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Cytogenetic and molecular basis of BCR-ABL myelodysplastic syndrome: diagnosis and prognostic approach

Mostafa Paridar, Omid Kiani Ghalesardi, Mohammad Seghatoleslami, Ahmad Ahmadzadeh, Abbas Khosravi, Najmaldin Saki

Health Research Institute, Thalassemia and Hemoglobinopathy Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz 61357-15794, Iran.

Correspondence to: Dr. Najmaldin Saki, Health Research Institute, Research Center of Thalassemia and Hemoglobinopathy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz 61357-15794, Iran. E-mail: najmaldinsaki@gmail.com

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ABSTRACT

Myelodysplastic syndromes (MDS) include a heterogeneous group of blood disorders generally afflicting older people. Several genetic factors have been reported from these patients that have an important role in the diagnosis, prognosis, and treatment of this disease. BCR-ABL1 is a genetic factor that has occasionally been reported in some studies. This review attempts to characterize MDS patients reported to harbor this fusion and to assess the diagnostic, therapeutic, and prognostic potential of BCR-ABL1 fusionin MDS patients. This review showed that BCR-ABL fusion has been reported in 22 MDS patients whose condition generally transformed to acute myeloblastic leukemia and was not responsive to conventional therapies. However, these patients showed a good response to treatment with tyrosine kinase inhibitors. Therefore, even though incidence of BCR-ABL fusion appears to be low in MDS patients, its detection is essential in assessing disease prognosis and choosing appropriate treatment.

INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of clonal myeloid disorders with morphological characteristics such as hypercellular bone marrow (BM), single- or multilineage dysplasia, and cytopenia in peripheral blood (PB).[1,2] Mortality associated with cytopenia and risk of transformation to acute myeloblastic leukemia (AML) are important problems for MDS patients. In fact, one-third of MDS patients become AML patients, and the remaining two-thirds succumb to progressive BM failure, which leads to bleeding, frequent infections, and severe anemia.[3] MDS is generally an adult disease with an average age upon diagnosis of 65-70 years; less than 10% of patients are younger than 50 years. The annual incidence rate of MDS is approximately 5 cases per 100,000 population; incidence increases to 22-45 cases per 100,000 in people over 70 years of age.[4] MDS is generally diagnosed by accurate assessment of PB followed by

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morphological BM examination. According to the 2016 WHO revision, MDS patients are divided into lower- and higher-risk MDS. Lower-risk MDS conditions that have below 5% of blasts include: MDS with single-lineage dysplasia, MDS with single-lineage dysplasia and ring sideroblasts (RS), MDS with multilineage dysplasia without RS and with RS, MDS with isolated del (5q), and MDS unclassifiable (MDS-U). Higher-risk MDS conditions (5-19 blasts) include: MDS-EB1 (5-9% blast and/or 2-4% in PBS) and MDS-EB2 (10-19% blasts; Auer rods, or 5-19% in PBS).[5]

t(9;22) (q34;q11.2) translocation and its variants give rise to Philadelphia chromosome (Ph), which results in juxtaposition of DNA sequence of BCR and ABL1 genes, mRNA translation of this chimeric gene, and eventual dysregulated expression of oncogenic tyrosine kinase of BCR-ABL1 fusion, which seems to be sufficient to initiate the leukemogenesis process.[6] Three different forms of BCR-ABL1 fusion protein are produced based on the breakpoint site in the BCR gene: p190, p210, and p230. Although they are all associated with development of leukemia, these three forms have different clinical outcomes.[7] Although BCR-ABL1 chromosomal abnormality is pathognomic for chronic myeloid leukemia (CML), it is observed de novo in B-cell precursor acute lymphoblastic leukemia (ALL), especially in adults, as well as in 0.48-3% of patients with AML.[8,9] In contrast, Ph is extremely rare in MDS patients and shows up in the last stages of disease, so it is associated with leukemic transformation in most cases.[10] Although few cases of Ph^+ MDS have been reported, diagnosis of this disorder is especially important, since these patients show a poor response to conventional therapeutic approaches.[11]

The presence of common traits in MDS and myeloproliferative disease (MPD) suggests that some genetic abnormalities associated with MPD are most likely involved in the development or progression of MDS. Lack of knowledge about the importance of this abnormality in MDS patients may lead to inaccurate assessment of BCR-ABL fusion and choice of an inappropriate therapeutic protocol. Therefore, besides studying the reported cases, this review aims to investigate the typical features of Ph^+ MDS patients and will assess the role of genetic abnormalities, especially the impact of BCR-ABL fusion, on response to treatment in MDS patients.

