Should We Look beyond Revised International Prognostic Scoring System: A Retrospective Observational Study of Progression of Myelodysplastic Syndrome to Acute Leukemia

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Abstract

Introduction  Myelodysplastic syndrome (MDS) is a clonal stem cell disorder and heterogeneous condition resulting in peripheral cytopenias with marrow dysplasia due to ineffective hematopoiesis. The revised International Prognostic Scoring System (IPSS-R) predicts the risk of progression to acute leukemia (AL). Indian data on MDS and its progression to AL are limited. Additionally, the cytogenetic findings are dictated by patients’ racial background. Study intended to analyze the cytogenetic profile of the patients with MDS.

Objectives  This study aimed to (1) evaluate the clinicohematologic and morphologic spectrum of newly diagnosed MDS cases, (2) evaluate the cytogenetic profile of these cases, and (3) study the cases progressed to AL.

Materials and Methods  MDS cases diagnosed and followed-up during a 5-year study period, from January 2015 to December 2019, were included in the study and the study was conducted at regional cancer center in Western India. De novo diagnosed MDS cases with complete workup were considered and MDS due to secondary causes were excluded. Baseline clinical, hematologic findings were tabulated along with cytogenetics and risk stratified as per IPSS-R, and their progression was studied.

Results  A total of 63 cases of de novo MDS were diagnosed over a period of 5 years with 45 cases on follow-up and 15 cases (33.3%) progressed to AL. Maximum number of cases belonged to MDS-EB category accounting to 48 cases (76.1%). Apparently normal karyotyping was the commonest cytogenetic finding in 33 MDS cases (61.2%) and in 8 cases that progressed to AL (53.4%).

Conclusion  MDS cases diagnosed at relatively early age were at higher risk of progression to AL. Majority of the cases that progressed to AL were risk stratified in high and very high risk groups and 10 cases which progressed to AL belonged to good category, interestingly apparent normal karyotyping was the commonest cytogenetic

Keywords ► myelodysplastic syndrome  ► acute leukemia  ► International prognostic scoring system  ► cytogenetics

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finding in more than 50% of the cases progressed to AL. Molecular mutations could only explain this progression and studies integrating molecular mutations with present IPSS-R scoring system should be conducted, as it could translate into better risk stratification and help in early identification and better management of cases at risk in progression to AL.

Introduction

Myelodysplastic syndrome (MDS) is a clonal hematological disorder with ineffective hematopoiesis in one or more bone marrow (BM) lineages. Clinically MDS presents with fatigue, dyspnea, infections, easy bruising due to dysplasia in cell lines, and peripheral cytopenias. BM failure occurs due to ineffective hematopoiesis as a result of excessive apoptosis, maturation arrest, and proliferation resembling the mechanism that play in acute myeloid leukemia (AML). Multiple factors are implicated in pathophysiology of MDS such as immunologic, cytogenetic, epigenetic, genetic factors, and therapy associated factors.

MDS progress to secondary AML (sAML) in 20 to 30% of cases, whereas the remaining succumb to progressive BM failure. The prognosis of patients transforming to AML is generally grave, as they are resistant to currently available treatment options and the long-term survival rate among treated patients is low.

Owing to the inherent nature of genetic heterogeneity, multiple cytogenetic abnormalities are detected; however, role of each of these in disease progression is not well established. Risk assessment and therapeutic planning is presently based on the revised International Prognostic Scoring System (IPSS-R). Cytogenetics (CG), one of the parameters in IPSS-R, is performed mostly by conventional CG. Based on the scoring system, the risk of transformation to AML is assessed and managed accordingly. With advent of sequencing, genetic information obtained can greatly impact the prognosis of the disease.

Deep sequencing studies has facilitated in better understanding of molecular pathogenesis of MDS and its progression. Majority of the mutations do not seem to play any causative role other than genetic instability. Disease progression of MDS is characterized by increasing blast count which is due to acquired additional mutations and genetic alterations in the new emerging clones. This explains the varied mutational profiles across the different stages of disease.

The model to understand MDS and its progression into AML is a multistep concept of leukemogenesis which is characterized by accumulation of different molecular and genomic alterations belonging to class-I and -II genes and epigenetic modifications that result in the expansion of the MDS/AML clone, this is well understood and accepted.

