

Cytogenetic Findings in Adult Greek Myelodysplastic Syndrome Patients: Predominance of Single Trisomy 8

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Abstract. *Myelodysplastic syndrome (MDS) is a clonal disorder of the pluripotent hematopoietic stem cells which is characterized by ineffective and dysplastic hematopoiesis. The pathogenesis of MDS is not well defined and it appears that multiple genetic changes are involved. Several studies have shown that certain chromosomal abnormalities may be influenced by environmental factors, while differences in the incidence of certain aberrations in different areas have also been reported. The aim of this study was to investigate the frequency and the type of chromosomal changes in Greek primary MDS patients. Single chromosomal abnormalities were focused on as possibly being primary changes implicated in the initiation of the neoplastic process. Using conventional cytogenetics, 239 MDS patients were studied and 63 cases were found with an abnormal karyotype (26.36%). Among the cytogenetically abnormal cases, 46 patients presented single chromosomal abnormalities (73.01%). These aberrations were according to frequency +8 (28.57 %), del(5q), -7/del(7q) and +14 (6.35 % each), i(17q) and del(11)(q13) (4.76 % each), +11, -Y, i(1q), del(8q), del(18p) and t(X;11) (1.59 % each). In conclusion, the incidence of chromosomal abnormalities in Greek MDS patients was lower than that reported in the literature. The most common single anomaly was trisomy 8, while a relatively high incidence of an isolated +14 was also observed. Notably, this is the first time an isolated i(1q) has been described in the literature.*

Myelodysplastic syndrome (MDS) is a clonal disorder of the pluripotent hematopoietic stem cells which is characterized by ineffective and dysplastic hematopoiesis. MDS patients

have peripheral blood cytopenia, a hypercellular bone marrow, while they frequently evolve to acute leukemia. MDS may arise *de novo* or secondarily after treatment with radiation or cytotoxic agents for other diseases. MDS constitutes a heterogeneous group from the morphological and biological points of view. The pathogenesis of MDS is not well defined and it appears that complex genetic changes are involved. Activation or mutation of certain oncogenes, loss of tumor suppressor genes, generation of fusion oncogenes and an increased apoptotic activity in the bone marrow cells have to date been suggested to play a role. Also, a number of epidemiological studies have shown that certain environmental factors may contribute to the development of primary MDS. Clonal chromosomal changes are found in 30-50% of MDS, but no specific cytogenetic abnormality has, as yet, been defined. The chromosomal abnormalities are characterized by chromosomal losses or gains and they mainly include -5/del(5q), -7/del(7q), del(11q), del(12p), del(17p), del(20q), -Y and +8. It is considered that some chromosomal abnormalities may be responsible for the initiation or progression of MDS. It was suggested that certain abnormalities may be influenced by environmental factors, whereas differences in incidence of certain abnormalities in different areas have also been reported (1-10).

The aim of this study was to investigate the frequency and the type of chromosomal findings in adult Greek primary MDS patients. Since single chromosomal abnormalities might be primary changes implicated in the initiation of the neoplastic process, these abnormalities were focused on and our findings compared with those found in the literature.

Materials and Methods

Two hundred and thirty-nine patients with primary MDS were cytogenetically studied by direct culture of the bone marrow cells and the G-banding technique. As many cells as possible were analyzed in each case, and never fewer than 20. Clinical data, French-American-British (FAB) subtypes as well as other hematological characteristics were not available for most of the cases studied.

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Key Words: Myelodysplastic syndrome, cytogenetics, chromosome abnormalities, chromosome 8 aberrations.