CYTOGENETIC AND MOLECULAR MARKERS

All classification and prognosis systems of MDS in recent decades have been based on cytomorphological findings in PB and BM, including May-Grünwald-Giemsa (MGG) staining, myeloperoxidase staining, nonspecific esterases (especially for CMML), as well as iron staining and assessment of cytopenia.[12] MDS diagnosis is often challenging for several reasons, such as varying clinical manifestations in different patients and the absence of dysplasia in some cases. For this reason, cytogenetic tests have been introduced for correct diagnosis of some MDS subtypes; for example, in the fourth classification of WHO, del 5q is considered as a separate subgroup. In patients whose diagnosis is controversial, cytogenetic analysis seems to be a helpful addition to clinical and hematological findings when seeking a definitive diagnosis.[13]

Genetic abnormalities in MDS patients include deletions, gains, and chromosomal rearrangements, as well as molecular changes such as point mutations, epigenetic changes, and dysregulated miRNAs.[13] Conventional cytogenetics and fluorescent in situ hybridization (FISH) analysis are commonly used methods for detection of karyotype abnormalities; both methods have advantages and disadvantages. Karyotype commonly evaluates 20 metaphase cells. FISH analysis can detect chromosomal abnormalities with a higher resolution, but it is limited to regions with predefined probes.[14] Therefore, it seems prudent to perform initial assessment by conventional karyotyping and to use FISH analysis for further investigations. Several studies have shown that FISH analysis in conjunction with karyotyping can provide further information, especially in cases where the karyotype appearsnormal.[15,16] Chromosomal abnormalities have been detected in approximately 50% of patients with de novo MDS and in more than 80% of MDS cases secondary to chemotherapy and toxic agents. In a large-scale study on 2124 MDS patients, 48% had normal karyotype and 52% showed abnormal karyotype. The most common cytogenetic abnormality was del 5q in 30% of patients, followed by -7/del 7q in 21%, and +8 in 16% of cases.[17] Detection of cytogenetic abnormalities plays a significant role in disease prognosis, so it has been recognized as a marker in all the prognostic systems, including international prognostic scoring system (IPSS), revised-international prognostic scoring system (IPSS-R), and WPSS. IPSS-R isone of the most widely used prognostic systems for MDS patients.[18] In this classification system, -Y and del (11q) have a very good prognosis; normal karyotype, del (5q), del (12p), del (20q), and double including del (5q) have good prognosis; del (7q), +8, +19, and i (17q) a moderate prognosis; -7, inv (3)/t (3q), double including -7/del (7q), complex 3 abnormalities have poor prognosis; and finally patients with karyotype of complex with > 3 abnormalities have a very poor prognosis.[19]

Technological advances in the field of genetic analysis, including high-through put next-generation sequencing (HT-NGS), led to the discovery of several genetic mutations in MDS patients.[20] Studies have shown that approximately 83% of MDS patients show genetic mutations.[21] In Table 1, some of the most common mutant genes in MDS patients are summarized.

Although these mutations involve a range of genes, their use as a diagnostic marker for MDS patients is difficult. A good diagnostic marker must have a high incidence in patients as well as an acceptable level of specificity, but none of these genes has a high prevalence in MDS patients (low frequency), and no mutant gene has been specifically reported for MDS.[34] Mutations have been partially assessed as prognostic markers and have generally been associated with poor prognosis.[14] Therefore, although these mutations seem to be good prognostic factors, prognostic systems have not yet taken advantage of them in their classifications.[18]

DIAGNOSIS AND PROGNOSIS

According to search of MEDLINE database, there have been 22 cases of MDS patients harboring BCR-ABL1 chromosome abnormality. There were 15 male and 7 female patients that were classified into two groups: adults with an average age of 64.5 years and children with an average age of 25 months. Mean hemoglobin concentration was 8.4 g/dL (94.7% had hemoglobin levels less than 11.5 g/dL, i.e. were anemic). Mean white blood cell count was 6.7 × 10^6/mL and mean platelet count was 135 × 10^3/mL (61.1% had platelet counts lower than 100 × 10^3). Karyotype analysis in 20 cases revealed t (9:22) translocation, but in two other cases, FISH test indicated the presence of Phfusion despite normal karyotype.[11,35] Molecular analysis was done in only 10 cases; of these 5 represented Ph P190 variant, 4 cases had Ph210, and 1 case had both variants [Table 2]. According to these findings, Ph fusion was most prevalent in RAEB subgroup; 54.6% of cases (including 27.3% RAEB, 9.1% RAEB2, and 18.2% of RAEBt) were classified in this subgroup, followed by RA in 13.6% of cases. This finding was in contrast to some extensive studies of the epidemiology of different subtypes of MDS, which indicate that RA, RARS, RAEB, and RAEBt are the most common subtypes, respectively.[17,36] There was a relatively poor prognosis in these patients. Only 5 patients responded to treatment, among which 2 cases were treated with imatinib.[11,13] Forty-five percent (n = 10) of patients progressed to AML, among whom 3 patients showed P190 variant, 3 patients showed P210, and 1 patient showed both variants [Table 2]. Only one patient showing P190 variant progressed to ALL. Three patients progressed to CML for whom unfortunately no molecular study was conducted.[4,9,13]

