—Review—

Myelodysplastic Syndromes: Recent Progress in Diagnosis and Understanding of Their Pathophysiology

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Abstract

Myelodysplastic syndromes (MDS) are common malignant disorders with a poor prognosis. MDS are a group of highly heterogeneous disorders but show certain universal findings including a high incidence in the elderly population, cytopenia, dysplastic myeloid cells, and frequent transformation to acute myeloid leukemia. Until recently, the vast majority of MDS patients were treated with supportive therapy alone, such as transfusions. Allogeneic stem cell transplantation (SCT) has the potential for cure, although due to the age and comorbidity of MDS patients, the role of allogeneic SCT in MDS has been limited. Recently, research in MDS has shown substantial advances that have deepened our understanding of MDS pathophysiology and changed our approach to MDS patients. This review touches on some recent developments in the diagnosis and pathophysiology of MDS.

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Key words: Myelodysplastic syndromes, diagnosis, pathophysiology

Introduction

Myelodysplastic syndromes (MDS) are malignant disorders in which the bone marrow (BM) is composed of clonal hematopoietic cells showing differentiation into myeloid cells (neutrophilic cells, erythroblasts, and megakaryocytes) to various degrees in each case. MDS show cytopenia (anemia, neutropenia, and/or thrombocytopenia) and often transform to acute myeloid leukemia (AML), which is called secondary AML and has much worse prognosis compared with de novo AML. MDS may develop in individuals who have been exposed to cancer chemotherapy (e.g., alkylating agents and topoisoerase II inhibitors), excess ionizing radiation (e.g., atomic bombs and radiotherapy for malignant diseases), and other chemicals (e.g., benzene). In particular, intensified cancer chemotherapy (such as autologous stem cell transplantation [SCT]) has increased the incidence of therapy-related MDS. Some congenital diseases (e.g., Down syndrome, Fanconi anemia) are also associated with MDS development. However, overall, the cause of a majority of MDS cases, especially in adult patients, is unknown (de novo MDS). MDS appears to be the most common malignancy among a variety of myeloid neoplasias, and the incidence of MDS increases profoundly with age. Therefore, MDS may become a burden to the healthcare systems in developed countries. Until recently, MDS had been considered to be untreatable; only allogeneic SCT

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had the potential for cure and probable survival benefit. However, mainly due to the age and comorbidity of MDS patients, the role of allogeneic SCT in MDS has been limited. Recent advances in MDS research have deepened our understanding of MDS pathophysiology and changed our approach to MDS patients13. This review touches on some recent developments in the diagnosis and pathophysiology of MDS.

1. Historical Background and Classification

From the early 20th century, patients likely to have had MDS based on the current criteria have been reported1. Those patients showed refractory cytopenia and cellular BM as well as dysplasia in myeloid cells and died due to cytopenia or transformation to acute leukemia. A variety of terms were used for such patients, including preleukemic anemia, leukamia, refractory normoblastic anemia, preleukemia, and hemopoietic dysplasia. In 1982, seven of the leading authorities in this field published diagnostic criteria (the French-American-British [FAB] classification) for this disease category and proposed the term MDS7. Their report was the underpinning of subsequent progress in MDS research continuing to the present. In particular, that report allowed investigators to exchange information on patients diagnosed using the same criteria, made MDS well known worldwide, and, by making the target disease (patients) clearer, recruited numerous investigators to MDS research. MDS, which are defined by cytopenia, cellular BM, and dysplastic myeloid cells, comprise heterogeneous disorders in terms of a wide spectrum of morphologic features, BM cytogenetics, clinical outcomes, and probable pathogenesis. MDS are classified into five subtypes in the FAB classification and into eight subtypes in the recent World Health Organization (WHO) classification8 that refined and evolved the FAB classification. However, each subtype is still heterogeneous; probably the “5q-syndrome” is the only subtype that is a virtually distinct disease10. The heterogeneity of MDS is in sharp contrast with chronic myelocytic leukemia, which is virtually homogeneous in terms of genetic

