Meeting report: Vienna 2008 Workshop of the German–Austrian Working Group for Studying Prognostic Factors in Myelodysplastic Syndromes

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Abstract Criteria, scoring systems, and treatment algorithms for myelodysplastic syndromes (MDS) have been updated repeatedly in recent years. This apparently results from increased awareness and early recognition of the disease, an increasing number of new diagnostic and prognostic markers and tools, and new therapeutic options that may change the course and thus prognosis in MDS. To

address these challenges and to create useful new diagnostic and prognostic parameters and scores, the German–Austrian Working Group for Studying Prognostic Factors in MDS was established in 2003 and later was extended to centers in Switzerland (D-A-CH group). In addition, the group cooperates with the European LeukemiaNet, the MDS Foundation, and other national and international

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working groups in order to improve diagnosis and prognostication. The current article represents a meeting report from the latest workshop organized by the group in Vienna in October 2008.

Keywords Myelodysplastic syndromes · Criteria · Prognostication · Standardization · MDS registry

Introduction

Myelodysplastic syndromes (MDS) usually develop in an advanced phase of life, often as slowly progressing anemia in comorbid patients [1]. The awareness for MDS has increased, and better diagnostic tests are available. On the other hand, many new questions concerning the diagnosis, classification, and prognostication in MDS have emerged in recent years [1]. Based on these developments, centers specialized in the diagnosis and management of MDS have started to discuss criteria, classification issues, and prognostic factors. Our working group has launched a series of annual meetings as well as several international meetings in order to intensify collaboration within the group and also with other working groups. A key aim is to initiate and conduct scientific projects and clinical trials in patients with MDS in order to identify new risk factors and to improve prognostication and therapy. In addition, we have established a central data registry. Table 1 shows a summary of major aims of the German–Austrian MDS Working Group. In the year 2006, a working conference in Vienna was

organized together with the MDS Foundation and other international MDS working groups in order to discuss various issues in MDS including minimal diagnostic criteria, classification, algorithms for management and treatment, and therapy [1]. Moreover, the meeting has been a starting point for new groups focusing on specific issues in MDS, such as hematopathology, flow cytometry, or molecular markers. The current meeting in Vienna was organized to provide an update on cooperative studies and to strengthen and support new groups and projects.

Diagnostic criteria and classification

Standard strategies and algorithms in the diagnosis and classification of MDS were discussed extensively. The group concluded that the diagnosis ‘MDS’ is based on a three-step algorithm: In a first step, minimal diagnostic criteria, as proposed [1], have to be applied to ensure the diagnosis of MDS. In a second step, it has to be clarified whether the disease is a primary (de novo) MDS (no known mutagenic event) or a secondary MDS following a mutagenic event (often chemotherapy or radio-chemotherapy) [1]. In a third step, WHO criteria [2, 3] are applied to define the variant of MDS. The currently available WHO criteria, updated in 2008 [3], represent an extension of French–American–British cooperative Study Group criteria [4] that were primarily based on morphologic variables and used as global standard for more than two decades. The WHO classification defines additional variants characterized by cytomorphological and cytogenetic features. Clinically, important variants are the 5q– syndrome (with good prognosis) and MDS with multilineage dysplasia often associated with a complex karyotype and a grave prognosis. The group discussed the current 2008 update of the WHO classification [3] extensively. Although several issues remain unsatisfactory, the group concluded that this classification, presented in 2008 (Table 2), should be recommended as a global standard.

Histology and immunohistochemistry

The histology and immunohistochemistry of the bone marrow is an integral and essential diagnostic tool in MDS. In fact, the final correct diagnosis is always based on multiple diagnostic parameters including the bone marrow smear and the bone marrow histology [1]. In the absence of a confirmatory histology, the diagnosis may be missed, incomplete, or incorrect [1]. Typical examples are an underestimated blast cell count (AML in the histology instead of MDS/RAEB in the smear) or overlooked concomitant systemic mastocytosis, SM (SM-MDS) [1, 5].