DISCUSSION AND FUTURE PROSPECTIVE

Using current advances in molecular diagnosis, several genetic factors have been identified in MDS patients with occasional diagnostic, prognostic, and therapeutic value. Ph chromosome is a factor intermittently reported in some cases of MDS. Given the pathognomic role of Ph in other hematologic neoplasms, it is assumed that in case of high incidence of Ph in MDS patients, an MDS subgroup known as Ph^+ MDS can be introduced. However, the importance of this genetic abnormality in MDS patients has not been extensively studied in MDS patients up to the present time.

The fact that only 22 cases of Ph^+ MDS have been reported to date is not conclusive evidence of low prevalence of this fusion in MDS patients. We state this for two reasons: (1) retrospective studies are inefficient for these patients because of the lack of careful examination of BCR-ABL fusion, and (2) no study up to the present time has specifically examined this fusion in MDS patients. Given that in some cases

Table 1: The most common mutations in myelodysplastic syndromes

	Mutated gene	Prevalence (%)	Prognosis	Ref.
RNA splicing	*SF3B1*	16	Favorable	[22,23]
	SRSF2	13	Poor	
	U2AF1	10	Poor	
DNA methylation	*TET2*	23	Favorable	[24]
	DNMT3A	9	Poor	[25]
	IDH1/2	7.5	Poor	[26]
Chromatin modification	*ASXL1*	20	Poor	[27]
	EZH2	6	Poor	[28]
Oncogenes	*Tp53*	9.4	Poor	[29]
	Ras	15	Poor	[30]
	EVI1	1-2	Poor	[31]
Others	*RUNX1*	12	Poor	[32]
	JAK2	53 in RARS-T	Not studied	[33]

Table 2: Characteristics of MDS patients with BCR-ABL fusion

No.	Age/gender	MDS subtype	Ph+ phase/type	Cytogenetic findings	Hematological findings	Outcome	Ref.
1	69/M	RAEBt	At diagnosis/P190	46, XY[3]/45, X, -y[2]/50, XY, +Y, -3, del5 (q12q34), +8, +14, add(18)(p11), +22, +min[11]/idem, t(9;22)(q34;q11)	Hb = 8.1 WBC = 5.3 Plt = 77	Progressed to AML/died	[37]
2	64/M	RAEB	At diagnosis/P190	46, XY[7]/47, XY, +8, t(9;22)(q34;q11)[6]	Hb = 7.8 WBC = 6.9 Plt = 98	Progressed to AML/died	[37]
3	3/M	RAEBt	AML late stage transformation/P210	46, XY, t(9;22)(q34;q11)	Hb = 6.2 WBC = 4.7 Hb = 47	Progressed to AML	[38]
4	54/M	RA	ALL transformation stage/P190	46, XY, t (9;22)(q34;q11).20q- (18/20)/46, XY, 20q-	Hb = 8.6 WBC = 3.2 Plt = 142	Progressed to ALL/died	[39]
5	78/M	RAEBt	At diagnosis/P190	46, XY, der (3) t(1;3)(p22;p14), del (5) (q13q33)/FISH revealed fusion signal of BCR and ABL probes on an apparently normal chromosome 22	Hb = 9.8 WBC = 13.5 Plt = 29	Died in 5 months	[35]
6	67/F	RAEB-2	At diagnosis/P210(b2a2)	Ph+ [29/30], normal [1/30]	Hb = 11.5 WBC = 3.4 Plt = 111	Complete remission with imatinibmesylate	[11]
7	39/M	RAEB	AML transformation/early stage p210 and late stage p210 and p190	46, XY, t (3;3)(y21:q26)[50] 46, XY, del (l)(p22). t(3;3)(q21: y26). -16[6] 46, XY, t(3;3)(q21:q26), t (9;22) (q34:q11)[3]	Hb = 7.1 WBC = 7.1 Plt = 547	Progressed to AML/died	[40]
8	25 months/F	unclassified	At diagnosis/-	46, XX, t (9;22) (q34;q11) [15]	Hb = 8.7 WBC = 7.9 Plt = 39	Died in 28 months	[10]
9	20 months/F	unclassified	24 months after diagnosis/-	37-45, XX, −18[7]/46, XX[4]. nuc fish 9q34 (*abl*×2), 22q11 (*bcr*×2) (*abl*con *bcr*×1) [4/200]	Hb = 5.9 WBC = 26.3 Plt = 71	Treated with low dose chemotherapy	[10]
10	73/M	CMMoL	7 months after diagnosis/-	46, XY, t(4;6) (p15;p12), t(9;22) (q34;q11) [10%]	Hb = 15.4 WBC = 18.1 Plt = 31	CML/died in 10 months	[41]
11	63/M	RA	During myeloproliferative phase/-	46, XY, t(9;22) (q34;q11) [100%]	Hb = 10.2 WBC = 1.4 Plt = 165	CML/died in 3 months	[41]
12	66/M	RAEB-2	AML transformation/P190	Karyotype was neg for Ph but FISH indicate a fusion signal in 60%	Hb = 6.2 WBC = 1.7 Plt = 33	Progressed to AML/died	[42]
13	73/M	RAEB	In CML transformation/P210	46, XY, t (9;22)/fish indicated single Ph 98.0%	-	Progressed to CML then all died	[43]
14	66/F	RAEB	At diagnosis/-	47, XX, +8, t(9;22;16)(q34;q11.2;q23) [4]/46, XX, idem, der (12) t(12;17)(p11.2;q11.2) [7]/46, XX[9]	Hb = 4.4 WBC = 0.9 Plt = 52	Progressed to granulocytic sarcoma skin in 9 months and died 1 month later	[44]
15	71/M	RAEB	At diagnosis/-	46, XY, t(9;22) (q34;q11) [20]	Hb = 9 WBC = 4000 Plt = 55	Progressed to RAEBt in 5 months and died 9 months after diagnosis	[44]
16	59/M	RAEB	At diagnosis/P210	46, XY, t(9;22) (q34;q11) [20]	Hb = 9.2 WBC = 1.3 Plt = 78	Progressed to AML/treated with allogeneic transplant	[44]