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood findings</th>
<th>BM findings</th>
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<tr>
<td>Refractory anemia (RA)</td>
<td>Anemia</td>
<td>Erythroid dysplasia only</td>
</tr>
<tr>
<td>RA with RS (RARS)</td>
<td>No or rare blasts</td>
<td>&lt;5% blasts, &lt;15% ringed sideroblasts (RS)</td>
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<tr>
<td>Refractory cytopenia with</td>
<td>Erythroid dysplasia only</td>
<td></td>
</tr>
<tr>
<td>multiligneage dysplasia</td>
<td>No blasts</td>
<td>&lt;5% blasts, &gt;̲  15% RS</td>
</tr>
<tr>
<td>RCMD and RS (RCMD-RS)</td>
<td>Cytopenias (bi- or pancytopenia)</td>
<td>Dysplasia in &gt;̲  10% of cells in 2 or 3</td>
</tr>
<tr>
<td>RCMD and RS (RCMD-RS)</td>
<td>No blasts</td>
<td>&lt;5% blasts, &gt;̲  15% RS, no Auer rods</td>
</tr>
<tr>
<td>RA with excess blasts-1 (RAEB-1)</td>
<td>Cytopenias, &lt;5% blasts, no Auer rods</td>
<td>Unilineage or multiligneage dysplasia</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>Cytopenias, 5% to 19% blasts</td>
<td>Unilineage or multiligneage dysplasia</td>
</tr>
<tr>
<td>MDS, unclassified (MDS-U)</td>
<td>Cytopenias</td>
<td>Unilineage dysplasia in neutrophil lineage cells or MKs</td>
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<td>MDS associated with isolated del (5q)</td>
<td>Anemia, &lt;5% blasts</td>
<td>Normal to increased MKs with hypolobated nuclei</td>
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<tr>
<td></td>
<td>Platelets normal or increased</td>
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MKs: megakaryocytes. *Neutrophil lineage cells, erythroblasts, and MKs.
Adapted from the original publication in Blood9 with permission from the American Society of Hematology.
change and response to specific therapy. The WHO classifications are summarized in Table 1.

2. Diagnosis

2.1. Issues in Diagnosis

Cytopenia (and/or elevated mean capsular volume of erythrocytes), cellular BM, dysplastic myeloid cells, and ruling out other diseases, especially conditions causing dysplastic myeloid cells, are cornerstones of MDS diagnosis. A substantial proportion of MDS patients show abnormal BM karyotypes and an increase in blasts and ringed sideroblasts. The presence of these clearly objective findings leads to a straightforward diagnosis. “Refractory anemia (RA),” “refractory cytopenia with multilineage dysplasia (RCMD),” and “MDS, unclassified (MDS-U),” in the WHO classification lack the increase in blasts and ringed sideroblasts in all cases by definition and show normal karyotypes in more than 50% of cases (these three categories are designated as low-grade MDS without ringed sideroblasts [LGw/orS] in this paper). Therefore, the diagnosis of LGw/orS requires a broad range of knowledge and experience in hematology including cytomorphologic training. Even to the experts, there are patients whose MDS diagnosis is uncertain, mainly due to unclear dysplasia in spite of the presence of unexplained cytopenia. This problem has long been recognized and remains unresolved. Clonal analyses using fluorescence in situ hybridization with multiple probes and other methods, e.g., examining random or nonrandom inactivation patterns of genes located on X chromosomes, may have value, although these analyses are not routinely performed in many laboratories. Currently, it is recommended that patients whose diagnosis is uncertain should be followed up and reevaluated at appropriate intervals. Also, the term “refractory cytopenia with undetermined significance (RCUS)” may be appropriate for such patients. This is especially important when considering the emotional impact on patients; patients may be less stressed by a diagnosis of RCUS rather than MDS (or “MDS, suspected”), because the latter term indicates a poor prognosis.