Spectrum of some mutated genes enriched in sAML is FLT3, NRAS, WT1, IDH1, and IDH2 (type-I genes) which are also the most frequently mutated genes in primary AML. The commonly mutated genes in high-risk MDS group are GATA2, RUNX1, TET2, TP53, and ASXL1 (type-II genes).

Leukemic transformation is faster in patients with type-I gene mutations than those without type-I mutations. Epigenetic and RNA splicing genes are commonly mutated in MDS and acquisition of type-I mutations, providing proliferation advantage and explaining the multistep concept of leukemogenesis.

Around 80 to 90% of MDS cases have somatic mutations identified which determine the clinical phenotype and overall survival. Sequencing studies help to identify mutations which are predictors of poor overall survival. These mutations are not commonly assessed during patient management as definitive guidelines are not well established. Currently the Indian data on MDS cases and its progression to AL is limited. The study was performed to evaluate clinicohematologic, morphological spectrum, and cytogenetic findings of newly diagnosed MDS along with outcome and also evaluate the cases which progressed to AL with emphasis on their cytogenetic findings.

Materials and Methods

Observational study was done in a retrospective manner and was conducted in patients diagnosed with MDS at a regional cancer center in western India, from January 2015 to December 2019. Sample size included all the cases diagnosed at our institute over a period of 5 years. Cases which were not evaluated for CG and secondary causes of MDS were excluded. Cases were diagnosed if they met the established criteria, diagnosis of de novo MDS was considered following correlation with morphologic, cytogenetic, and clinical criteria. Cytopenia was diagnosed as per the recommended and established thresholds in IPSS-R (hemoglobin concentration < 10 g/dL, platelet count < 100 × 10^9/L, and absolute neutrophil count < 1.8 × 10^9/L); BM examination which is considered hallmark in diagnosis of MDS was evaluated for morphologic dysplasia in all the three cell lineages and the established cut-off was 10% in each lineage to call unilineage or multilineage dysplasia. Dysplastic changes observed in nucleus of erythroid lineage (nuclear budding, internuclear bridging, karyorrhexis, multinuclearity, and megaloblastoid changes) and in cytoplasm (ringed sideroblasts with an aid of Perl stain and cytoplasmic granulations). Dysgranulopoiesis is characterized by small or overtly large cell size, nuclear hypo- or hypersegmentation, decreased granularity, and auer rods. Dysplastic changes in megakaryocytes include micromegakaryocytes, nuclear hypolobation, and multinucleation. Immunohistochemistry was performed to correlate with BM biopsy findings in necessary cases. Biochemical tests such as vitamin B-12, folate, and iron
profile were performed in all cases to rule out nutritional causes of dysplasia. Any occupational exposure to heavy metals or pesticides and anticancer drugs was excluded. Cases without workup for secondary causes of dysplasia and prior history of treatment for any other malignancy were excluded.

Conventional cytogenetics: BM aspirate sample was sent in heparinized tube for CG. Karyotyping was performed using short-term culture technique and metaphase chromosomes were banded by Giemsa- trypsin- guanine cytosine (GTG) technique and documented as per International System for Human Cytogenetic Nomenclature (ISCN) 2016 guidelines. At least 20 normal metaphases were necessary to consider a patient cytogenetically normal.

Fluorescence in situ hybridization (FISH): interphase and metaphase FISH was performed and tests were performed as per clinician request. Slides were prepared by phase-contrast microscopy and probes were added to target area of interest. Slides were subjected to denaturation and hybridization process, counterstained with 4',6-diamidino-2-phenylindole (DAPI), and visualized under fluorescence microscope.

FISH was performed with commercially available probes (Vysis), the following probes were used: LSI 5q31 (EGR1) and 7q31 (D7S486). Probe of interest was simultaneously applied (cohybridized) with a different color-labeled probe (internal control). The combinations used were 5q31 (spectrum orange) and D5S721:DSS23 (spectrum green), 7q31 (spectrum orange), and CEP 7 (spectrum green). Cells were considered harboring a gene deletion when carrying two signals due to the internal control and only one signal due to the target sequence and monosomic when carrying one signal each for the internal control and target sequence probes. A total of 200 cells were analyzed and cut-off was 2% for del 7q and 4% for del 5q.

