By: Mostafa Kamal Helmi El-Razzaz

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of acquired clonal bone marrow disorders characterized by varying degrees of pancytopenia, morphological and functional abnormalities of hematopoietic cells, and an increased risk of transformation into acute myeloid leukemia (AML). Childhood MDS is extremely rare (incidence rate = 0.01/100,000), representing 4% of all pediatric hematological cancers. Approximately 80% of the patients are older than 60 years at diagnosis. MDS are divided in two groups, de novo and therapy related based on the absence or presence of previous cytotoxic therapy ***(Strom et al., 2008).***

Recent studies provide some insight into the pathophysiology of MDS. One mechanism contributing to the constellation of hypercellular marrow and peripheral blood cytopenia is a significant increase in programmed cell death (apoptosis) in hematopoietic cells. Tumor necrosis factor (TNF)-α, Fas ligand, TNF-related apoptosis-inducing ligand, and other proapoptotic cytokines are upregulated in early-stage/low-risk MDS, and neutralization of these signals can improve hematopoiesis. The role of the microenvironment in the pathophysiology and progression of MDS has remained controversial ***(Kerbauy and Deeg, 2007).***

Some patients with MDS have an autoimmune-mediated pathophysiology that results in hematopoietic compromise by T-cell–mediated killing and cytokine release. Patients treated with immunosuppression show improvement in their marrow function and potentially increased survival. Careful analysis of patients responding to immunosuppression and a better understanding of its pathophysiology may lead to more directed therapy for these individuals ***(Sloand and Rezvani, 2008).***

Transcriptional silencing of tumor suppressor genes occurs in cancer cells by DNA methylation and by histone deacetylation (HDAC). Recently, novel agents that target these mechanisms have been developed. At present, the demethylating agents azacytidine and decitabine are the most promising drugs for the treatment of elderly patients with high-risk MDS ***(Leone et al., 2002).***

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Myelodysplastic syndromes show a profound heterogeneity regarding not only morphological features and clinical course but also cytogenetic findings. Recently, the German– Austrian MDS study-group presented a database of cytogenetic findings in 2072 patients with MDS which serves as a basis for the characterization of the cytogenetic subgroups discussed in this article. In this analysis, 52.1% of patients displayed clonal chromosome abnormalities. The most frequent changes were 5q- (29% of abnormal cases), complex changes (27%), -7/7q- (24%), +8 (16%), 20q- (7%), -Y (5%). The advent of new therapeutic options for MDS targeted on distinct entities characterized by a specific chromosome abnormality ***(Haase, 2007).***

Treatment of myelodysplastic syndromes (MDS) has evolved to encompass a broad spectrum of therapies aiming to inhibit apoptosis, promote hemopoiesis, and reduce proliferation of clonal immature cells. A small cohort of younger patients may show excellent responses to anti-thymocyte globulin. Patients with more advanced disease may respond to treatment with the hypomethylating agents azacytidine and decitabine. In addition, there are several new agents under clinical investigation targeted to potential mechanisms of disease and progression in MDS. New therapeutic drug include inhibitors of angiogenesis, histone deacetylation, tyrosine kinases and farnesylation, as well as drugs interacting with apoptotic mechanisms ***(Lindberg and Malcovati, 2008).***

Many patients with myelodysplastic syndromes (MDS) have severe anemia. However, regular blood transfusions, which are widely used to maintain quality of life and prevent anemia-related morbidity and mortality, have a negative impact on survival as a result of iron overload. However, iron chelation therapy reduces serum ferritin levels and is associated with significantly improved survival in patients with MDS ***(Dreyfus, 2008).***

Hematopoietic cell transplantation (HCT) offers potentially curative therapy for patients with myelodysplastic syndromes (MDS). However, who should and can be transplanted, with which approach, and when is a matter of debate. Modifications of transplant conditioning regimens have reduced transplant-related mortality and allow successful HCT even in older patients ***(Marcondes and Deeg, 2008).***

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Summary and conclusion

Myelodysplastic syndromes (MDS) are a heterogeneous group of acquired clonal bone marrow disorders characterized by varying degrees of pancytopenia, morphological and functional abnormalities of hematopoietic cells, and an increased risk of transformation into acute myeloid leukemia (AML). Substantial morbidity and mortality are associated with MDS even without progression to AML.

