



Cytogenetic Features of Elderly Turkish Myelodysplastic Syndrome Patients

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ABSTRACT

Objective: Myelodysplastic syndrome (MDS) represents one of the most frequent and serious hematologic diseases among the elderly. Chromosomal abnormalities have been detected in 23%–78% patients with MDS. We analyzed the cytogenetics of elderly MDS patients in Turkey.

Materials and Methods: Data on patients (>65 years old) diagnosed with primary MDS from 2011 to 2013 were retrospectively collected from Erciyes University. Chromosome analysis was performed in 54 patients using conventional karyotyping and fluorescence in situ hybridization (FISH).

Results: Of the 54 patients recruited, karyotype abnormalities were found in 8 (15%) of 54 cases, among which, 5 (9%) were Trisomy 8 and 3 (6%) were del 5q.

Conclusion: The incidence of chromosomal abnormalities in elderly Turkish MDS patients was lower than that reported in the literature. Although the pathogenesis of MDS is still poorly understood, environmental and biological factors could induce mechanisms that are associated with diverse karyotypes and variable frequencies of chromosomal abnormalities.

Keywords: Cytogenetics, elderly, myelodysplastic syndrome

INTRODUCTION

Myelodysplastic syndrome (MDS) is a group of heterogeneous stem cell disorders with different clinical behaviors and outcomes. They are common in elderly patients and are characterized by morphological abnormalities with evidence of one or more lineage dysplasia, ineffective hemopoiesis, and a propensity of transformation to acute myeloid leukemia (AML) (1-3). The International Prognostic Scoring System (IPSS) identified three critical factors that influence survival and AML evolution: risk-based cytogenetic subgroups, bone marrow blast percentage, and the number of cytopenias (4). The pathogenesis of MDS is not well defined, and it appears that complex genetic changes are involved (5, 6). Karyotyping is important for the diagnosis and prognosis of MDS. Conventional cytogenetics and fluorescence in situ hybridization (FISH) are useful tools of molecular cytogenetics for the detection of common chromosome abnormalities in MDS (7-10). Also, whole-genome scanning technologies such as single nucleotide polymorphism microarray (SNP-A)-based molecular karyotyping improve the risk stratification in MDS. The chromosomal abnormalities are characterized by chromosomal losses or gains, and they mainly include del 5q, del 7q, del 20q, and trisomy 8 (11). Chromosomal findings are independent prognostic variables that contribute to the definition of prognosis in MDS. Chromosomal abnormalities have been detected in 23%–78% patients with primary MDS (12). Several studies have shown that chromosomal abnormalities may be influenced by environmental factors, while differences in the incidence of certain aberrations in different areas have been reported (13).

In the current study, 54 Turkish elderly patients with primary MDS were retrospectively analyzed for their chromosomal abnormalities using conventional karyotyping and FISH.

MATERIALS and METHODS

We retrospectively reviewed 54 patients (over 65 years of age) with diagnosed primary MDS treated at Erciyes University between 2011 and 2013. Diagnosis was based on morphological, cytochemical, immunophenotypic, and cytogenetic analyses. The patients were classified according to the World Health Organization (WHO) criteria, and none of these patients were previously treated for a malignancy (14). Fifty-four patients with MDS were cytogenetically studied. Cytogenetic analysis was conducted at the time of diagnosis (15). Patients who had secondary MDS were excluded from the analysis. All MDS cases were analyzed with conventional cytogenetics and

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FISH. For conventional cytogenetics, unstimulated bone marrow or peripheral cells were cultured for 48–72 h, and cytogenetic analysis was performed using GTG banding and karyotyped according to the International System for Human Cytogenetic Nomenclature (ISCN) (16). When possible, at least 20 metaphases were analyzed for each case. Clonal abnormalities were defined as two or more cells with the same additional whole chromosome or chromosome rearrangement or three or more cells with the same chromosome missing. Also, cases were analyzed with a panel FISH using CYTOCELL (5q33-34), DIAGEN CEP 8 (+8), CYTOCELL (7q31), and CYTOCELL (20q12) probes to detect the frequently occurring chromosome abnormalities (-5/5q, -7q, +8, 20q-) in MDS. For the FISH procedure, we used the samples of cytogenetic cultures, and approximately 100 interphase cells were analyzed. This study was performed according to the Declaration of Helsinki, 2013.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS; 15.0, Chicago, IL, USA) software and correlation analysis were used for statistical analysis. Patient survival was measured from the time of diagnosis until death from any cause or until the last follow-up date. Kaplan–Meier analysis was used for the evaluation of survival. Differences were considered significant when the p value was less than 0.05.