Continued...

No.	Age/gender	MDS subtype	Ph+ phase/type	Cytogenetic findings	Hematological findings	Outcome	Ref.
17	78/F	RCMD	At CML transformation/-	46, XX, t(9;22) (q34;q11)	Hb = 10.2 WBC = 2.6 Plt = 152	Progressed to CML accelerated phase/response to imatinib with significant cytopenia	[45]
18	56/M	RA	At diagnosis/-	Complex karyotype with PH1 chromosome	Hb = 4.8 WBC = 2.4 Plt = 350	Progressed to AML/died	[46]
19	49/F	-	At diagnosis/-	t(9;22) (q34;q11) [38%]	Hb = 8.2 WBC = 6.5 Plt = 425	Progressed to AML/died	[47]
20	62/M	RAEB	AML transformation	t(9;22) (q34:q11) [100%]	Hb = 9.8 WBC = 3.2 Plt =120	Progressed to AML/died	[48]
21	70/F	RARS	At diagnosis/-	46, XX[3]/46, XX, t(9q;22q) [12]	Hb = 9.5 WBC = 6.4 Plt = 316	Stable/alive	[49]
22	69/M	t-MDS	AML transfomation	46, XY, t(9;22)(q34;q11) [35]	Hb (no data) WBC = 1.3 Plt = 129	Progressed to AML	[50]

MDS: myelodysplastic syndromes; AML: acute myeloblastic leukemia; CML: chronic myeloid leukemia; ALL: acute lymphoblastic leukemia

only FISH analysis has managed to detect BCR-ABL fusion in MDS patients, lack of detection in normal karyotype analysis does not indicate definitive absence of this fusion.[5,11] Assessment of reported cases shows that MDS patients harboring this chromosomal abnormality typically do not respond well to conventional treatments but do show a good response to imatinib therapy.[11,13] Since imatinib is not routinely used in treatment of MDS patients, lack of Ph detection in these patients may lead to incorrect treatment and thus put the patient's life at risk.

In general, although the findings of this study indicate the importance of Ph detection in MDS patients, they are not sufficient to clarify the precise role of Ph in MDS patients. Therefore, specific assessment of this chromosomal abnormality in MDS patients is recommended in future studies.

Authors' contributions

Manuscript's conception and revision: N. Saki, M. Paridar

Writing the manuscript: O.K. Ghalesardi, M. Seghatoleslami, A. Ahmadzadeh

Tables' preparation: A. Khosravi

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Patient consent was obtained.

Ethical approval

This article does not contain any studies involving human or animal subjects.

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