Diagnosis was based on the World Health Organization (WHO) 2016 criteria and cases prior to this were reevaluated and classified as per the present criteria. With the necessary data, the patients were risk stratified as per IPSS-R system. During the follow-up period, the cases which progressed to AL were identified using the WHO determined blast cut-off of 20%.

**Statistical Analysis**

Statistical analysis was performed with Statistical Package for Social Science (SPSS) software version 20 (IBM SPSS Statistics, Armonk, New York, United States; IBM Corp.). Continuous variables were reported as median with standard deviation (SD) and categorical variables as percentages. The association between categorical variables was evaluated for significance, period of progression to AL was calculated in the each risk group and Student’s t-test was applied to study the significance of age and its progression also among different risk categories of MDS. The test was considered significant if the p-value is <0.05.

**Results**

Over a period of 5 years, 63 cases of primary MDS were reported (45 men and 18 women) and out of 45 cases on follow-up, 15 cases (33.3%) progressed to AL during the median follow-up period of 6 months (range: 1–53 months).

Median age at diagnosis of primary MDS is 52 years (range: 11–79 years) and median age of cases which progressed to AL is 51 years. Among the cases that progressed to AL, 53 cases (range: 11–74 years) was the median age in men (11 cases) and 56 years (range: 51–71 years) in women (4 cases). Most patients complained of fatigue (58 cases [92.0%]), breathlessness on exertion (33 cases [52.4%]), bleeding or easy bruising was presenting complaint (7 seven cases [11.1%]), six cases (9.5%) were incidentally detected due to cytopenia/s which was unresponsive to therapy, and two asymptomatic cases (3.1%) were also referred due to presence of atypical cells/blasts in peripheral blood.

Of the 63 patients, 38 cases (71.9%) had hemoglobin concentration of <8 g/dL, 20 cases (31.7%) had between 8 and 10 g/dL, and 4 cases (6.3%) had >10 g/dL. Mean hemoglobin concentration (MHC) was 7.4 g/dL (SD $\pm$ 1.74). Absolute neutrophil count (ANC) was less than 800/µL was seen in 21 cases (31.7%) and remaining case had count more than 800/µL. Overall, 31 cases (49.2%) had platelet count <50,000/cmL, 17 case (26.9%) had between 50,000 and 100,000/cmL, 15 cases (23.8%) counts were above 100,000/cmL. (~Supplementary Material S1, available in the online version), and 12 cases (19.0%) had isolated anemia and 29 cases (46.0%) were pancytopenic. Macrocrytic morphology was the commonest finding followed by dimorphic picture and in three cases, microcytic red blood cell (RBC) was noted. Eight cases had blasts in peripheral blood. Vitamin B-12 and serum folate levels evaluated were within normal limits and iron profile in few cases revealed an overload picture.

The distribution of WHO defined MDS entities along with median age in each of the entity is enumerated in (~Table 1). Maximum number of cases belonged to MDS-excess blast (EB) EB2 category accounted to 32 cases (50.7%), Cyto genetic study results are available in 54 cases and it includes all cases which progressed to AL. Twenty-one cases (38.9%) had abnormal karyotype and the CG findings in decreasing order of their prevalence in the study is normal karyotyping (33 cases), del (7q; 8 cases), del (5q; 5 cases), monosomy 7 (3 cases; >Fig. 1) trisomy 8 (3 cases), complex karyotyping (+der (7) del(7) i(17; 1 case), and hyperdiploidy (1 case; >Table 2). Risk groups stratified by IPSS-R and median age in each of the risk groups is tabulated (~Table 3). Forty-five cases were on follow-up and 15 cases (33.3%) progressed to AL which included one case of acute lymphoblastic leukemia (ALL; >Table 4). Estimated EFS was 5 months (95% confidence interval [CI]: 0–12 months), 17 cases were on lenalidomide and 5 cases (29.4%) progressed to AML over 6 months, and 7 out of 13 cases (53.4%) on hypomethylating agents (HMA) transformed to AML over 6 months. Six cases were on bone transfusion and four cases were on erythropoietin, one case each progressed to AML over 11 and 12 months, respectively. Patient aged 35 years with 15% blast and marrow fibrosis was treated as AML, 11 months of follow-up period was uneventful. Hematopoietic stem cell transplantation (HSCT) was performed in an 18-year-old patient belonging high-risk category with normal karyotyping, patient progressed to AML in 48 months and is on follow-up from past 12 months. Patient aged 11 years who progressed to ALL after 4 months of diagnosis of MDS with del 7q and is on follow-up.
from past 53 months and is stable. All cases which progressed to AL belonged to MDS-EB category only and majority of them fell into high and very-high-risk IPSS-R groups (Table 2).

