Predicting survival and leukemic evolution in patients with myelodysplastic syndrome

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Myelodysplastic syndromes (MDS) are a group of hematologic disorders that occur mainly in older persons and are characterized by peripheral cytopenias and an increasing risk of progression into acute myeloid leukemia (AML).[1,2] The impressive heterogeneity of the natural history of MDS, ranging from indolent conditions with near normal life expectancy to forms rapidly progressing to leukemia, complicates clinical decision-making regarding therapeutic modalities and timing of interventions.[3]

In 1982, the French-American British (FAB) co-operative group proposed a classification of MDS based on morphological criteria.[4] For the following 20 years this classification represented the benchmark for clinical management and investigational studies in MDS. However, considerable heterogeneity was observed within FAB subgroups, raising the need for prognostic systems with a better ability to predict survival and leukemic progression in MDS patients. Various prognostic models were proposed based on demographic and disease-related variables, including age, peripheral cytopenias, bone marrow blast count, lactate dehydrogenase level and karyotypic abnormalities.[5,6] In 1997 an International MDS Risk Analysis Workshop defined the International Prognostic Scoring System (IPSS), which combines information on bone marrow blast percentage, cytogenetic abnormalities and number of peripheral cytopenias detected at the time of the diagnosis, enabling the distinction of four risk groups with different survivals and risks of leukemia evolution.[7] The IPSS has been extensively validated in independent patient populations, and despite some discrepancies, has become the gold standard for clinical trials and decision-making.

In 2002, the WHO formulated a new proposal for the classification of MDS.[8] This new classification is based on variables which had been demonstrated to be able to stratify survival and leukemic progression in MDS patients, including a uni- or multi-lineage hematopoietic dysplasia, narrower blast count intervals and specific cytogenetic abnormalities. The unresolved question of the distinction between MDS and AML was also addressed with different proposals, such as lowering the bone marrow blast threshold to define progression into acute leukemia, comprising therapy-related AML and MDS in a sole category, and recognizing a new entity defined as acute myeloid leukemia with multilineage dysplasia.

The prognostic relevance of this classification was recently confirmed in retrospective studies by different groups.[9,10] Among patients with MDS without excess blasts, an isolated involvement of the erythroid lineage has been confirmed to be associated with a better prognosis than that of multilineage dysplasia. The relevance of this observation has been strengthened by the finding that patients with purely erythroid disorders aged 70 years or older have a life expectancy not significantly shorter than that of the general population.[10] As far as advanced MDS are concerned, the definition of two categories of refractory anemia with excess blasts has been proven to identify two groups of patients with significantly different survival and risks of leukemic evolution. Interesting data have also been emerging on the ability of the WHO classification to guide clinical decision-making regarding therapeutic choices. Patients with unilineage dysplasia have been shown to have a significantly higher probability of responding to treatment with hematopoietic growth factors compared to those with multilineage dysplasia,[11] while patients with 5q deletion were found to have a high response rate to lenalidomide.[12]

In this issue of Haematologica/the Hematology Journal, the Düsseldorf MDS registry reports the first prospective validation of the WHO classification on a large cohort of MDS patients.[13] This study confirms the results of previous retrospective analyses, substantiating the clinical utility of the proposed WHO classification. In particular, the significant difference in both survival and risk of leukemic evolution between patients with isolated erythroid involvement and those with multilineage dysplasia has been validated.

The WHO proposal has raised some concern regarding minimal diagnostic criteria for formulating the diagnosis of refractory anemia, in particular when the diagnosis of MDS has to be based exclusively on morphological criteria, as well as for correctly classifying patients into WHO categories. In this regard, flow cytometric immunophenotyping might be of help in discriminating between MDS and other acquired anemias.[14] In addition it might be useful to identify patients with ringed sideroblasts through the detection of mitochondrial ferritin, and those with multilineage dysplasia with high sensitivity and specificity.[14,15]

The implementation of the WHO classification compels a refinement of the role of demographic and disease-related prognostic factors within MDS subgroups. The IPSS was shown to retain a significant prognostic value in MDS patients classified according to WHO cri-

teria.[10] However, both the systems are based on very similar criteria, in particular with regard to the ranking of bone marrow blasts. When testing the significance of the IPSS variables in the WHO categories, as expected bone marrow blast count failed to show a prognostic value. Likewise, the number of peripheral cytopenias did not retain an independent predictive value for the outcome when marrow lineage involvement was included the analysis. The only IPSS variable that maintains a prognostic value in MDS patients classified into the WHO subgroups is cytogenetics. In addition, the assimilation of refractory anemia with excess blasts in transformation into AML resulted in a significant cutback of the higher IPSS risk groups. Therefore, the definition of new prognostic scoring systems tailored on the patients' population defined by the WHO criteria, and including the most significant prognostic variables of the WHO proposal, is warranted.

The onset of a regular transfusion requirement has been found to affect the outcome of MDS patients classified into WHO subgroups.[10] Transfusion dependency is associated with both shorter survival and increased risk of leukemic evolution, suggesting that this effect is at least in part due to a more aggressive disease. Based on these results, transfusion-dependency can be considered an independent indicator of disease severity in MDS. The effect of transfusion-dependency is more noticeable in patients with low-risk MDS and is significantly associated with the severity of transfusion requirement (Figure 1). The increased risk of non-leukemic death observed in transfusion-dependent patients is certainly in part related to these patients having more severe anemia. However, developing secondary iron overload significantly worsens survival of patients requiring regular red cell transfusion therapy.[10] The effect of iron overload is mainly noticeable among patients with refractory anemia according to WHO criteria, who have a median survival of more than 100 months and are, therefore, more prone to develop long-term toxicity of iron overload, whereas iron overload does not affect the survival of patients with refractory cytopenia who have a median survival of about 50 months (Figure 2).

