Cytogenetic findings and their prognostic impact in myelodysplastic syndrome patients

Anomalii citogenetice şi impactul prognostic al acestora la pacienţii cu sindrom mielodisplazic

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Abstract

Myelodysplastic syndrome (MDS) represents a group of clonal hematological disorders characterized by ineffective hematopoiesis and an increased risk for transformation into acute leukemia. Our aim was to identify the chromosomal abnormalities in patients with myelodysplastic syndrome and to evaluate the prognostic value of cytogenetic findings. Twenty-five patients from the Hematology Clinics in Tg.Mureș, newly diagnosed with MDS, were included in the study. We carried out bone marrow cultures according to standard methods. We successfully analyzed the karyotype of 24 patients (96%) and identified 15 (62.5%) cases with chromosomal abnormalities. According to the cytogenetic risk status, 13 patients have been classified in the good, 7 in the intermediate and 4 in the poor risk group. Patients with abnormal karyotype exhibited a high tendency to evolve into the leukemic phase (33%), as compared with those with normal karyotype. There were significant differences in overall survival (OS) noted among patients who had a normal karyotype and patients who had chromosomal abnormalities (p=0.012). Taking into account our results we consider that patients with an abnormal karyotype had a shorter survival and higher risk of leukemic transformation than those with a normal karyotype. In conclusion, cytogenetic results have an important role in the diagnosis and identification of prognostic subgroups of MDS.

Keywords: *myelodysplastic syndrome, cytogenetic, prognosis.*

Rezumat

Sindromul mielodisplazic (SMD) reprezintă un grup de afecţiuni hematologice clonale caracterizate prin hematopoieză ineficientă un risc crescut de transformare în leucemie acută. Scopul nostru a fost de a identifica anomaliile cromozomiale la pacienţii cu sindrom mielodisplazic şi de a stabili valoarea lor prognostică. În studiu au

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fost incluşi douăzeci şi cinci de pacienţi recent diagnosticaţi cu SMD, din Clinicile de Hematologie din Tg.Mureş. S-au efectuat culturi celulare din măduva osoasă hematogenă conform metodelor standard. Analiza citogenetică a reuşit în 24 dintre cazuri (96%), în 15 dintre ele (62.6%) evidenţiind anomalii cromozomiale. Conform grupelor de risc citogenetic, 13 pacienţi au fost incluşi în grupa cu prognostic bun, 7 în cea cu prognostic intermediar şi 4 în cea cu prognostic sever. Pacienţii cu cariotip anormal au prezentat o tendinţă mai mare de transformare leucemică (33%), comparativ cu cei cu cariotip normal. S-a observat o diferenţă statistic semnificativă privind supravieţuirea medie la pacienţii cu cariotip normal comparativ cu cei cu anomalii cromozomiale (p=0.012). Ţinând cont de rezultatele noastre, considerăm că pacienţii cu un anomalii cromozomiale au avut o supravieţuire mai scurtă şi un risc mai mare de transformare leucemică comparaiv cu cei cu un cariotip normal. În concluzie, rezultatele citogenetice au un rol important în diagnosticul şi identificarea de subgrupuri prognostice în SMD.

Cuvinte cheie: *sindrom mielodisplazic, citogenetică, prognostic*

Introduction

The myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders characterized by peripheral cytopenias due to ineffective hematopoiesis (1). Myelodysplastic syndromes (MDS) are characterized by an increased risk of acute myeloid leukemia (AML) development (2). The etiology of MDS is generally unknown, but some cases of MDS (secondary MDS) can occur after the use of anti-neoplastic agents (mainly alkylating agents) or after exposure to benzene derivatives (3).