There is a lack of reliable data concerning the epidemiology and etiology of MDS due to difficulties in diagnosis and classification, which have made large-scale population-based studies problematic. MDS is considered a disease of elderly people. Childhood MDS is extremely rare (incidence rate = 0.01/100,000), representing 4% of all pediatric hematological cancers. Approximately 80% of the patients are older than 60 years at diagnosis, making MDS as common as chronic lymphocytic leukemia and multiple myeloma in this age group.

MDS are divided in two groups, de novo and therapy related based on the absence or presence of previous cytotoxic therapy. Features of therapy-related MDS (t-MDS) include a myelodysplastic phase after use of cytotoxic chemicals, especially alkylating agents, and/or radiotherapy for a malignant or nonmalignant disease. Patients with t-MDS tend to be younger than de novo MDS patients.

Recent studies provide some insight into the pathophysiology of MDS. One mechanism contributing to the constellation of hypercellular marrow and peripheral blood cytopenia is a significant increase in programmed cell death (apoptosis) in hematopoietic cells. Tumor necrosis factor (TNF)-α, Fas ligand, TNF-related apoptosis-inducing ligand, and other pro-apoptotic cytokines are up-regulated in early-stage/low-risk MDS, and neutralization of these signals can improve hematopoiesis. TNF-related apoptosis inducing ligand induces apoptosis preferentially in clonal cells, which can contribute to containment of the clone.

In a proportion of patients, MDS will eventually evolve to acute leukemia. This progression has been correlated with up-regulation of nuclear factor κB; altered expression of adaptor molecules, such as Flice inhibitory protein; and enhanced activity of anti-apoptotic members of the Bcl-2 and inhibitors of apoptosis protein families. Also, the ratio of TNF receptors 1 and 2 changes in favor of receptor 2. The role of the microenvironment in the pathophysiology and progression of MDS has remained controversial, although there

is evidence that stroma and matrix components, and their interactions with clonal cells, play an important role. Microarray gene-expression studies are consistent with dysregulation of apoptosis, but not all data are in agreement.

Some patients with MDS have an autoimmune-mediated pathophysiology that results in hematopoietic compromise by T-cell–mediated killing and cytokine release. Patients treated with immunosuppression show improvement in their marrow function and potentially increased survival. Careful analysis of patients responding to immunosuppression and a better understanding of its pathophysiology may lead to more directed therapy for these individuals.

Transcriptional silencing of tumor suppressor genes occurs in cancer cells by DNA methylation and by histone deacetylation (HDAC). Recently, novel agents that target these mechanisms have been developed. At present, the demethylating agents azacytidine and decitabine are the most promising drugs for the treatment of elderly patients with high-risk MDS or for young patients without a compatible donor. Combinations with histone deacetylation inhibitors, such as sodium phenyl-butyrate, could further increase the efficacy of these drugs.

Recently, refined definitions and standards in the diagnosis and treatment of MDS are proposed in a report from an international working conference convened in 2006 in Vienna. In this consensus manuscript, minimal diagnostic criteria are defined by introducing two MDS prerequisite-type criteria (A-criteria), at least one out of three additional MDS-related (decisive) criteria (B-criteria) and several MDS co-criteria (C-criteria).