Results

Among 239 patients cytogenetically studied, 176 had a normal karyotype while 63 presented chromosomal abnormalities (26.36%). Among the abnormal MDS patients, 46 had single abnormalities (73.01%) while 19 cases had 2 abnormalities or complex karyotypes. Single chromosomal abnormalities included +8 (in 18 cases) (28.57%), del(5q), -7/del(7q) and +14 (in 4 cases each) (6.35% each), i(17q) and del(11)(q13) (in 3 cases each) (4.76% each), +11, -Y, i(1q), t(X;11)(q13;q23), del(8q) and del(18p) (in 1 case each) (1.59% each). Three cases had an extra unidentified chromosome, while in 1 case a missing unidentified chromosome was also found. In a few cases, some of the single abnormalities were accompanied by other chromosomal changes. Thus +8, del(5q) and i(1q) coexisted with additional changes in 3, 6 and 2 cases, respectively (Table I).

Discussion

Clonal chromosomal changes are found in 30-50% of MDS, but no specific cytogenetic abnormality has been defined to date. The pathogenesis of MDS is not well established and it seems that multiple genetic pathways are involved in MDS. Several epidemiological studies have suggested that certain environmental factors may contribute to the development of primary MDS. In contrast to leukemias, in MDS recurrent translocations have been rarely identified. The chromosomal abnormalities are mainly characterized by partial/total chromosomal losses or chromosomal gains. Among them monosomies 5, 7 and Y are more frequently found, while partial chromosomal losses mainly include del(5q), del(7q), del(11q), del(12p), del(17p) and del(20q). Trisomy 8 represents the most common chromosomal gain. It is thought that loss of genetic material may lead to loss of tumor suppressor genes, while gain of chromosomal material may lead to a gene dosage effect. Chromosomal abnormalities found in neoplastic diseases as a sole anomaly are of major importance. They may constitute primary changes implicated in the initiation of the neoplastic process (2-5, 7-10).

By conventional cytogenetics, 239 primary MDS cases were investigated for the frequency and the type of cytogenetic abnormalities. We focused on single chromosomal abnormalities comparing them with those reported in the literature. Sixty-three cases had an abnormal karyotype (26.36%), though in most of the reported studies the incidence of chromosomal abnormalities in MDS was higher than in our study. Although, in the present study, the number of the analyzed metaphases for each case was sufficient, an overlooked small abnormal clone could not be excluded. Among the cytogenetically abnormal cases, single chromosomal abnormalities were found in 46 cases

Table I. Single chromosomal abnormalities in 46 primary MDS patients among 63 cytogenetically abnormal cases.

Single chromosomal abnormalities	Cases (%)*	Cases**	Total cases (%)
+8	18 (28.57)	3	21 (33.34)
del(5q)	4 (6.35)	6	10 (15.87)
-7/del(7q)	4 (6.35)	—	4
+14	4 (6.35)	—	4
i(17q)	3 (4.76)	—	3
del(11)(q13)	3 (4.76)	—	3
+11	1 (1.59)	—	1
i(1q)	1 (1.59)	2	3 (4.76)
del(8q)	1 (1.59)	—	1
del(18p)	1 (1.59)	—	1
-Y	1 (1.59)	—	1
t(X;11)(q13;q23)	1 (1.59)	—	1
+C	3 (4.76)	—	3
-C	1 (1.59)	—	1

*Percentage of abnormalities among cytogenetically abnormal cases.

**Cases with additional chromosomal abnormalities.

(73.01%). These aberrations were, according to frequency, +8 (28.57%), del(5q), -7/del(7q) and +14 (6.35% each), i(17q) and del(11)(q13) (4.76% each), +11, -Y, i(1q), del(8q), del(18p) and t(X;11) (1.59% each). In 4 cases an extra or a missing chromosome could not be identified by the banding technique.

