Overview

The last decade has witnessed the emergence of several therapeutic options for patients with myelodysplastic syndromes. Objective criteria for diagnosis, proper classification, and risk stratification are, now, more important than ever before. Therapeutic strategies are tailored based on the classification and prognostic risk groups.

Myelodysplastic syndromes (MDS) represent a spectrum of neoplastic clonal stem cell disorders characterized by bone marrow failure with variable cytopenias and a percentage of leukemic blasts that range from less than 5% to 19%. The evolution into acute myeloid leukemia (AML) is highly dependent on the initial blast %. The presence of “dysplastic” abnormal morphologic features in one or more cell lines is required to make the diagnosis. In lower grade MDS apoptosis is the hallmark of the disease explaining the discrepancy between normal to hypercellular bone marrow findings and the noted peripheral cytopenias.

MDS is a disease of the elderly, the incidence of MDS in the recently published Surveillance, Epidemiology, and End Results (SEER) data increases from less than 5 per 100,000 for patients less than 60 year to 36.2 per 100,000 in patients more than 80 year old. The median age of diagnosis was 76 years. Men and white race have a higher incidence of the disease.

With a population in Turkey, approaching 80,000,000 and 5,000,000 over the age of 65 years, one could expect to discover 2500 new cases per year, contrasted to 15,000 cases in the USA.

WHO classification

The World Health Organization (WHO) revised and updated the MDS classification in 1997. The changes from the FAB classification can be summarized as follows:

Recognition of the importance of multi-lineage dysplasia in low risk disease (<5% blasts) with two new categories; refractory cytopenia with multi-lineage dysplasia (RCMD) and refractory anemia with multi-lineage dysplasia with ring sideroblasts (RCMD-RS). The old RA and RARS categories were restricted to erythroid dysplasia with less than 10% dysplasia in myeloid or megakaryocytic line. This was based on previous observations that presence of multi-lineage dysplasia carries a worse prognosis even in presence of ring sideroblasts.

Further refine the RAEB group into RAEB 1 (5-9%) myeloblasts and RAEB 2 (10-19%) blasts. However this split of the RAEB group creates more homogeneous categories. The higher the percentage of myeloblasts the higher the risk of the disease progression to AML.

Lower the threshold for diagnosing AML to ≥ 20% myeloblasts rather than ≥ 30%. The RAEB-t category was therefore omitted. This is probably the most important clinical change. This was based on observations that RAEB-t patients had similar outcome to older patients with AML. The classification does not dictate the treatment for this group since younger patients that meet this cutoff are treated as AML. Clinical judgment and further studies are needed to decide on how to treat an elderly patient in this category (MDS type of therapy or intensive AML induction). It is also important to note that WHO recognizes presence of certain...
cytogenetic abnormalities t(8;21), t(15;17), and inversion 16 as being acute leukemia defining even if the blast percentage is less than 20%.

Recognize the importance of cytogenetics by adding del. 5q syndrome as a good prognostic separate group. At the time of the WHO proposal this represented a great advancement where for the first time cytogenetics was recognized in the classification. The 5q syndrome is a subset of patients with isolated 5q deletion, less than 5% blasts, a distinct clinical picture with refractory macrocytic anemia and normal to elevated platelet counts. The disease occurs in middle age to older women. It has unique bone marrow findings with mononuclear megakaryocytes. Finally 5q- syndrome patients have a very good prognosis with a low risk of transformation to AML.

CMML was incorporated in a new category: myelodysplastic/myeloproliferative disorders (MDS/MPD). It was clear that CMML group in the FAB classification was heterogeneous. The prognosis of CMML depends on the percentage of bone marrow blasts and as recognition of this the WHO classified CMML into type 1 and 2 based on that rather than on peripheral white blood count (WBC). The clinical behavior of “proliferative” CMML is more of a MPD rather than MDS. Recent studies showing more presence for JAK-2 mutation in CMML and MPN unclassified is reassurance that this was a right step in further understanding this disease, as demonstrated by the finding of the mutation in most patients with RARS and thrombocytosis.

A new category of MDS unclassified was added to include less common patients with neutrophilic or megakaryocytic unii or bi lineage dysplasia without erythroid dysplasia.

Therapy related MDS/AML is recognized as separate category outside the WHO classification for de novo MDS. This category, with exposure to alkylating agents, has known recurrent cytogenetic abnormalities and unfortunately a poor prognosis. The exception is those patients exposed to topoisomerase-II inhibitors, who develop specific translocation AML’s such as t(8;21) and respond well to combination chemotherapy.

**Diagnosis of MDS**

The evaluation of unexplained cytopenias, with normal B12, folate and iron stores, requires a careful examination of the peripheral blood smear, a bone marrow aspirate and biopsy and iron stains.

Cytogenetics are critical to obtain since prognostic information is provided and is an important component of several scoring systems. For example the presence of 5q– will also impact on the therapeutic choice. Conventional cytogenetics obtained from bone marrow aspirate could be complemented by interphase FISH tests that could be obtained from bone marrow or peripheral blood samples. In fact a “FISH panel” with probes for 5q-, 7, 8, and 20q– are in common use.