Diagnostic prerequisites as described in the consensus paper are: (a) marked and constant cytopenia (≥6 months unless cytogenetic studies reveal MDS) in at least one of the following hematopoietic cell lineages: erythroid cells (<11 g/dL), neutrophil granulocytes (<1500 μL^{-1}), platelets (<100,000 μL^{-1}); and (b) exclusion of another clonal or non clonal hematopoietic disease or non-hematopoietic disease as primary reason for cytopenia or/and dysplasia. In addition, at least one of the following decisive criteria (i–iii) must be fulfilled to call a condition MDS. (i) Morphologic dysplasia in at least 10% of all cells in one or more of the following cell lineages in the BM smear: (a) erythroid cells (>15% ringed sideroblasts also counts as criterion of erythroid dysplasia), (b) neutrophils and their precursors, (c) megakaryocytes. (ii) Typical cytogenetic abnormality (recurrently reported to occur in MDS). (iii) A constant blast cell count of 5–19%. In patients with ‘sub diagnostic’ or

questionable results in (i–iii) (e.g., atypical chromosome aberration, dysplasia in <10% of cells, 4% blasts, etc.) but otherwise typical MDS-related clinical findings (e.g., transfusion-dependent macrocytic anemia), additional tests (co-criteria) can be applied and may help in reaching the conclusion the patient has a clonal myeloid neoplasm with BM failure resembling (highly suspicious of) MDS. In the proposed minimal diagnostic criteria, flow-cytometric analysis of BM cells is introduced as such a co-criterion.

Myelodysplastic syndromes show a profound heterogeneity regarding not only morphological features and clinical course but also cytogenetic findings. The great prognostic relevance of cytogenetics is generally appreciated, however, it is only known for the most frequent karyotype abnormalities, not for combinations of anomalies and not for more rare changes. To overcome these limitations multicentric co-operations are needed.

Nevertheless, recent clinical and basic research allows for a delineation of myelodysplastic syndromes (MDS) subtypes defined by the most frequent chromosomal changes. Recently, the German– Austrian MDS study-group presented a database of cytogenetic findings in 2072 patients with MDS which serves as a basis for the characterization of the cytogenetic subgroups discussed in this article. In this analysis, 52.1% of patients displayed clonal chromosome abnormalities. The most frequent changes were 5q- (29% of abnormal cases), complex changes (27%), -7/7q- (24%), +8 (16%), 20q- (7%), -Y (5%). The advent of new therapeutic options for MDS targeted on distinct entities characterized by a specific chromosome abnormality, as shown paradigmatically for lenalidomide in patients with 5q- syndrome, underlines the important role of cytogenetics for the clinical management of MDS.

Current staging and morphologic classification systems permit more objective comparisons among patients entered on clinical trials but provide only rough guides about prognosis and, in particular, only approximations of the outcome in individual patients. Indeed, it is likely that serial follow-up represents the best means of determining the clinical course in individuals and the need for therapy. With regard to the selection of specific treatments, with the exception of the use of lenalidomide in patients with del 5q–, it is difficult to choose among “standard” or experimental treatments for patients in different IPSS or WHO subgroups.

Of particular interest, given the long durations of benefit seen in some MDS patients responding to treatment with immunosuppression, it would be helpful if patients likely to

respond could be identified by biologic characteristics, perhaps by flow-cytometric detection of small subclones of T cells that can suppress hematopoiesis. Thus, although newer classifications that juggle the currently available clinical and laboratory data will be forthcoming, characterization of risk groups in this fashion is insufficient. Future advances will derive from more biologically sophisticated classifications of subsets of MDS, providing guidance towards development of drugs with more selective mechanisms of action. Given the stem cell nature of MDS and the difficulties encountered in the treatment of epithelial cancers that also share complex and redundant signaling pathways and mechanisms of resistance, this will not be a simple task.

Treatment of myelodysplastic syndromes (MDS) has evolved to encompass a broad spectrum of therapies aiming to inhibit apoptosis, promote hemopoiesis, and reduce proliferation of clonal immature cells. A small but expanding cohort of patients with MDS may be cured, but for the majority the aim of treatment is to prolong survival and to improve quality of life. Patients with low-risk MDS mainly suffer from the effects of severe anemia and an important therapeutic goal is to maintain acceptable hemoglobin levels by optimal transfusion regimens or by erythropoietin ± granulocyte-colony-stimulating factor, which normalizes hemoglobin levels or abolish transfusion need in around 40% of patients.