The incidence of trisomy 8 in MDS is about 10% and it is found in all FAB subtypes. Trisomy 8 as the sole anomaly accounts for two-thirds of the cases (11). In the present study, +8 was found in 21 of the 63 cytogenetically abnormal cases (33.34%), while it was observed as a sole anomaly in 18 cases (28.57%). Possible underlying mechanisms for trisomies include gene dosage effects, while cryptic abnormalities in duplicated chromosomes have also been found in some instances. However, for trisomy 8 no hidden anomalies have, as yet, been identified (12). Lee *et al.* (10) reviewed the cytogenetic results of 205 MDS cases in Korea and they compared their results with those reported in the literature. They found differences in the incidence of chromosomal abnormalities for different areas. Trisomy 8 was one of the most common anomalies in Korea and also the most common sole anomaly. The authors discussed the probability that the pathogenesis of MDS is different for different races. This might reflect inherited genetic changes as well as effects of environmental factors such as chemicals, natural substances and foods. Therefore, it is likely that chromosomal abnormalities may be different for different areas.

Del(5q) was found in 10 cases (15.87%), while as a sole anomaly it was observed in 4 cases (6.35%). Del(5q) is a common finding in MDS accounting for 15-20% of the

abnormal cases. A number of important genes have been mapped on chromosome 5q. However, the exact role of any of these genes in the pathogenesis of MDS has not been established, while molecular studies have not definitively identified critical suppressor genes in 5q- associated MDS. Interestingly, it is reported that patients with primary MDS and del(5q) have a significant occupational exposure to potential carcinogens and it was suggested that abnormalities of chromosome 5 may be a marker of mutagen-induced MDS (13-18).

Monosomy 7/del(7q) was found in 4 cases (6.35%), in all as a sole anomaly. Monosomy 7/del(7q) is a frequent finding in MDS, accounting for 4.5-5% of the abnormal cases. Several genes have been mapped on 7q, while the deleted segment of 7q may encode a tumor suppressor gene implicated in the pathogenesis of MDS. As with -5/del(5q), environmental exposure to mutagens has been suggested to be associated with -7/del(7q) (19-21).

Trisomy 14 is an uncommon non-random chromosomal abnormality associated with MDS. Horton *et al.* (22) reported 2 cases of MDS with trisomy 14 and, on reviewing the literature, they found 32 MDS patients with this anomaly. To our knowledge, 25 cases of MDS with trisomy 14 as a sole anomaly have been reported (23). In the present study, 4 cases with an isolated +14 (6.35%) were found, which we consider to be a high incidence.

Isochromosome i(17q) as a sole anomaly was found in 3 cases (4.76%). Abnormalities resulting in loss of 17p material have been found in up to 4% of MDS patients and they include simple deletions, i(17q) or unbalanced translocations. The gene p53 located on 17p13 is typically lost in these cases, while an inactivation of the second allele very often occurs (24,25).

Del(11)(q13) was found as a sole anomaly in 3 cases (4.76%). Abnormalities of 11q are among the most common found in myeloid malignancies and they often harbor a breakpoint at 11q23. Del(11)(q13) as a sole anomaly has been very rarely described in MDS (26).

Isochromosome i(1q) was found in 3 of our cases (4.76%) and in 1 of them as a sole anomaly. To our knowledge, i(1q) has been reported in 2 MDS cases, but not as a sole anomaly (23). Lee *et al.* (10) reported predominantly structural aberrations of chromosome 1 in MDS cases in Korea, but none of the cases presented i(1q). Eighty percent of their cases with a chromosome 1 anomaly were accompanied by other chromosomal abnormalities and the authors suggested that the changes of chromosome 1 may be evolutionary events occurring during multistep oncogenesis. The authors compared their results with those reported in the literature and they suggested the likelihood of ethnic differences.

In conclusion, the incidence of chromosomal abnormalities in Greek MDS patients was lower than that

reported in the literature. The most common single anomaly was trisomy 8, while a relatively high incidence of an isolated +14 was also observed. Notably, this was the first time that an isolated i(1q) has been described in the literature.

Acknowledgements

The technical assistance of Mrs Athanasia Babanaraki and Mrs France Stamatelli is gratefully acknowledged.

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Received August 17, 2005

Accepted November 3, 2005