Cytogenetic changes have been reported to play an important role in MDS pathogenesis and progression to AML. The pathogenetic models consider initiation and progression of MDS to be a multi-step process associated with accumulation of genetic alterations (4). During the course of disease genetic instability of the malignant clone takes to karyotype evolution and the development of cytogenetic heterogeneity with occurrence of subclones (5). In myelodysplastic syndromes (MDS), the karyotype is one of the most significant prognostic markers with great impact on differential diagnosis and therapeutic decisions (4).

Approximately 50-60% of patients with de novo MDS and more than 85% of individuals with secondary MDS show chromosomal abnormalities that may involve isolated or multiple abnormalities. According to Znoyko et al., analysis of recurrent cytogenetic aberrations in MDS is widely used for diagnosis and for determining prognosis and management (6). In general, clones with complex karyotypes are more frequent in the advanced French-American-British (FAB) groups of MDS and often associated with shortened survival and an increased frequency of transformation to AML (7).

Cytogenetic analyses are presumed to be strongly predictor of clinical outcome in MDS. They allowed the definition of a risk-based classification system for MDS: the International Prognostic Scoring System (IPSS). So, patients were divided into cytogenetic categories. Poor risk MDS was defined as normal karyotype, loss of Y chromosome, del(5q) or del(20q) as sole anomalies. High risk MDS was defined as having structural abnormalities or loss of chromosome 7 and/or a complex karyotype with $\geq$3 abnormalities. Intermediate-risk MDS was defined as having any other anomalies, e.g. trisomy 8 (8).

In the study described in this paper we determined the spectrum of chromosomal alterations in 25 Romanian patients with myelodysplastic syndrome and investigated the correlation between cytogenetic findings and their prognostic value.

Methods

Twenty-five patients from the Hematology Clinics in Tg. Mures, newly diagnosed with MDS, were included in the study. Bone marrow specimens were obtained and direct, overnight, 48- and 72-h cultures were set up in Medium M (Euroclone), and slides were prepared according

to standard laboratory methods. We used the Giemsa staining (GTG staining) technique. Metaphase cells were analyzed using a BX51 Olympus microscope and images captured with the Cytovision System (Applied Imaging). Cytogenetic abnormalities were described according to the International System of Human Cytogenetic Nomenclature (ISCN) 2005 (9). At least 20 metaphases were analyzed for each probe after bone marrow cell culture. Clonal abnormalities were defined as 2 or more cells with the same whole chromosome gain or chromosome rearrangement, or 3 or more cells with the same chromosome loss. A complex karyotype was defined as three or more cytogenetic abnormalities.

Patient survival was estimated by using the Kaplan-Meier method from the date of MDS diagnosis until death from any cause or until the last patient follow-up. Survival curves were compared statistically using the log-rank test. Differences between 2 groups were considered statistically significant if P values were < 0.05 in a 2-tailed test (10). Statistical analysis was performed using the software SPSS 17 (Statistical Package for the Social Sciences).

Table 1. Patients' clinical, hematological, and cytogenetic features at clinical diagnosis

Characteristics	Number
Number of patients	25
Gender, male/female	15/10
Type of MDS, no.	
Primary	23 (92%)
Secondary	2 (8%)
FAB classification (n = 25), no	
RA	4 (16%)
RARS	3 (12%)
RAEB	9 (36%)
RAEB-t	1 (4%)
CMML	1 (4%)
MDS-AL	5 (20%)
MDS-s	2 (8%)
WHO classification (n = 19), no.	
5q- syndrome	2 (10,5%)
RA	7 (36,8%)
MDS	1 (5,2%)
RCMD	0
RAEB	9 (47,3%)
IPSS cytogenetic risk group, no.	
Good	14 (56%)
Intermediate	7 (28%)
Poor	4 (16%)

RA - refractory anemia, RARS - refractory anemia with ringed sideroblast, RAEB - RA with excess of blasts, RAEBt - RAEB in transformation, CMML - chronic myelomonocytic leukemia, MDS - AL acute leukemia following MDS, MDS-s secondary MDS, RCMD - refractory cytopenia with multilineage dysplasia, WHO - World Health Organization

Results

The disease was more frequent in males (15 patients, 60%) than females (10 patients, 40%), with a male/female ratio of 1.44. Median age at diagnosis was 64 years (range 21–77). Hematological and genetic characteristics of the 25 cases of MDS are summarized in *Table 1*.