Lenalidomide has emerged as a drug of choice for patients with low-risk MDS and a 5q deletion, leading to complete erythroid response and cytogenetic remission in 2/3 of patients. A small cohort of younger patients may show excellent responses to anti-thymocyte globulin. Patients with more advanced disease may respond to treatment with the hypomethylating agents azacytidine and decitabine, who both have been shown to prolong time to leukemic transformation / death in MDS. In addition, there are several new agents under clinical investigation targeted to potential mechanisms of disease and progression in MDS. New therapeutic drug include inhibitors of angiogenesis, histone deacetylation, tyrosine kinases and farnesylation, as well as drugs interacting with apoptotic mechanisms.

Many patients with myelodysplastic syndromes (MDS) have severe anemia. However, regular blood transfusions, which are widely used to maintain quality of life and prevent anemia-related morbidity and mortality, have a negative impact on survival as a result of iron overload. Retrospective surveys have shown an association of transfusion dependence with hepatic, pituitary, and pancreatic dysfunction, cardiac failure, and cardiac death. Survival is significantly decreased in transfusion-dependent patients, and the main cause of non-leukaemic death is cardiac failure.

However, iron chelation therapy reduces serum ferritin levels and is associated with significantly improved survival in patients with MDS. Current guidelines recommend starting iron chelation therapy after 25 - 50 units of blood have been transfused, or when serum ferritin levels rise above 1,000 - 2,000 µg/L. The patients who are most likely to benefit from iron chelation therapy are those who have low-risk disease (International Prognostic Scoring System low or intermediate-1 risk) with a life expectancy of more than 1 year.

Hematopoietic cell transplantation (HCT) offers potentially curative therapy for patients with myelodysplastic syndromes (MDS). However, who should and can be transplanted, with which approach, and when is a matter of debate. Various classification schemes and prognostic scoring systems have helped in the decision-making process. Offering HCT to patients who were not considered transplant candidates in the past is now possible with the development of new transplant strategies. In addition to disease stage, patient age, comorbid conditions, pre-HCT chemotherapy, type of donor, source of stem cells, and possibly other factors, need to be considered prior to transplant.

Patients without substantial comorbid conditions up to 60 years with the availability of unrelated donor grafts or 65 years with related donor grafts can be transplanted with more conventional (higher dose) regimens (e.g. targeted BU/CY; Flu/BU). Older patients and patients with comorbid conditions should be enrolled in trials aimed at optimizing RIC/non-myeloablative HCT (e.g. Flu/melphalan; Flu/low dose TBI). Patients who present with ‘advanced’ MDS or are transfusion dependent, and do not have a del(5q), should probably be transplanted early in their course.

GVHD (in all patients) and post-HCT relapse (in patients with high risk disease) remain major problems. Modifications of transplant conditioning regimens have reduced transplant-related mortality and allow successful HCT even in older patients. However, prospective randomized trials are needed to determine the role of pre-HCT chemotherapy and the type of transplant conditioning regimen best suited for a given patient.

For some patients lacking a human leukocyte antigen (HLA)-compatible donor, chemotherapy followed by autologous SCT may be a reasonable alternative, especially for patients with therapy-related MDS/acute myeloid leukemia (AML). A substantial number of candidates may not be eligible for autologous SCT due to failure to induce remission or failure to collect sufficient numbers of stem cells.

Careful clinical evaluation of the prognostic factors, such as age, cytogenetic characteristics, chances of achieving complete remission (CR), and availability of a matched unrelated donor, may guide the treating physician in advising the patient about the available treatment options. Mobilized peripheral blood stem cells are the preferred stem cell source for young patients, especially in view of the more rapid hematopoietic recovery after transplantation with mobilized stem cells, but bone marrow stem cells also may be considered for patients older than 50 years.