Median time taken to progress to AL in high and very high risk groups was 11 and 6 months, respectively, while longer time duration of 16 months was taken by intermediate risk group. Progression to AL in high ($p = 0.01$) and very high risk group ($p = 0.002$) was statistically significant, while intermediate risk group was insignificant ($p = 0.3$). Monosomy 7 belonging to poor cytogenetic risk group, showed 100% transformation to AL. One case with complex karyotyping was lost for follow-up.

### Discussion

Median age of diagnosis is 51 years and 40 cases (63.5%) fell in age group less than 60 years which is similar to the Indian study and other Asian studies.\(^{18-20}\) Presentation age in Indian population is quite early when compared with the

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**Table 1** WHO defined MDS entities with number of cases, median age, cases progressed to AL, and cytogenetic findings in each of the category

<table>
<thead>
<tr>
<th>WHO defined MDS entities</th>
<th>Primary MDS (63 cases) $n$ (%)</th>
<th>Median age (y)</th>
<th>AL (15 cases)</th>
<th>Cytogenetic profile (54 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS-SLD</td>
<td>2 (3.2)</td>
<td>60</td>
<td>0</td>
<td>Normal karyotyping [2]</td>
</tr>
<tr>
<td>MDS-MLD</td>
<td>6 (9.5)</td>
<td>52.5</td>
<td>0</td>
<td>Del (7q) [3], trisomy 8[1], normal karyotyping [1]</td>
</tr>
<tr>
<td>MDS-RS</td>
<td>SLD 1 (1.6)</td>
<td>77</td>
<td>0</td>
<td>Trisomy 8[1]</td>
</tr>
<tr>
<td></td>
<td>MLD 2 (3.2)</td>
<td>59</td>
<td>0</td>
<td>Normal karyotyping [2]</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>1 (1.6)</td>
<td>67</td>
<td>0</td>
<td>Del (5q) [1]</td>
</tr>
<tr>
<td>MDS-EB</td>
<td>EB1 16 (25.4)</td>
<td>55</td>
<td>5</td>
<td>Normal karyotyping[8],del (5q)[1],del (7q) [2], hyperdiploidy [1]</td>
</tr>
<tr>
<td></td>
<td>EB2 32 (50.8)</td>
<td>45.5</td>
<td>9 + 1 (ALL)</td>
<td>Normal karyotyping [18], del (5q) [3], del (7q) [3], monosomy 7 [3], trisomy 8[1], +der (7) del(7) i(17) [1]</td>
</tr>
<tr>
<td>MDS-U</td>
<td>3 (4.7)</td>
<td>52</td>
<td>0</td>
<td>Normal karyotyping [2]</td>
</tr>
</tbody>
</table>

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; EB-excess blast; MDS, myelodysplastic syndrome; MLD-multi lineage dysplasia; WHO, World Health Organization; RS- ringed sideroblast; SLD-single lineage dysplasia; U-unclassifiable.

Note: Number of cytogenetic aberration in each subtype is mentioned in within flower brackets.
MDS diagnosed in relatively early age had higher risk for progression to AL. Most of the patients with age group less than 60 years were in high or very high risk category of IPSS-R (p = 0.02). Maximum number of cases belonged to MDS-EB category accounting to 48 cases (76.1%) and 37 cases (68.5%) belonged to high or very high risk group which is supported by an Asian study which discusses the regional differences in CG.24 Cytogenetic information plays crucial role along with degree of dysplasia and blast percentage in risk stratification of de novo MDS by using IPSS-R scoring system and is able to predict the risk of progression to AL (Table 3). From a total of 15 cases which progressed to AL, 13 cases belonged to high and very high risk groups, but interestingly 10 cases (66.67%) belonged to good cytogenetic group and consisted of normal karyotyping (eight cases) and del 5q (two cases) and these findings were supported by the Indian study as well.25 Progression to AL in cases stratified into high and very high risk groups despite having good cytogenetic subgroup can only be explained by somatic mutations identified by sequencing studies. These mutations also addresses the clinical heterogeneity in the same IPSS-R risk groups with same cytogenetic abnormality.26,27