24 of 25 patients (96%) were successfully karyotyped. One patient with MDS could not be karyotyped because of inadequate metaphases. Out of the 24 patients karyotyped, 9 patients (37.5%) had normal karyotype and 15 patients (62.5%) had a chromosomal abnormality. Among the 24 patients with successful cytogenetic analyses, 8 (54%) had clonal cytogenetic abnormalities in primary MDS and 2 (100%) in secondary MDS.

According to the cytogenetic risk status, 13 patients have been classified in the good, 7 in the intermediate and 4 in the poor risk group (*Table 2*).

Of the 25 patients studied, 5 patients (20%) progressed to AML. Transformation into AML was frequently associated (2 cases) with abnormality of chromosome 7. Chromosomal aberrations were found in 80% of our MDS patients in patients with MDS in leuk-

Table 2. International Prognostic Scoring System cytogenetic prognostic groups

Prognostic	Chromosome abnormality	Number of patients
good	normal karyotype	9
	del(5q)	2
	del(20q)	1
	loss of the Y chromosome	1
intermediate	+8	2
	+19	1
	Other numerical or structural chromosomal aberration (+ mar; del(17p); +21)	4
poor	complex karyotype (≥ 3 abnormalities)	1
	any chromosome 7 anomaly (-7 or 7q-)	3

emic transformation. Patients with abnormal karyotype exhibited a high tendency to evolve into the leukemic phase (33%), as compared with those with normal karyotype (12.5%).

Deletion of the short arm of chromosome 17 [del(17p)] was present in our MDS patients (*Figure 1*).

The survival curves with respect to IPSS classification and cytogenetic findings are presented in *Figure 2*.

There were significant differences in overall survival (OS) noted among patients who had a normal karyotype and patients who had chromosomal abnormalities (p=0.012). It is noteworthy that patients who had normal karyotype and deletion demonstrated better OS compared with patients who had monosomy or isochromosome.

A comparison of the median overall survival (OS) between the IPSS good, intermediate and poor cytogenetic risk groups is shown in *Figure 3*. The median OS was 72 months for the good cytogenetic risk group, 44 months for the intermediate cytogenetic risk group, and 32 months for the poor cytogenetic risk group. The median survival time was 45.8 months for SMD patients. There was no statistically significant

