Classification and Staging of Myelodysplastic Syndromes

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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 (Mufti et 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 cytology 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 cytology, cytochemistry, and iron stains. Recent data suggest that multiparameter flow cytometry (FACS) should be included in the diagnostic work-up for MDS (Stelzer-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, cytomylography 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 inapplicable 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-