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Table 1 Major project lines of the German–Austrian–Swiss MDS group

Validation of the IPSS and of other scoring systems in MDS
Standardization and prognostic impact of cytogenetics in MDS
Identification of new cytogenetic risk patterns and categories in MDS
Influence of transfusion dependence and iron overload on prognosis in MDS
Impact of gender, age, and comorbidity in MDS
Evaluation of prognostic factors in transplanted MDS patients
Evaluation of prognostic and predictive factors in MDS patients receiving demethylating agents
Evaluation of prognostic and predictive factors in lenalidomide-treated patients
Classification and prognosis of tMDS/tAML
Prognostic impact of eosinophils, basophils, and mast cells
Prognostic impact of bone marrow fibrosis in MDS
Impact of molecular somatic mutations in MDS
Impact of loss of key regulators and tumor suppressor genes in MDS
Impact of HFE gene mutations on iron overload in MDS
Prognostic value of other germ line mutations in MDS
Prognostic value of serum markers (LDH, sCD44, tryptase,...) in MDS
Development of dynamic scoring systems in MDS
Evaluation of rare forms of MDS (AT-MDS, MDS-F, SM-MDS,...)
Identification of risk factors in CMML
Separate scoring for the two different end points in MDS survival and AML
Evaluation of CD34+/CD38– MDS stem cells and their response to targeted drugs

In addition, the histology provides information regarding cellularity, fibrosis, angiogenesis, focal blast cell accumulations, and megakaryocyte morphology and topology [5–7]. This is especially important in patients with hypoplastic MDS and MDS with fibrosis [5–7]. Immunohistochemistry should be performed in a two-step approach: in a first step, three markers are applied, i.e., CD34 (and KIT), a platelet marker (CD42 or CD61) and tryptase that is expressed in mast cells and less abundantly in (neoplastic) basophils [5]. If the diagnosis is in question, or the histology is pointing at a non-MDS disease, additional markers are applied, the selection of markers depending on clinical, histologic, and molecular findings [5].

Cytogenetics

Cytogenetic findings in MDS are important with regard to diagnosis, classification, prognostication, and treatment. In patients presenting with only mild signs of dysplasia, the presence of an abnormal karyotype confirms the diagnosis ‘MDS’ [1]. The presence of an isolated del(5q) in ‘non-

blastic’ MDS is of clinical significance [3]. The overwhelming prognostic relevance of cytogenetic findings has recently been confirmed by a collaborative study of the German–Austrian MDS Study Group [8]. In addition, new insights into the prognostic impact of rare cytogenetic anomalies have accumulated and standards for performing cytogenetic analyses in MDS have been proposed [9, 10]. In the last few years, cytogenetic findings also influenced the choice of treatment. Likewise, patients with isolated del(5q) can be treated successfully with lenalidomide [11, 12], patients with aberrations of chromosome 7 may preferentially respond to decitabine [13] or 5-Azacitidine [14], whereas patients with normal (but not high risk) karyotypes may sometimes benefit from intensive (AML-like) induction chemotherapy [15]. Our group cooperates with other international groups with the goal of refining cytogenetics and prognostic scores, one special focus being the relative impact of cytogenetic variables in comparison to blast counts in predicting outcomes in multi-parameter score systems.

Molecular markers and gene variants

Molecular defects in MDS can be divided into (1) translocation-related fusion gene products, like AML1/MDS1-EVI-1, found in patients with t(3;21), (2) somatic gene defects and mutations not reflected by a chromosome defect, like mutations in receptor kinases, RAS, or other signaling molecules, (3) loss of key molecules through deletions (example: loss of RPS14 in 5q patients) or epigenetic silencing, and (4) germ line gene polymorphisms and mutations that may influence the natural course of

Table 2 Classification of MDS according to the WHO proposal (update 2008)