Introduction

Myelodysplastic syndromes (MDS) constitute a heterogeneous group of hemopoietic stem cell disorders characterized by varying degrees of anemia, leukopenia and thrombocytopenia, and an increased risk for progression to acute myeloid leukemia (AML). The hematopoietic progenitors in MDS show a decreased capacity for differentiation and an increased propensity for apoptosis, leading to ineffective hematopoiesis and often to a compensatory marrow hyperplasia ***(Lindberg and Malcovati, 2008)***.

The incidence of MDS varies from 2.1 to 12.6 cases per 100,000 population per year, but approaches 50 cases per 100,000 per year in persons over the age of 70.Prevalence is estimated to be 55,000 patients in the United States. The median age of patients is between 60 and 70 years with a male predominance. The increased incidence of MDS has been attributed to an improvement in geriatric medical care and diagnosis as well as to a general aging of the population ***(Catenacci and Schiller, 2005)***.

Several risk factors have been implicated in the etiology of MDS, including age, male gender, alcohol, cigarette smoking, ionizing radiation, immunosuppressive therapy, viral infection, benzene and other environmental/occupational exposures. These risk factors are seen infrequently and are estimated to account for disease in only 20–30% of patients, who are often described as having secondary MDS. The

remainder of idiopathic cases constitutes primary MDS. The major subset of secondary MDS is therapy-related MDS (t-MDS) that is increasingly frequent in patients previously treated with chemotherapy and/or radiotherapy ***(Catenacci and Schiller, 2005)***.

MDS is thought to arise from mutations in the multi-potent bone marrow stem cell, but the specific defects responsible for these diseases remain poorly understood. Differentiation of blood precursor cells is impaired, and there is a significant increase in levels of apoptotic cell death in bone marrow cells ***(Mufti and Bennett, 2008)***.

Cytogenetic and molecular data provide evidence for the existence of a clonal phase prior to the acquisition of the characteristic cytogenetic abnormalities associated with MDS. The initiating genetic lesions in a clonal hematopoietic stem cell population may be inherited or acquired. The primary genetic abnormalities promote the acquisition of secondary genetic lesions. These latter are the cytogenetic abnormalities associated with MDS, characterized by stepwise gains and loss of specific chromosomal regions (e.g. 5q-,7q-,12p-,+8), and accompanied during disease progression by point mutations of members of the RAS family of proto-oncogenes and inactivation of the p53 and p15 tumor suppressor genes by point mutations and hypermethylation ***(Alessandrino et al., 2001)***.

Clonal expansion of the abnormal cells results in the production of cells which have lost the ability to differentiate. If

the overall percentage of bone marrow blasts rises over a particular cut off (20% for WHO and 30% for FAB) then transformation to acute myelogenous leukemia (AML) is said to have occurred. The progression of MDS to AML is a good example of the multi-step theory of carcinogenesis in which a series of mutations occur in an initially normal cell and transform it into a cancer cell ***(Mufti and Bennett, 2008)***.

The disease usually presents as a result of marrow failure in one or more cell lines. Symptoms of fatigue, pallor, exertional dyspnea, infection, bleeding, or bruising are the most common. The diagnosis may be suggested by hematologic abnormalities, commonly macrocytic anemia, found on routine laboratory evaluation ***(Catenacci and Schiller, 2005)***.

It has been a challenge, given the heterogeneity of the disease, to create a classification for MDS that accurately predicts prognosis and guides therapy. In 1982, a French, American, and British (FAB) conference agreed upon an MDS classification scheme. Five MDS categories derived from morphologic criteria of marrow aspirates included refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-t), and chronic myelomonocytic leukiemia (CMML). Presence of more than 30% blasts in the bone marrow was defined as AML. In general RA and RARS are associated with low-risk disease, while RAEB and RAEB-t are associated with poor prognosis and progression to AML. The FAB system, still used

presently, has several limitations regarding correspondence of particular FAB subgroups to new cytogenetic findings, treatment and prognosis ***(Catenacci and Schiller, 2005)***.