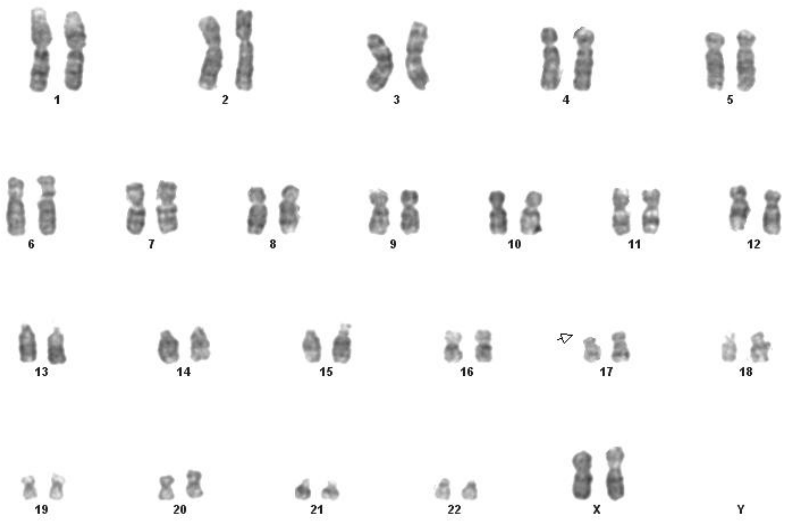

Figure 1. Karyotype 46,XX,del(17)(p12). Involved chromosome is pointed by arrows

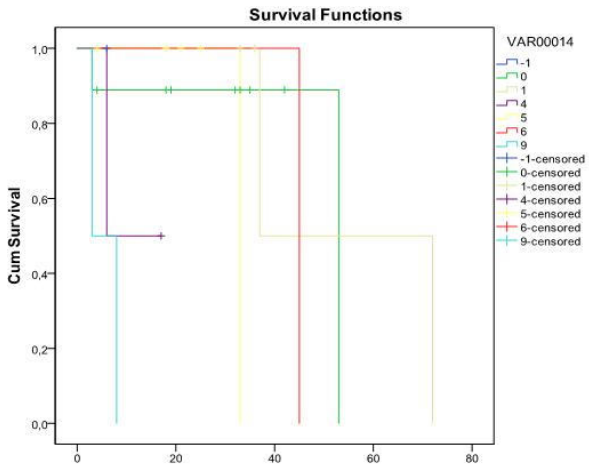

Figure 2. Kaplan–Meier survival curves in MDS patients according to the chromosomal abnormalities, (0) normal karyotype, (1) deletion, (4) monosomy, (5) trisomy, (6) complex karyotype, (9) isochromosome.

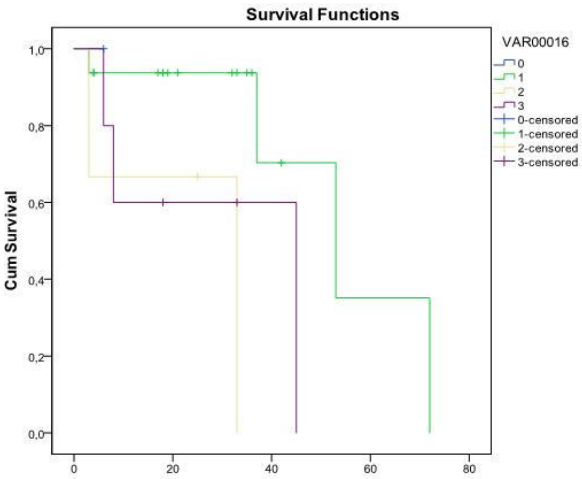

Figure 3. Kaplan–Meier analyses of overall survival in the cytogenetic risk subgroups. (1) good-risk subgroup; (2) intermediate-risk subgroup; (3) poor-risk subgroup.

difference in the median OS between the 3 cytogenetic risk groups (p=0.067).

Discussion

Karyotype, percentage of bone marrow myeloblasts and number of cytopenias have been identified as important prognostic variables in MDS by the International Prognostic Scoring System (IPSS). According to this classification, there are three cytogenetic categories. Normal karyotype, loss of Y, del(5q) or del(20q) as sole anomalies constitutes the low risk group [6]. According to this classification 13 patients from our study belong cytogenetically to the low risk group.

High risk MDS has been defined as having structural abnormalities or del(7q) and/or complex karyotype with ≥3 abnormalities. Loss of chromosome 7 has been reported in a variety of hematological disorders. Loss or deletion of chromosome 7 is noteworthy in MDS where, if detected, the prognosis for development of acute leukemia has been reported to be especially high. Four of our patients belong to this group. Intermediate risk MDS was defined as having any other abnormalities such as trisomy 8. Seven of our patients belong to the intermediate risk group.

At primary diagnosis, 40%–70% of MDS patients had normal karyotypes. In our study, this ratio was 62.5% which is comparable with the previous reports. Patients with MDS and a normal karyotype are a heterogeneous group and their prognosis has been reported to be unpredictable (2). Our incidence of abnormal karyotype (62.5%), was higher than that described in German and Swiss MDS patients where 52.1% and 45% had clonal anomalies, respectively (11, 12) but lower than that found in Brazil where Borgonovo et al. reported more than 69% of abnormal karyotypes (13).