Proportion of abnormal karyotyping in our study accounted for 21 cases (38.9%) and normal karyotyping was 33 cases (61.1%) which was supported by Kawata et al study and accounted for 36.4 and 63.6%, respectively.28 Apparent normal karyotyping is the commonest cytogenetic finding in cases which progressed to AL (53.4%) and the reason could be because karyotyping carries inherent limitation of not identifying chromosomal aberration less than 5 × 10⁶ base pairs of DNA, microdeletions, and cryptic translocations.17 The study by Kawata et al underscores the importance of gene sequencing, approximately 81% of cases with normal karyotype revealed mutations which were helpful in better therapeutic decision-making.28

Sequencing studies have helped in better understanding of this dynamic and complex nature of MDS and mutations are identified in around 50 genes in 80 to 90% of MDS cases.16 However, the causal relationship of these mutations in AML is not well established. Studies have proven that biological events, such as mutations of type-I genes or epigenetic changes, play driver role in progression to leukemia than chromosomal abnormalities.6

Serial sequencing studies help to identify subclones in MDS to sAML which are detected months to years prior to progression become abundant in sAML and also study the clonal evolution during progression to sAML due to selective pressure arising from chemotherapy. Further studies are required to define how to incorporate serial sequencing study results into traditional response criteria in better monitoring of tumor burden.29

Currently, there is no consensus on which mutation should be assigned to particular risk category, except for SF3B1 mutation which carries a good prognosis and its association with specific morphology is the only mutation incorporated in WHO classification. Mutations associated with poor prognosis are known; however, their morphological correlation is not well found.30 Studies have shown TP53

| Table 2 Cytogenetic profile of MDS patients and cases progressed to acute leukemia along with median time to progress to AL in each of the cytogenetics |
|-----------------|-------------|-----------------|-------------------|-------------------|
| Cytogenetics    | MDS (54 cases) | MDS progressing to AL (15 cases) | Median time for progression to AL (mo) |
| 5q deletion     | 5            | 2/5 (40)        | 5                 |
| Monosomy 7      | 3            | 3/3 (100)       | 7                 |
| 7q deletion     | 8            | 1/8 (12.5)      | 3                 |
| Trisomy 8       | 3            | 1/8 (12.5)      | 1                 |
| Normal karyotyping | 33         | 8/33 (24.4)     | 8.5               |
| Complex karyotyping | 1          | –                | –                 |
| Hyperdiploidy   | 1            | –                | –                 |

Abbreviations: AL, acute leukemia; MDS, myelodysplastic syndrome.

| Table 3 Risk stratification of cases based on IPSS-R along with age and median period of progression to AL |
|-----------------|-----------------|-----------------|-------------------|
| IPSS-R          | MDS (54 cases) | Median age of MDS (y) | Median age of AL (15 cases) | Median time for progression to AL (mo) |
| Very low        | 1 (1.5)        | 26               | –                | –                       |
| Low             | 4 (6.3)        | 59               | 5                 | 6                       |
| Intermediate    | 12 (19.0)      | 64.5             | 2 (16.7)          | 65                      |
| High            | 21 (33.3)      | 52.0             | 5 (23.8)          | 56                      |
| Very high       | 16 (25.3)      | 40.5             | 8 (53.3)          | 53                      |

Abbreviations: AL, acute leukemia; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome.
Table 4 Details of the 15 cases progressed to AL pertaining to hematologic parameters, dysplasia in cell lineage, MDS subtype, cytogenetics with risk group, and treatment received prior to follow-up is enumerated

