Classification and Staging of Myelodysplastic Syndromes

Torsten Haferlach, Wolfgang Kern

Contents

5.1 Introduction ............................................ 40

5.2 Diagnostic Procedures Needed for Staging and Classification .......... 40
  5.2.1 Sample Collection and Preanalytic Procedures ................. 40
    5.2.1.1 Cytomorphology and Cytochemistry ................. 41
    5.2.1.2 Multiparameter Flow Cytometry by FACS .......... 42
    5.2.1.3 Cytogenetics ........................................ 42

5.3 Diagnostic Criteria ..................................... 42
  5.3.1 Cytomorphology and Cytochemistry .......................... 43
    5.3.1.1 Dysplasia in MDS: The FAB Criterian (1982) ........ 43
    5.3.1.2 Dysplasia as Defined for AML by Goasguen et al. (1992) (also WHO 2001) . . 43
    5.3.1.2.1 Criteria for Dysgranulopoiesis .................. 43
    5.3.1.2.2 Criteria for Dyserythropoiesis .................. 44
    5.3.1.2.3 Criteria for Dysmegakaryopoiesis ............... 44
    5.3.1.3 Ringed Sideroblasts According to FAB and to WHO Criteria ................. 44
    5.3.1.3.1 FAB Criteria ....................................... 44
    5.3.1.3.2 WHO Criteria ..................................... 44
    5.3.1.4 Definition of Chronic Myelomonocytic Leukemia (CMML) .... 44

5.3.1.4.1 CMML: Proliferative and Non-proliferative Subtype, According to FAB Criteria (1994) (Bennett et al. 1994) 44
      5.3.1.4.2 WHO Criteria for CMML (Dysplastic Type) (Jaffe et al. 2001) .................. 44

5.3.2 Multiparameter Flow Cytometry (MFC) .................................. 44
  5.3.2.1 Granulocytes .......................................... 44
  5.3.2.2 Monocytes ............................................. 45
  5.3.2.3 Erythrocytes .......................................... 45
  5.3.2.4 “Blasts” .............................................. 45
  5.3.2.5 Additional Flow Cytometric Findings .................. 46

5.3.3 Cytogenetics and FISH ..................................... 46
  5.3.4 Molecular Methods ....................................... 47
  5.3.5 Other Laboratory Features ................................ 47

5.4 Overview of Classification and Staging Systems .......................... 47
  5.4.1 Proposed Classification and Scoring Systems .................... 47
  5.4.2 FAB Classification ....................................... 47
  5.4.3 International Prognostic Scoring System (IPSS) (1997) ........ 47
      5.4.4 WHO Classification (2001) ............................ 48

5.5 Future Developments in Classification and Staging ....................... 50
  5.5.1 Molecular Genetics .................................... 50
  5.5.2 Microarrays for Classification and Staging in MDS? ............ 50

5.6 Conclusions ............................................... 51

References .................................................. 51
5.1 Introduction

The myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal hematological disorders that are usually diagnosed based on findings in peripheral blood, and especially the bone marrow. MDS is characterized by ineffective hematopoiesis, showing dysplastic features in at least one lineage in the bone marrow.

With the use of standard classification systems, e.g., the French-American-British (FAB) classification (Bennett et al. 1982), the new World Health Organization (WHO) proposal (Jaffe et al. 2001) or several other scoring systems such as the IPSS (Greenberg et al. 1997), the Düsseldorf score (Aul et al. 1992) or the Bournemouth score (Mufﬁet al. 1985), staging and classiﬁcation of MDS are readily achieved. However, various problems surface in daily routine. “Standard” classiﬁcation systems and problems will be discussed below. Some of the important issues include:

- How to diagnose early stages of MDS and discriminate these from other non-malignant disorders
- How to measure and reproducibly assess dysplasia, the hallmark of MDS staging and classiﬁcation
- How to reproducibly determine the proportion of blasts, an essential parameter for MDS classiﬁcation and treatment decisions
- How to incorporate biological markers, e.g., cytogenetics and molecular alterations, into prognostic staging and scoring systems
- Researching other techniques to support or enhance our knowledge, and integrating those ﬁndings into staging and classiﬁcation in the future
- Determining whether MDS is different from AML and if current classiﬁcation systems propagate artiﬁcial distinctions by adhering to rigid deﬁnitions

Clearly, more than 20 years after development of the FAB classiﬁcation many questions remain or have arisen since.

5.2 Diagnostic Procedures Needed for Staging and Classiﬁcation

During the past 20 years the diagnosis, classiﬁcation, and staging of MDS have evolved from relying on cytomorphology alone to a comprehensive array of different methods that have improved our ability to establish the diagnosis and to arrive at treatment decisions. For state of the art staging and classiﬁcation an algorithm that combines cytomorphology and cytochemistry with immunophenotyping, accompanied by cytogenetics and molecular genetic methods has to be established in a laboratory setting (Haferlach and Schoch 2002).

Generally, we start with peripheral blood smears and bone marrow cytomorphology, cytochemistry, and iron stains. Recent data suggest that multiparameter ﬂow cytometry (FACS) should be included in the diagnostic work-up for MDS (Stetler-Stevenson et al. 2001; Wells et al. 2003). In addition, metaphase cytogenetics should be obtained in every case in which MDS is suspected. Where possible, the latter should be accompanied by FISH or 24-color FISH to conﬁrm aberrant ﬁndings observed in metaphase karyotyping. As abnormalities of chromosomes 5 and 7, loss of a Y chromosome, or a complex aberrant karyotype play an important role in MDS classiﬁcation according to IPSS (Greenberg et al. 1997) and WHO (Jaffe et al. 2001) (see below), these determinations are mandatory.

5.2.1 Sample Collection and Preanalytic Procedures

Several prerequisites must be fulﬁlled for reproducible results:

- Different methods rely on different sources of biological materials. For example, cytomorphology is impaired by heparin, and good metaphase spreads cannot be expected if EDTA was added to the sample.
- In all cases with cytopenia or suspected MDS blood and bone marrow samples should be obtained at the same time (Ludwig et al. 2005).
- A trephine biopsy may be necessary, especially in cases with very hypocellular or inaspirable bone marrow (punctio sicca) and peripheral cytopenia (Cheson et al. 2003). In these circumstances peripheral blood should be analyzed, but smears for cytomorphology can also be produced from trephine cylinders.
- Similarly, for cytogenetics (in case of a punctio sicca) a metaphase analysis can be done after culturing the trephine biopsy in appropriate medium and processing the medium (plus cells) for karyotyping.

A comprehensive investigation at diagnosis requires 3–5 ml EDTA anticoagulated bone marrow, 10 ml periph-