A new proposed revision to the IPSS cytogenetic risk groups was also published recently. For Overall Survival, del(11)(q14q23) and del(12p) were included within the good risk category, del(7) (q31q35) within the intermediate risk category and 3q rearrangements within the high-risk category. For risk of evolution to AML, del(11)(q14q23) and del(12p) were included within the good risk category, del(20q) within the intermediate risk category and +8 within the high-risk category.

**Implications of WHO classification**

The Dusseldorf MDS registry was the first to validate the prognostic superiority of the WHO classification. In a retrospective reclassification of 1600 cases of MDS, the new classification was able to distinguish differences in outcome between RA/RS and RCMD/RCMD-RS as well as between RAEB1 and RAEB2. Later on the same group validated the WHO classification prospectively where 1095 patients were included; the median overall survival for RA and RARS was not reached. The median overall survival for RCMD was 31 months, RCMD-RS: 28 months, RAEB-1: 27 months, RAEB-2: 12 month, and 5 q-: 40 months. The frequency of AML progression 2 years after diagnosis was: RA 0%, RARS 8%, RCMD 9%, RCMD-RS 12%, RAEB-1: 13 %, RAEB-2: 40%, and 5 q-: 8%.

The MDS Foundation has developed a website based educational program highlighting myelodysplastic features and morphology. Hopefully this will be a useful tool to improve reporting on MDS (now available at www.mds-foundation.org). In addition there is a link to a new nomogram to calculate the risk based on the IPSS-R (Blood, in press, 2012)

**The 2008 WHO classification**

In the summer of 2008 a revised version of the WHO syllabus was published. For the first time,
the WHO 2008 classification proposes diagnosis of “Presumptive MDS” in cases with persistent clinical cytopenias without dysplasia if certain cytogenetic abnormalities are present. On the other hand, the term idiopathic cytopenia of unknown significance (ICUS) is applied if patients had persistent cytopenias without alternative explanation, no dysplasia and without the specific cytogenetic abnormalities.

MDS unclassified includes patients with pancytopenia and unilineage dysplasia; Patients with no overt dysplasia but cytogenetic evidence of MDS and cases of RCUD and RCMD where bone marrow blasts are less than 5% and peripheral blasts are 1%.

**International Prognostic Scoring System and its modification**

In the era of new therapeutic agents proposed treatment algorithms are based on “MDS risk assessment”. This risk stratification was done utilizing the International Prognostic Scoring System (IPSS). The prognostic model and the scoring system were built based on blast count, degree of cytopenia, blast percentage and cytogenetic risk. Risk scores were weighted relative to their statistical power.

This system is widely utilized to divide patients in two categories “low risk” which includes low risk and Int-1 IPSS groups, the goal in “low risk” MDS patients is to improve quality of life and achieve transfusion independence. In the “high risk” group Int-2 and high risk IPSS the goal is slowing progression of disease to AML and improve survival. The IPSS is usually calculated upon diagnosis. The role of LDH, marrow fibrosis and beta-2 microglobulin should be considered as well after establishing the IPSS. If elevated the prognostic category becomes worse, by one category change.

A new prognostic scoring system based on the WHO classification was recently proposed. The WHO Prognostic Scoring system (WPSS) uses WHO subtype, cytogenetics (from the IPSS) and transfusion requirements to calculate the prognostic score. The results provide five distinct survival curves compared to the four in the IPSS. The WPSS is a dynamic scoring system and can be used at any time during disease course where the IPSS is only predictive of outcome at diagnosis. The WPSS, however, requires knowing the WHO subtype.

“To refine the IPSS, MDS patient databases from international institutions were merged to assemble a much larger combined database [Revised-IPSS (IPSS-R), n=7012, IPSS, n=816] for analysis. Bone marrow cytogenetics, marrow blast percentage and cytopenias remain the basis of the new system. Novel components of the current analysis included: five rather than three cytogenetic prognostic subgroups with specific and new classifications of a number of less common cytogenetic subsets, splitting the low marrow blast percentage value, and depth of cytopenias. This model defined five rather than the four major prognostic categories that are present in the IPSS.

Patient age, performance status, serum ferritin and LDH were significant additive features for survival but not for AML transformation.

This IPSS-R should prove beneficial for predicting the clinical outcomes of untreated MDS patients and aiding design and analysis of clinical trials in this disease.” (Blood, 2012, in press)

Finally the introduction of molecular aberrations in patients with primary MDS has provoked considerable interest. The presence of one or more mutations of certain genes can impact the IPSS.

**Future**

There is a clear need for standardized way to diagnose MDS and classify it, a need for minimal required diagnostic criteria and more objective criteria. Answers for such needs may come from incorporation of flow cytometry findings, cytogenetic findings and identifying molecular signatures by gene arrays or proteomics or applying different technologies. A committee is examining how to combine the most salient features of these prognostic scoring systems into one universally acceptable program.

It is more important than ever to appropriately diagnose and classify MDS patients given our new treatment options and hopefully more armamentarium in the near future.
References