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>HB (g/dL)</th>
<th>ANC (µL)</th>
<th>Platelet (µL)</th>
<th>PS (blast)</th>
<th>Blast % (marrow)</th>
<th>Dysplastic cells</th>
<th>MDS subtype</th>
<th>Cytogenetics</th>
<th>Risk group</th>
<th>Treatment</th>
<th>Time to progress (mo)</th>
<th>Progressed to follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>M</td>
<td>8.6</td>
<td>0.6</td>
<td>0.21</td>
<td>11</td>
<td>EGM</td>
<td>EB2</td>
<td>NK</td>
<td>VH</td>
<td>HMA</td>
<td>13</td>
<td>AML</td>
<td>LFU</td>
</tr>
<tr>
<td>62</td>
<td>F</td>
<td>8.6</td>
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<td>0</td>
<td>9</td>
<td>EGM</td>
<td>EB1</td>
<td>NK</td>
<td>HMA</td>
<td>19</td>
<td>AML</td>
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<td>0</td>
<td>16</td>
<td>G</td>
<td>EB2</td>
<td>del 5q</td>
<td>VH</td>
<td>5</td>
<td>AML</td>
<td>4</td>
</tr>
<tr>
<td>56</td>
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<td>0.05</td>
<td>0</td>
<td>6</td>
<td>EGM</td>
<td>EB1</td>
<td>NK</td>
<td>I</td>
<td>Lena*</td>
<td>20</td>
<td>AML</td>
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<td>0.34</td>
<td>8</td>
<td>16</td>
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<td>HMA*</td>
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<td>EM</td>
<td>EB2</td>
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<td>H</td>
<td>Lena</td>
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<td>G</td>
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<td>trisomy 8</td>
<td>VH</td>
<td>HMA</td>
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Abbreviations: AL, acute leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; BT, blood transfusion; E, erythroid; F, female; G, HB, hemoglobin; HMA, hypomethylating agents; HSCT, hematopoietic stem cell transplantation; myeloid; H, high; I, intermediate; LFU, lost for follow up; M, male; M, megakaryocyte; MDS, myelodysplastic syndrome; NK, normal karyotyping; PS, peripheral smear; VH, very high.

*aLenalidomide.  
*bHypomethylating agents.  
*cErythropoietin.
mutation particularly biallelic mutations and specially in complex karyotypes are known to be poor prognostic marker and advocates its incorporation into the scoring system, as it helps in identifying the distinct prognostic subgroups.\textsuperscript{31,32} MDS carries inherent limitation due to heterogeneous nature of the disease; however, laboratory advances have identified genetic mutations and their therapeutic targets and is being translated into personalized medicine in clinical practice.\textsuperscript{33} Sequencing studies are increasingly used in diagnostic practice, validation, and standardization as per the established guidelines increase the reproducibility of the test results.\textsuperscript{34,35} Conducting large multicentric studies with participation of many countries could help in overcoming the racial heterogeneity and the generated high quality sequencing results will help in recognizing significant mutations that can be incorporated into specific risk categories in the prognostic scoring.\textsuperscript{36,37}

As modern management strategy, prior identification of somatic mutations along with IPSS-R helps in better risk stratification and can categorize at risk cases. Mutational studies should commonly be performed in all cases, if not feasible at least in cases diagnosed at young age, apparent normal karyotyping, complex karyotypes, and in cases which fail to respond to treatment or show signs of clinical deterioration such as increased transfusion dependency or manifestations of proliferative disease. Above-mentioned cytogenetic findings in MDS cases progressed to AL highlight the need for mutational data and its incorporation into the current risk assessment system, as it could offer better insights in risk stratification and in devising specific targeted therapies or transplantation before cases could progress to leukemia.

Serial cytogenetic monitoring was not performed, even in cases which progressed to AL, to assess that the additional cytogenetic finding was the limitation; however, these findings would have limited implications in patient management.

Conclusion

The study presents the cytogenetic spectrum of MDS cases in western Indian population with special emphasis on its progression to AL. CG continues to be a useful parameter in prognostic scoring. Majority of the cases that progressed to AL were risk stratified in high and very high risk groups and 66.7% cases had CG belonging to good category, interestingly apparent normal karyotyping was the commonest cytogenetic finding in more than 50% of the cases that progressed to AL. Mutations could probably explain the reason for progression to AL despite good CG.

Since the study was retrospective, informed consent was not required and the study did not include any intervention. Waiver of informed consent was obtained from the Ethics Committee.

Conflict of Interest
None declared.

References

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Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. The Gujarat Cancer & Research Institute (GCRI) ethical committee board approval was obtained, no: IRC/2021/P-14 on March 19, 2021.


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