Refractory cytopenias with unilineage dysplasia (RCUD)
Refractory anemia (RA)
Refractory neutropenia (RN)
Refractory thrombocytopenia (RT)
Refractory anemia with ring sideroblasts (RARS, ≥15% ring sideroblasts)
Refractory cytopenia with multilineage dysplasia (RCMD)
Myelodysplastic syndrome—unclassified (MDS-U)
MDS associated with isolated del(5q)
Refractory anemia with excess blasts-1 (RAEB-1, medullary blasts 5–9%)
Refractory anemia with excess blasts-2 (RAEB-2, medullary blasts 10–19%)
Childhood myelodysplastic syndrome (separate subchapter, separate authors)

Brunning RD, Orazi A, Germing U, Le Beau MM, Porwit A, Baumann I, Vardiman JW, Hellstrom-Lindberg E (2008) WHO classification of tumours of hematopoietic and lymphoid tissues, Chapter 5, pp 88–107

disease or disease-related features [16]. One example for the latter are *HFE* mutations that are otherwise found in patients with hereditary hemochromatosis. The frequency of *HFE* gene mutations (polymorphisms) in MDS is rather high [17] and may influence iron overload in transfusion-dependent patients.

Flow cytometry

Flow cytometry may be helpful in the diagnosis and prognostication in MDS [1, 18, 19]. The group concluded that evaluation of the percentage of CD34+ myeloid progenitor cells in MDS can be regarded as standard and used in the evaluation of the subtype of MDS, e.g., when the aspirate (smear) is contaminated with blood. CD34+ progenitor cells in MDS may also display aberrant expression of surface molecules confirming the presence of a myeloid neoplasm. In addition, granulocyte and monocyte dysplasia can be recorded by flow cytometry [1, 18, 19]. In fact, aberrant expression of three or more markers on granulocytic and/or monocytic cells can be regarded as a relatively safe indication that the myeloid cells are of monoclonal origin [18–20]. A disadvantage of flow cytometry is that up to now, no standards for evaluations and tests have been developed. Therefore, the group concluded that for the future, it is essential to propose global standards for flow cytometric assessment in MDS.

Prognostication and prognostic score systems

The prognosis in MDS varies depending on (1) patient-related factors (age, comorbidity, availability of a stem cell donor) and (2) disease-specific variables, including the variant of disease, cell types affected, cytogenetic features, and genes involved in the malignant process [1, 3, 21]. In addition, the response to specific drugs can in part be predicted by assessment of patient-related and disease-related variables. Several useful multi-parameter-based scoring systems have been developed in the past. A widely accepted standard is the International Prognostic Scoring System (IPSS) [22] that includes the medullary blast count, number of cytopenias, and cytogenetic findings. A refinement of the IPSS including the serum LDH has been developed by our group [22]. More recently, several attempts have been made to identify molecular defects that are linked to specific cytogenetic abnormalities or signaling pathways in neoplastic cells in patients with MDS. In addition, the genetic background, including gene polymorphisms and mutations (e.g., deletions), have been discussed as prognostic variables. It has to be pointed out, however, that most data are derived from observational

studies on untreated patients. Recently, the WHO-adapted scoring system has been developed, taking into account the degree of dysplasia, chromosomal findings, and transfusion need [23]. This score is even more accurate in identifying patients with a very low risk [23]. Comorbidity scores are currently evaluated in MDS patients. These patient-related parameters not only influence the prognosis but also the choice of treatment [24]. Several projects investigating comorbidity, transfusion effects, and iron overload have recently been started in our MDS study group [24–28]. Recent data suggest that Lenalidomide [11], Decitabine [29, 30], 5-Azacytidine [31], erythropoietin [32], Antithymocyte globulin [33], and others [34] may be beneficial in defined subgroups of MDS patients. We have recently established cooperation projects in our group with the aim to collect data in MDS patients who underwent various therapies in order to better characterize predictive parameters for each patient group.

Future perspectives

Because of the heterogeneity and complexity of the disease, collaborative work on MDS is essential and should focus on the topics mentioned above, with the ultimate goal of gaining new insights into the pathogenesis of the disease and improving prognostication and therapy [29]. In the future, these studies will also include gene expression profiling, SNP array analysis, and proteomics, as well as flow cytometry and hematopathology. The D-A-CH MDS group will serve as an open forum aiming at intensifying collaborations in these ‘subfields’ in MDS research.

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