Median age of this Romanian MDS population analyzed was 64 years as found in German and Tunisian MDS patients (14, 15).

The frequency of clonal cytogenetic abnormalities was 56.5% among patients with primary MDS (n=23) and 100% among those with secondary MDS (n=2).

In our patients, chromosomal deletions [del(5q), del(7q), del(20q) and del(17p)] were the most frequent structural alterations. Similar findings were reported by Gmidene et al. (14) and Bernasconi et al (16).

According to FAB classification, the highest frequency of chromosome abnormalities was observed in RA and RAEB subtypes, and the lowest in CMML. Lee et al. reported that abnormal clones were commonest in patients with RARS and RAEB-t followed by those with RAEB, and least common in patients with RA and CMML (17).

Solé et al. proposed four categories of karyotypes, called GCECGH (Grupo Cooperativo Espanol de Citogenetica Hematologica) categories. These categories are as follows: good prognosis: normal karyotype, loss of Y chromosome, del(5q), del(12p), del(11q) and del(20q) as a single anomaly; intermediate prognosis: trisomy 8, rearrangements of 3q21q26, translocations of 11q, del(17p), trisomy 18 and trisomy 19; poor prognosis: complex karyotypes, monosomy 7, deletion 7q and i(17q); unknown prognosis: all remaining cases with single or double abnormalities (18).

According to GCECGH classification, 50% of our patients belong to the good prognosis group and 16.66% in each of the intermediate, poor and unknown prognosis groups.

Among karyotypic aberrations, numerical chromosomal abnormalities found were 46.66% (+8, +19, +21, loss of Y chromosome).

The incidence of trisomy 8 as the sole abnormality in MDS was 13%. Our incidence of +8 was similar to that described by Paulsson et al. (10%) (19), but higher than that found (3%) by Gmidene et al. (15). According to Bernasconi et al. the incidence of trisomy 8 varies between 5% and 20%; it occurs in 19% of chromosomally abnormal patients and in 10% of all MDS patients (16). Patients with only trisomy 8 have an intermediate prognosis by IPSS and GCECGH although some studies has shown that these patients have an increased risk for progression to AML (20). We found +8 in one patient with MDS associated with AML transformation. This chromosomal abnormality is not specific to MDS because it can be discovered in other hematological disorders.

Trisomy 19 was found in one patient with MDS. According to IPSS and GCECGH, +19 has an intermediate prognosis. Trisomy 19 has been reported as the sole numerical chromosomal abnormalities in MDS and AML (21, 22). Trisomy 19 as the sole anomaly is a rare but recurrent change in chronic myelomonocytic leukemias (CMML), in particular of the proliferative type (23).

Although +21 is one of the commonest acquired chromosomal abnormalities in hematologic malignancies, +21 as the sole anomaly is a very rare event (24). Trisomy 21, found in 7.7% in de novo MDS, is associated with an intermediate prognosis according to IPSS criteria while GCECGH included it in unknown prognosis group. Trisomy may contribute to leukemogenesis by a gene dosage effect whereby the presence of an increased copy number of certain genes gives a cell survival advantage and hence neoplastic potential. Gains and losses of whole chromosomes in neoplastic diseases could be explained by the amplification of an active primary aberration, which may be a submicroscopic chromosomal change (25). Trisomies or monosomies may be due to subsequent nondisjunction event (24).

Loss of the Y chromosome as a sole anomaly was present in 6.66% of patients with chromosomal abnormalities. This anomaly is also seen as the sole cytogenetic abnormality in the bone marrow of 7–8% healthy old men and its clonal nature is questioned (15). Loss of the Y chromosome is associated with a good prognosis according to IPSS criteria. Bernasconi et al. considered that elderly people with a high percentage of loss of the Y chromosome in marrow cells are at risk of developing a hematological disorder and in MDS patients the abnormality is surely clonal because it is present at the onset of the disease and disappears upon achievement of complete remission (16).