2.2. Role of Flow Cytometry

Immunophenotyping using flow cytometry (FCM) is an objective and reliable method to identify dysregulated antigen expression of neoplastic cells. In acute leukemia and non-Hodgkin lymphoma, the diagnostic power of FCM has been firmly established. In the past several years, several studies have examined the diagnostic power of FCM in MDS. Initially, investigators used a pattern-recognition approach based on extensive knowledge of the normal pattern of hematopoietic cells in FCM, investigators identified abnormal patterns (such as hypogranulation of neutrophils by orthogonal light scatter) without establishing an objective definition.
Fig. 2  Models of AML development. (A and B) The most accepted models are based on the notion that all hematopoietic cells are derived from PHSCs in a hierarchically ordered fashion. In panel A, all events (black arrowheads) causing the transformation and loss of lymphopoietic potential occur at PHSCs. In panel B, an event (open arrowhead) that creates “preleukemic” cells occurs at PHSCs. After the preleukemic PHSCs commit to the myeloid lineage, additional oncogenic events (shaded arrowhead) occur to create leukemic stem cells. (C) Our model based on data showing that HSCs consist of heterogeneous populations, i.e., PHSCs and myeloid- and lymphoid-restricted HSCs. In this model, events causing the transformation occur at the myeloid-restricted HSCs. LSC: leukemic stem cell, CMP: common myeloid progenitor, CLP: common lymphoid progenitor, MyHSC: myeloid-restricted HSC, LyHSC: lymphoid-restricted HSC. Reproduced from the original publication in Leukemia Research.

of the abnormal pattern. Therefore, the usefulness of this approach was debated. More recent studies have tried to quantify flow abnormalities in MDS. Our group confirmed that MDS blasts show a variety of abnormalities in FCM. Based on this finding, we showed that FCM analysis of CD34+ cells help to diagnose LGw/oRS patients. Figure 1 shows the scheme of our FCM analysis method. Establishing a diagnostic FCM strategy that is usable and reproducible with ease by many laboratories with high sensitivity/specificity will be the next important mission in this field. Finally, I would like to emphasize the points that are often overlooked: FCM may be useful to reveal pathophysiology and predict prognosis in MDS.

3. Pathophysiology

3-1. Cell Origin of MDS: Lessons from AML

Among myeloid neoplasia, the transformation site (the neoplasm-initiating cells) in AML has been intensively investigated. In general, myeloid cells alone are involved in a malignant clone in AML patients, and this is also true in MDS. However, the most accepted hypothesis is that the transformation occurs in pluripotent hematopoietic stem cells (PHSCs), which can differentiate into both myeloid and lymphoid cells. This hypothesis is mainly based on the following two key findings. 1) CD34+CD38- cells, which are a well-documented cell population containing human PHSCs, are often clonal in AML patients. 2) Cells capable of initiating human AML in nonobese diabetic/severe
combined immunodeficiency (NOD/SCID) mice have been confined within the CD34+/CD38− cell fraction in the majority of AML patients. The reason why the transformed PHSCs in AML do not differentiate into lymphoid cells can be explained by the concept that specific leukemogenic mutations may inhibit the lymphopoietic potential of transformed PHSCs. An alternative explanation is that the initial event occurs in PHSCs to create “preleukemic” stem cells that differentiate into myeloid lineage cells, and additional oncogenic alterations occur in these myeloid preleukemic cells to create leukemic stem cells. Meanwhile, recent data from multiple laboratories have indicated the presence of myeloid HSCs that have a similar immunophenotype to PHSCs but virtually lack lymphopoietic potential (MyHSCs). Therefore, our group proposed the hypothesis that MyHSCs may be the transformation site in AML. Further investigations are required to obtain a definitive answer on this issue.

The approaches that had been used for examining AML stem cells were applied to MDS with limited success. CD34+/CD38− cells were reported to be clonal in MDS, although probably due to the defective or unstable hematopoietic potential of MDS stem cells, MDS CD34+/CD38− cells seldom reconstitute hematopoesis in NOD/SCID mice. A recent report has indicated that NOD/SCID-β2 microglobulin-null mice might be more suitable for examining the in vivo stem cell activity of MDS cells.