MDS show impressive clinical heterogeneity, ranging from indolent conditions with a near-normal life expectancy to conditions with life-threatening cytopenia, rapid progression to acute leukemia, and poor response to chemotherapy. An accurate definition of individual risk for death and leukemic transformation is therefore a crucial step in the clinical management of MDS patients, and a risk adapted treatment strategy is mandatory. In 1997, the International Prognostic Scoring System (IPSS) provided a tool to predict the prognosis for untreated patients with MDS. The model is based on karyotype, number of significant cytopenias, and percentage of bone marrow myeloblasts, and patients are divided into four categories with different probabilities for survival and risk for progression towards AML. The median survival times were 5.7, 3.5, 1.2 and 0.4 years for the good, intermediate-1, intermediate-2 and high-risk groups, respectively. The IPSS system has been widely accepted, and is presently used in most scientific publications on MDS ***(Lindberg and Malcovati, 2008)***.

Therapeutic guidelines have been proposed incorporating age, performance status, IPSS score, WHO classification, and marrow donor availability. Therapy of MDS has been generally supportive for the majority of patients. Marrow transplants and intensive chemotherapeutic regimens are reserved for those patients with available donors, adequate performance status,

higher-risk disease and younger age-a minority of MDS patients. Therefore, several investigational approaches targeting several areas of the pathogenesis model have been evaluated. In this regard, clinical trials base conclusions on hematologic and cytogenetic improvements defined by standardized response criteria. These criteria define complete response (CR), partial response (PR), hematologic improvement (HI), survival, and disease free state ***(Catenacci and Schiller, 2005)***.

Assessment of disease severity and prognosis using the International Prognostic Scoring System (IPSS) has proven to be a useful tool to guide initial treatment strategies with recombinant growth factors, hypomethylating agents such as azacitidine (Vidaza) and decitabine (Dacogen), and the immunomodulatory agent lenalidomide (Revlimid). However, the majority of patients will eventually progress or fail to respond to standard agents, and there is an urgent need for novel and active therapeutics. Furthermore, current approaches remain noncurative, and for the majority of patients with MDS, the risks associated with allogeneic stem cell transplantation are prohibitive in a generally elderly population. Novel treatment strategies must fill the void of treatment alternatives for those who fail the few currently available effective therapies. As our understanding of the molecular biology of MDS advances, several innovative strategies have developed impacting exciting new pathways for ameliorating cytopenias and eradicating the malignant clone. Some of the agents that have emerged from preclinical studies include immunosuppressive therapies,

immunomodulatory drugs, anti-angiogenic and pro-apoptotic agents, survival signal inhibitors, pharmacologic differentiators, and thrombopoiesis stimulating agents ***(Melchert and List, 2008)***.

Hematopoietic stem cell transplantation (HSCT) remains the only curative option for patients with myelodysplastic syndromes (MDS). Developing conditioning regimens with low toxicity, at the same time as preserving an effective graft versus tumour response, is pivotal to expanding the scope for allogeneic transplantation in older patients with MDS. With the introduction of reduced intensity conditioned regimens, transplant centers worldwide are able to offer allogeneic HSCT to a much larger cohort of patients. Graft versus host disease (GvHD) remains a significant cause of morbidity and mortality, however with the use of T-cell depletion, centers have been able to utilize volunteer unrelated donors with an increasing degree of HLA disparity. The graft versus dysplasia effect resulting from allogeneic HSCT and the infusion of donor leukocytes has led to a greater understanding of the immunological mechanisms that govern outcome following transplantation in MDS ***(Ingram et al., 2007)***.