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

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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 fusion in 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.

Key words: Myelodysplastic syndrome, cytogenetics, BCR-ABL

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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
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).[8]

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 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.[13] 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 appears normal.[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 is one 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-throughput next-generation sequencing (HT-NGS), led to the discovery of several genetic mutations in MDS patients. Studies have shown that approximately 83% of MDS patients show genetic mutations. 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. Mutations have been partially assessed as prognostic markers and have generally been associated with poor prognosis. Therefore, although these mutations seem to be good prognostic factors, prognostic systems have not yet taken advantage of them in their classifications.

**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 × 10^9/mL and mean platelet count was 135 × 10^9/mL (61.1% had platelet counts lower than 100 × 10^9). Karyotype analysis in 20 cases revealed t (9:22) translocation, but in two other cases, FISH test indicated the presence of Ph fusion despite normal karyotype. 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. 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 RAEB1) 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 RAEB1 are the most common subtypes, respectively. There was a relatively poor prognosis in these patients. Only 5 patients responded to treatment, among which 2 cases were treated with imatinib. 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. Only one patient showing P190 variant progressed to ALL. Three patients progressed to CML for whom unfortunately no molecular study was conducted.

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

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/gender</th>
<th>MDS subtype</th>
<th>Ph+ phase/type</th>
<th>Cyogenetic findings</th>
<th>Hematological findings</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69/M</td>
<td>RAEBt</td>
<td>At diagnosis/P190</td>
<td>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)</td>
<td>Hb = 8.1, WBC = 5.3, Plt = 77</td>
<td>Progressed to AML/died</td>
<td>[37]</td>
</tr>
<tr>
<td>2</td>
<td>64/M</td>
<td>RAEB</td>
<td>At diagnosis/P190</td>
<td>46, XY(7)/47, XY, +8, t(9;22) (q34;q11)</td>
<td>Hb = 7.8, WBC = 6.9, Plt = 98</td>
<td>Progressed to AML/died</td>
<td>[37]</td>
</tr>
<tr>
<td>3</td>
<td>3/M</td>
<td>RAEBt</td>
<td>AML late stage transformation/P210</td>
<td>46, XY, t(9;22)(q34;q11)</td>
<td>Hb = 6.2, WBC = 4.7, Hb = 47</td>
<td>Progressed to AML</td>
<td>[38]</td>
</tr>
<tr>
<td>4</td>
<td>54/M</td>
<td>RA</td>
<td>ALL transformation stage/P190</td>
<td>46, XY, t(3;3)(y21:q26)</td>
<td>Hb = 6.6, WBC = 3.2, Plt = 142</td>
<td>Progressed to ALL/died</td>
<td>[39]</td>
</tr>
<tr>
<td>5</td>
<td>78/M</td>
<td>RAEBt</td>
<td>At diagnosis/P190</td>
<td>46, XY, t(9;22)(q34;q11)</td>
<td>Hb = 9.8, WBC = 13.5, Plt = 29</td>
<td>Died in 5 months</td>
<td>[35]</td>
</tr>
<tr>
<td>6</td>
<td>67/F</td>
<td>RAEB-2</td>
<td>At diagnosis/ P210 (b2a2)</td>
<td>Ph+ [29/30], normal [1/30]</td>
<td>Hb = 11.5, WBC = 3.4, Plt = 111</td>
<td>Complete remission with imatinibmesylate</td>
<td>[11]</td>
</tr>
<tr>
<td>7</td>
<td>39/M</td>
<td>RAEB</td>
<td>AML transformation/ early stage p210 and late stage p210 and p190</td>
<td>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]</td>
<td>Hb = 7.1, WBC = 7.1, Plt = 547</td>
<td>Progressed to AML/died</td>
<td>[40]</td>
</tr>
<tr>
<td>8</td>
<td>25 months/F</td>
<td>unclassified</td>
<td>At diagnosis/-</td>
<td>46, XX, t(9;22) (q34;q11)[15]</td>
<td>Hb = 6.7, WBC = 7.9, Plt = 39</td>
<td>Died in 28 months</td>
<td>[10]</td>
</tr>
<tr>
<td>9</td>
<td>20 months/F</td>
<td>unclassified</td>
<td>24 months after diagnosis/-</td>
<td>37-45, XX, -18[7]/46, XX[4], nuc fish q9q4 (abl2), 22q11 (bcr3), 4q[20] (abl1)</td>
<td>Hb = 5.9, WBC = 26.3, Plt = 71</td>
<td>Treated with low dose chemotherapy</td>
<td>[10]</td>
</tr>
<tr>
<td>10</td>
<td>73/M</td>
<td>CMMoL</td>
<td>7 months after diagnosis/-</td>
<td>46, XY, t(4;6) (p15:p12), t(9;22) (q34;q11) [10%]</td>
<td>Hb = 15.4, WBC = 18.1, Plt = 31</td>
<td>CML/died in 10 months</td>
<td>[41]</td>
</tr>
<tr>
<td>11</td>
<td>63/M</td>
<td>RA</td>
<td>During myeloproliferative phase/-</td>
<td>46, XY, t(9;22) (q34;q11) [100%]</td>
<td>Hb = 10.2, WBC = 1.4, Plt = 165</td>
<td>CML/died in 3 months</td>
<td>[41]</td>
</tr>
<tr>
<td>12</td>
<td>66/M</td>
<td>RAEB-2</td>
<td>AML transformation/ P190</td>
<td>Karyotype was neg for Ph but FISH indicate a fusion signal in 60%</td>
<td>Hb = 6.2, WBC = 1.7, Plt = 33</td>
<td>Progressed to AML/died</td>
<td>[42]</td>
</tr>
<tr>
<td>13</td>
<td>73/M</td>
<td>RAEB</td>
<td>In CML transformation/P210</td>
<td>46, XY, t(9;22)fish indicated single Ph 98.0%</td>
<td>-</td>
<td>Progressed to CML then all died</td>
<td>[43]</td>
</tr>
<tr>
<td>14</td>
<td>66/F</td>
<td>RAEB</td>
<td>At diagnosis/-</td>
<td>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[8]</td>
<td>Hb = 4.4, WBC = 0.9, Plt = 52</td>
<td>Progressed togranulocytic sarcoma skin in 9 months and died 1 month later</td>
<td>[44]</td>
</tr>
<tr>
<td>15</td>
<td>71/M</td>
<td>RAEB</td>
<td>At diagnosis/-</td>
<td>46, XY, t(9;22) (q34;q11) [20]</td>
<td>Hb = 9, WBC = 4000, Plt = 55</td>
<td>Progressed to RAEBt in 5 months and died 9 months after diagnosis</td>
<td>[44]</td>
</tr>
<tr>
<td>16</td>
<td>59/M</td>
<td>RAEB</td>
<td>At diagnosis/P210</td>
<td>46, XY, t(9;22) (q34;q11) [20]</td>
<td>Hb = 9.2, WBC = 1.3, Plt = 78</td>
<td>Progressed to AML/treated with allogeneic transplant</td>
<td>[44]</td>
</tr>
</tbody>
</table>

Continued...
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.\cite{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.\cite{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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**REFERENCES**


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

MDS: myelodysplastic syndromes; AML: acute myeloblastic leukemia; CML: chronic myeloid leukemia; ALL: acute lymphoblastic leukemia.
26. Paridar et al. BCR-ABL and myelodysplastic syndrome