3-2. Cytogenetics, Genetics, and Epigenetics

About a half of de novo MDS patients have abnormal BM cytogenetics. No universal cytogenetic abnormality exists in MDS, and the predominant abnormalities are nonrandom chromosomal deletions that include monosomy 7 and partial deletions of chromosome arms 5q, 7q, 11q, and 20q. Trisomy 8 is also common and interestingly associated with a good response to immunosuppressive therapy. Similarly, a variety of genetic alterations have been reported which include mutations in RAS, p53, and FLT3. Hopefully, more advanced searches for genetic alterations, such as the Cancer Genome Atlas project under the auspices of the US National Institutes of Health, will identify fairly universal genetic changes. Identification of such changes is expected to lead to the development of an effective targeted therapy. Epigenetic abnormalities are also reported in MDS. Many tumor-suppressor genes are often inactivated by hypermethylation of their promoter sequences in a variety of human cancers. A gene of a cyclin-dependent kinase inhibitor, the p15INK4B gene, is hypermethylated in MDS, especially in advanced stages. In clinical trials, the demethylating agents 5-aza-cytidine (azacytidine) and 5-aza-2′-deoxycytidine (decitabine) improved cytopenia and have been approved for MDS treatment by the US Food and Drug Administration in the last two years. In accordance with the hypermethylation status, the clinical effect of these drugs is more marked in advanced stages of MDS compared with early stages.

3-3. Apoptosis

MDS exhibit cytopenia in spite of cellular BM. This finding may be explained by two major mechanisms: MDS hematopoietic cells in the myeloid lineage have a defect in differentiation capability and undergo excess apoptosis. The latter mechanism, which was formally hypothesized in 1993, has been confirmed by multiple groups. Apoptosis is more marked in early stages of MDS compared with advanced stages and with MDS transformed into AML. Cytopenia in the early stages of MDS may reflect a balance between the capability of cell production and degree of cell apoptosis. Furthermore, a decrease in the apoptosis of MDS clonal cells, especially CD34+ cells, may be one of the mechanisms leading to disease progression in MDS. Combined therapy with granulocyte colony-stimulating factor and erythropoietin improves cytopenia in a substantial proportion of MDS patients and this clinical effect is reported to be associated with a decrease in the apoptosis of BM cells. A recent paper has reported that a molecule, p38 mitogen-activated protein kinase (MAPK), that is involved in regulating apoptosis and controlling the cell cycle was overactivated in early stages of MDS, but not in advanced stages. p38 MAPK overactivation and apoptosis were observed in the
same cells in MDS BM, and inhibitors of p38 MAPK, such as SCIO-469, improved the hematopoiesis of MDS BM cells in vitro.

3.4. Immunology

Although lymphocytes are not clonal in a majority of MDS patients, lymphopenia, especially a decrease in T lymphocytes, is a common finding in MDS. Furthermore, a variety of lymphocyte functions are impaired in MDS, often involving functions of T lymphocytes and natural killer cells. Usually, immunologic defects are more marked in advanced stages of MDS compared with early stages. The circulating level of the soluble interleukin-2 receptor (sIL-2R), which is a soluble form of the IL-2R α-chain (CD25) and has the capability to bind and neutralize IL-2, is often elevated in MDS patients, especially in the advanced stages. One hypothesis is that sIL-2R is created by cleaving CD25 expressed on MDS blasts and plays a role in immunologic defects in MDS. The immunologic competence of hosts is considered to be important to defend against MDS clones, which is supported by the following observations. Although immunosuppressive therapies, such as anti-thymocyte globulin (ATG) and cyclosporin therapies, increase myeloid cell counts in some cases of MDS, the increased myeloid cells are thought to be clonal in origin. MDS clones develop in a substantial proportion of patients with aplastic anemia who were treated with ATG therapy. Therefore, elucidating the mechanisms by which immunologic defects occur and their correction may have clinical value.

4. Concluding Remarks

The history of MDS illustrates the importance of establishing usable diagnostic criteria and of elucidating disease pathophysiology. That has led to the development of effective therapies for MDS (for therapies of MDS, please refer to other reviews). It is expected that therapies such as intensive chemotherapies and SCT that eliminate both malignant and normal cells will become old-fashioned and replaced with more sophisticated, targeted therapies based on disease pathophysiology. Meanwhile, the current diagnostic approach and understanding of pathophysiology are still unsatisfactory in MDS. Much work remains to be done in this field.

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