
Ratio inv/not inv	/	139.1	746.8
β2-microglobulin	2.9	11.0	75.8
Standard Karyotype	t(8;14) not reciprocal	Complex	Complex
FISH analysis	IGH/C-MYC not reciprocal	IGH/C-MYC and Ampl 8q, ampl 14q, tris18	Monosomy 4, t(2;14)N-MYC/IGH, ampl 1q, del 1p
ISS classification	Low	High	High
R-ISS classification	Int	Int	Int
1st line treatment	VTD → ABMT	VTD	VTD
Response to 1st line	VGPR	VGPR	SD
Relapse (Y/N)	Y	Y	/
2nd line treatment	RD	Dara-RD	Dara-RD
Response to 2nd line	PD	PR	SD
3rd line treatment	CTX-HD	Poma-Dex	Isa-PD
Response to 3rd line	PD	PD	SD
Overall survival (months)	88.1	29.0	41.2

Legend: VGPR=very good partial response; PR=partial response; SD=stable disease; PD=progressive disease