Molecular Cytogenetic Analysis of Chromosome 8 Aberrations in Patients With Multiple Myeloma Examined in 2 Different Stages, at Diagnosis and at Progression/Relapse

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Abstract

This retrospective study of 62 patients with multiple myeloma examined at 2 different phases (diagnosis and progression/relapse), revealed chromosome 8 aberrations in 24 (38.7%) patients at diagnosis and in 29 (46.8%) patients at progression/relapse. We did not confirm a significant increase of chromosome 8 aberrations at progression/relapse; however, we confirmed the heterogeneity of the aberrations and their poor prognostic impact on overall survival.

Background: The genome of multiple myeloma (MM) clonal plasma cells is characterized by genetic changes of prognostic importance. Disease progression is accompanied by a number of secondary chromosomal aberrations including chromosome 8. We focused on the detection of chromosome 8 aberrations in patients with MM who were examined at 2 different phases: diagnosis and progression/relapse. **Patients and Methods:** A total of 62 patients with MM were examined at the time of diagnosis and at relapse/progression. The median age was 64 years (range, 39-78 years); the study included 29 males and 33 females. We analyzed bone marrow samples for detecting aberrations on chromosome 8 by the fluorescence immunophenotyping and interphase cytogenetics as a tool for the investigation of neoplasms (FICTION) and fluorescence in situ hybridization methods with specific probes. **Results:** Chromosome 8 aberrations were detected in 24 (38.7%) patients at diagnosis and in 29 (46.8%) patients at progression/relapse. Only 5 (8%) patients developed additional chromosome 8 changes at progression/relapse. The aberrations were heterogeneous, involving numerical and structural changes of the *MYC* gene. Aberrations of the short arm of chromosome 8, involving the genes *TRAIL-R1*/*-R2*, were less frequent (4 of 62 patients, 6.4%). All aberrations of chromosome 8 were accompanied with additional changes and with an advanced clinical phase of the disease. This finding significantly influenced the overall survival of patients. **Conclusion:** In the current study, chromosome 8 aberrations were highly heterogeneous, were presented at diagnosis in patients with advanced clinical stage, and were associated with worse overall survival. We have not confirmed the increase of frequency aberration of chromosome 8 in disease progression. The findings demonstrate the importance of fluorescence in situ hybridization examination of chromosome 8 in newly diagnosed patients with MM.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. 6, 358-65 © 2016 Elsevier Inc. All rights reserved.
Keywords: FICTION, MYC, TRAIL-R1, TRAIL-R2, genetic changes

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Submitted: Dec 30, 2015; Revised: Feb 9, 2016; Accepted: Feb 18, 2016; Epub: Feb 27, 2016

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Introduction

The genome of multiple myeloma (MM) plasma cells is characterized by acquired genetic changes with a high level of genomic complexity. About 40% of cases harbor chromosomal translocations resulting in overexpression of genes, including *CCND1*, *CCND3*, *MAF*, *MAFB*, *WHSC1* (also called *MMSET*), and *FGFR3*, by their juxtaposition to 1 of the 3 immunoglobulin (IG) loci (immunoglobulin heavy chain [*IGH*], kappa [*IGK*], and lambda [*IGL*]

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http://dx.doi.org/10.1016/j.clml.2016.02.038

genes), whereas other cases (∼60%) exhibit hyperdiploidy. These abnormalities are probably insufficient for malignant transformation as they are also observed in the monoclonal gammopathy of undetermined significance pre-malignant stage.[1,2] Additional recognized genetic changes lead to activation or deregulation of a number of genes such as *MYC*, *FGFR3*, *KRAS* and *NRAS,* and activation of the NF-kB pathway.[3-7]

Of the genes involved in the pathogenesis and progression of MM, the *MYC* gene is the most frequently concerned in chromosomal translocations involving the immunoglobulin loci (*IGH*>*IGL*>*IGK*), which juxtapose the strong B-cell enhancers present at these loci and *MYC*, resulting in overexpression of the oncogene.[8] The findings of these rearrangements are associated with an overall aggressive course and a poor outcome in MM.[9-12] The gene *c-MYC,* mapped to the long arm of chromosome 8 at the 8q24.1 region, is a transcriptional factor that has a crucial role in regulation of cell growth, proliferation, translation of proteins, metabolism, apoptosis, and, last but not least, in tumorigenesis.[13-15] This proto-oncogene may play a primary oncogenic role in tumors such as Burkitt's lymphoma, where it was identified initially,[16,17] and in the subset of acute lymphoblastic leukemia.[18] *MYC* is dysregulated or overexpressed in a wide variety of human cancer cells, resulting in genomic changes in response to the activation of many diverse signaling pathways. It still unclear whether *c-MYC* overexpression is primarily responsible for the metabolic changes induced by transformation, or whether it is a result of the complex metabolic changes that occur when cells become malignant.[14,19]