In our study structural abnormalities were found in 8 cases. Chromosomal deletions, being present in about 60% of patients with structural aberration, are the most common defects in either de novo or secondary MDS. The most frequent

deletions involve the long arms of chromosomes 5, 7, 20, and the short arms of chromosomes 17. The deletion is often present as a single defect in low-risk MDS, whereas it occurs along with other abnormalities in advanced MDS (16).

Deletion of the long arm of chromosome 5 [del(5q)] is the most common chromosomal abnormality in MDS, occurring at a frequency of 10-15% (7, 20). Del(5q) also occurs in AML and several other cancers (26). The commonly deleted region or critical region has been defined as 5q31~q33 (27) and contains multiple genes involved in cellular growth, hematopoiesis, cell cycle control, cell adhesion, and tumor suppression (28).

The abnormalities of chromosome 7 [monosomy 7(-7) or del(7q)] were present in 13.3% of MDS patients. The presence of -7 or del(7q) in MDS or AML patients is a very poor prognostic indicator and correlates with short survival and high risk for AML transformation. The loss of chromosomal material from the short arm of chromosome 17 was not only determined by simple deletions, but also by isochromosome 17q. Deletion 17p occurred in 6.66% of patients with primary MDS and isochromosome i(17)(q10) was found in one patient with MDS in leukemic transformation. According to GCECGH classification this anomaly is associated with a poor prognosis.

Deletion of the long arm of chromosome 20 [del(20q)] was detected as a single anomaly in one case. According to Panani et al. del(20q) can occur as the sole anomaly or in association with other changes and it is seen in about 5% of MDS. Del(20q) is usually interstitial with the most common deleted region being between 20q11 and 20q13. The International MDS Risk analysis Workshop found that patients with a del(20q) observed in association with a complex karyotype had a poorer prognosis, whereas the prognosis for patients with an isolated del(20q) was favorable. However, a few studies reported that this anomaly is associated with a poor prognosis (29, 30).

The proportion of good, intermediate and poor prognosis cytogenetic subgroups was 54%, 29% and 17%, respectively. Subgroups were different than that previously reported by Gmidene et al. (67%, 17% and 16%, respectively) (15). However, the median survival time for the poor-risk patients was slightly longer than the intermediate-risk patients (44 months versus 32 months), contrary to the large published series (15, 16, 20). This finding might be explained by the relatively small size of our cohort.

The intermediate cytogenetic risk group represented a cytogenetically diverse population that included patients with structural or numeric abnormalities.

Within the poor cytogenetic risk category defined by the current IPSS criteria, our patients who had del(7q) as a sole cytogenetic abnormality had a superior median OS compared the patients who had a complex karyotype. This observation is in agreement with the reports by Bernasconi et al (16).

We observed that leukemic transformation occurred more frequently in patients with chromosomal abnormalities (33.3%) than in those patients with a normal karyotype (12.5%). Taking into account our results we consider that patients with an abnormal karyotype had a shorter survival and higher risk of leukemic transformation than did those with a normal karyotype.

In conclusion, cytogenetic results have an important role in the diagnosis and identification of prognostic subgroups of MDS.

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Abbreviations list

AML – acute myeloid leukemia

CMML – chronic myelomonocytic leukemia,
del – deletion
FAB – French-American-British
GCECGH – Grupo Cooperativo Espanol de Citogenetica Hematologica
IPSS – International Prognostic Scoring System
MDS – AL acute leukemia following myelodysplastic syndrome,
MDS – myelodysplastic syndrome
MDS-s secondary MDS,
OS – overall survival
RA – refractory anemia,
RAEBt – RAEB in transformation,
RARS – refractory anemia with ringed sideroblast,
WHO – Word Health Organization

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