RESULTS

Of 54 patients recruited, 36 were males and 18 females; the median age was 67 years (range 65–73). All WHO classification subgroups were represented (Table 1). Overall, 31 patients (57%) were diagnosed as having refractory anemia (RA), 4 patients (7%) as RA with excess of blasts (RAEB)-1, 16 patients (30%) as RAEB-2, and 3 patients (6%) as deletion (del) 5q MDS. According to IPSS stratification, there were 33 patients with low-risk, 12 patients with intermediate-1 risk, and 9 with intermediate-2 risk MDS. At the time of diagnosis, the median Hb was 9 g/dL (5.6–13.7), Plt count was $163 \times 10^9/L$ (13–360), absolute neutrophil count was $1.87 \times 10^3/L$ (0.05–6.2), LDH was 195 u/L (102–692), and median bone marrow blast count was 3% (0–14). Of 54 patients karyotyped, 46 had normal karyotype (85%) and 8 patients (15%) had a chromosomal abnormality. Trisomy 8 was observed in 5 patients (9%), and del 5q was observed in 3 patients (6%). The distribution of trisomy 8 in the WHO subgroup was 40% in RA, 40% in RAEB-1, and 20% in RAEB-2. There was no specific chromosomal abnormality associated with a subtype of MDS. Patients with cytogenetic abnormalities were younger than those who were cytogenetically normal, possibly included more men, but none of these differences were statistically significant.

The patients received different treatments: supportive care, lenalidomide, azacitidine, decitabine, and allogenic hematopoietic stem cell transplantation(1). Peripheral cytopenias were the most common adverse events for all treatments. In total, transformation to AML occurred in 5 (9%) of patients, and none of these patients had an abnormal karyotype. Of these patients, three patients (60%) were in the RAEB-2 subgroup, and two patients (40%) were in the RAEB-1 subgroup. The median time for AML transformation was 4 months. The median overall survival was 18 months (6–36).

Table 1. Patient characteristics and cytogenetic findings

Variable	Median (Range)
Age, years	67 (65–73)
Hemoglobin, g/dL	9 (5.6–13.7)
Platelet count, $\times 10^3/L$	163 (13–360)
WBC, $\times 10^3/L$	3.8 (0.7–35)
ANC, $\times 10^3/\mu L$	1.7 (0.05–6.2)
LDH, u/L	195 (102–692)
Bone marrow blasts, %	3 (0–14)
	Number (%)
Gender	
Male	36 (67)
Female	18 (33)
WHO classification	
RA	31 (57)
RAEB-1	4 (7)
RAEB-2	16 (30)
Del 5q	3 (6)
Karyotypes	
Normal	46 (85)
Abnormal	8 (15)
Trisomy 8	5 (9)
Del 5q	3 (6)
IPSS	
Low	33 (61)
Intermediate-1	12 (22)
Intermediate-2	9 (17)
WBC: white blood cell count; ANC: absolute neutrophil count; LDH: lactic dehydrogenase; WHO: World Health Organization; RA: refractory anemia; RAEB: refractory anemia with excess blasts; Del 5q: deletion 5q; IPSS: International Prognostic Scoring System	

DISCUSSION

MDS prevalence increases with age, and the median age of patients at the time of diagnosis varies between 65 and 74 years (17). In our study, the median age of patients was 67 years. Also, in our cases, the sex ratio was 2:1, in favor of men, and it is in concordance with the literature. The aim of this study was to investigate the frequency of chromosomal changes in elderly Turkish MDS patients. Using conventional cytogenetics and panel FISH, 54 primary MDS cases were investigated for the frequency and the type of cytogenetic abnormalities. Eight cases had an abnormal karyotype (15%), although the incidence of chromosomal abnormalities in MDS in most of the reported studies was higher than that in our study. Few reports have indicated geographical and ethnic differences in the frequency of specific chromosomal changes. The incidence of chromosomal abnormalities was between 37% and

88% in India and varied between 37% and 50% in China, Hong Kong, and Japan (17, 18). Also, Haase et al. (19) reported that the incidence of chromosomal abnormalities was 49% in Austria and Germany. In our study, this ratio was 15%. Also, the frequency of del 5q was 6% in our MDS patients, which was lower than that in the MDS patients of other countries (8.7%–23.4%) (18). These patients received lenalidomide treatment. It is reported that in patients with MDS, chromosome 5 abnormalities may be a marker of mutagen-induced MDS (20, 21). In our study, the frequency of trisomy 8 was 9%. This result was similar to the other studies (7%–10%) (22). On the other hand, Panani et al. (5) reported that the most common anomaly was trisomy 8 (28%). The possible underlying mechanisms for trisomy 8 include gene dosage effects, while cryptic abnormalities in duplicated chromosomes have also been found in some instances (21). Although the pathogenesis of MDS is still poorly understood, environmental and biological factors could induce mechanisms that are associated with diverse karyotypes and variable frequencies of chromosomal abnormalities. Therefore, it is likely that clonal abnormalities may be different for different areas.

Chromosomal abnormalities in MDS are associated with a strong prognostic value in the pathogenesis of the disease. On the other hand, in our study, of the five patients (9%) who transformed to AML, all of these patients had a normal karyotype. We also observed that leukemic transformation occurred in patients with RAEB-1 (40%) and RAEB-2 (60%). Wang et al. (2) reported that the AML transformation rate was 9.2%. Also, according to another study, the progression to AML occurred in 15% of patients.

CONCLUSION

In conclusion, the incidence of chromosomal abnormalities in elderly Turkish MDS patients was lower than that reported in the literature. Further prospective studies are warranted to precisely elucidate the ethnic differences in the pathogenesis of MDS.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”, (amended in 2013).

Informed Consent: Written informed consent was not received due to the retrospective nature of this study.

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