The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors, TRAIL-R1 (TNFRSF10A, DR5) and TRAIL-R2 (TNFRSF10B, DR4), are located on the short arm of chromosome 8 (8p).[20,21] In vitro studies showed that they play pivotal roles in inducing apoptosis in a variety of tumor cells and may be critical for tumorigenesis as candidate tumor suppressor genes in B-cell malignancies.[22-28] Deletion of the 8p21.3 region suggests a probable important role in the tumorigenesis of MM.[29,30]

The aim of the present study was to evaluate and summarize the frequency of chromosome 8 aberrations in patients with MM examined at 2 different phases, at the time of diagnosis and during progression or relapse. In addition, we aimed to examine the correlation with other aberrations routinely monitored, with focus on the prognostic impact.

Material and Methods

Patients

A cohort of 62 patients with MM was enrolled to this retrospective analysis. The patients were diagnosed and treated at the Third Department of Internal Medicine, and examined in the Cytogenetic and Molecular Cytogenetic Laboratories of the Department of Hemato-oncology, Palacky University and University Hospital Olomouc, between May 2000 and December 2014. This study was approved by the institutional independent ethics committee and performed in accordance with the Helsinki Declaration. The study included 29 males and 33 females, with a median age of 64 years (range, 39-78 years at diagnosis). Bone marrow samples were obtained at the time of diagnosis and at progression or relapse of the disease (22 patients at the first relapse and 3 patients at the second relapse, from the total of 25 patients with myeloma relapse).

All analyzed samples had more than 10% plasma cells confirmed in the bone marrow aspirate. The patient characteristics are summarized in Table 1.

Cytogenetics

Heparinized bone marrow samples were cultured in RPMI-1640 medium (Sigma-Aldrich, Steinheim, Germany) overnight without stimulation. Cells were than treated with Colcemide (Gibco) and processed according to standard procedure.[31] At least 10 metaphases were karyotyped and classified according to the International System for Human Cytogenetic Nomenclature.[32-34]

FICTION Method

Plasma cells (PCs) were analyzed by fluorescence immunophenotyping and interphase cytogenetics as a tool for the investigation of neoplasms (FICTION) cytoplasmic light chain immunofluorescence, as described previously.[35] We used the panel of commercially available locus-specific probes for detecting chromosomal aberrations 1q21/1p32 (1q21/1p36), del(13q14), t(4;14), t(11;14), t(14;16), and del(17p13), and centromeric probes for chromosomes 15 and 17 (Abbott Molecular, Des Plaines, IL; Dako, Glostrup, Denmark; Kreatech, Amsterdam, The Netherlands; MetaSystems, Altlusheim, Germany) according to the manufacturers' instructions. Cut-off levels for probes were determined to be 10% for fusion or break-apart probes and 20% for numerical abnormalities.

Detection of chromosome 8 aberrations was performed using a specific probe for the 8q24.1 region (LSI c-MYC dual-color, breakapart rearrangement probe) (Dako; MetaSystems), probe IgH/MYC (Abbott Molecular), and probes IGK and IGL (Dako;

Table 1 Clinical Characteristics of the 62 Patients With Multiple Myeloma

	Diagnosis	Progression/ Relapse
Gender (n, %)		
Male	29 (46.8%)	
Female	33 (53.2%)	
Age, years (median, range)	64 (39-78)	68 (41-81)
Type of MM (n, %)		
IgG	37 (59.7%)	
IgA	20 (32.3%)	
BJ	4 (6.5%)	
Nonsecretory	1 (1.6%)	
Deceased (n, %)		22 (35.5%)
Disease status (n, %)		
Progression		37 (59.7%)
Relapse		25 (40.3%)
Time to progression/relapse, mo (median, range)		30.1 (4.0-170.4)
D-S staging system (n, %)		
I	15 (24.2%)	7 (11.3%)
II	24 (38.7%)	31 (50.0%)
III	23 (37.1%)	24 (38.7%)

Abbreviations: BJ = Bence-Jones type; D-S = Staging according to Durie-Salmon; MM = multiple myeloma.

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