The adverse outcome of anemia in MDS appears to be sustained by both a more severe underlying disease and the harmful effect of the anemia *per se*, although the relative contributions of these two factors remain to be established. The accurate assessment of anemia in the elderly does, however, appear to be rather problematical because of changes in hemoglobin levels associated with aging, as well as differences between genders and ethnic groups.[16] Relying on a single hemoglobin level to define the severity of anemia might introduce a bias in the prognostic stratification of elderly MDS patients. At present, adopting symptomatic anemia as a major criterion for estimating the severity of anemia in MDS pop-

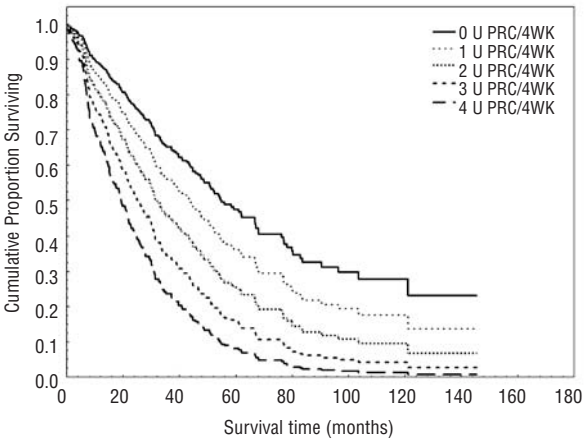

Figure 1. Survival of MDS patients according to the intensity of their red cell transfusion requirement, calculated as the number of packed red cell (PRC) units per month (U/4WK) (data obtained from 426 patients diagnosed with MDS according to WHO criteria at the IRCCS Policlinico San Matteo, Pavia, Italy, between 1992 and 2004. The between-group comparison was performed by applying a Cox proportional hazard regression model with time-dependent covariates).

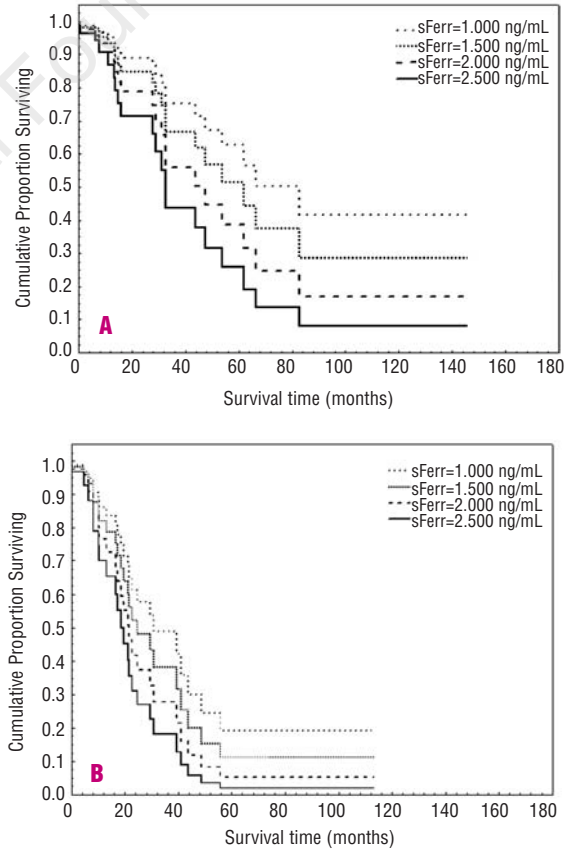

Figure 2. Overall survival of transfusion-dependent MDS patients according to iron overload (data obtained from 426 patients diagnosed with MDS according to WHO criteria at the IRCCS Policlinico San Matteo, Pavia, Italy, between 1992 and 2004. A between-group comparison was performed by applying a Cox proportional hazard regression model with time-dependent covariates). A: patients with refractory anemia (RA), RA with ringed sideroblasts (RS) or MDS with isolated del (5q); B: patients with refractory cytopenia with multilineage dysplasia (RCMD) or RCMD-RS.

ulation and for making clinical decisions appears the most reliable approach to adjust for the variability of hemoglobin values. The most relevant improvement in prognostic ability produced by the WHO classification is seen among the so-called low risk MDS, mainly comprising subgroups without excess blasts. The finding that a not negligible proportion of these patients retain a near normal life expectancy, together with the availability of new therapeutic agents active against the myelodysplastic clone, such as lenalidomide, strongly support the use of prognostic instruments able to refine the stratification of this subset of patients and improve our clinical decision making. This aspect takes on even more relevance in view of the results of the clinical decision analysis from the International Bone Marrow Transplant Registry, which demonstrated that life expectancy of patients with MDS low-risk IPSS scores was higher when transplantation was delayed by some period but performed prior to the development of AML.[17] Although there is substantial evidence that the earlier the transplantation is performed in MDS the better the outcome, many patients with low-risk MDS experience a long survival without signs of disease progression. For these patients, the risk of immediate morbidity and mortality associated with transplantation is often felt as unacceptably high. Therefore, identifying hematologic and clinical variables associated with adverse outcome in low-risk patients is mandatory in order to avoid progression to leukemia or non-leukemic events that could preclude transplantation, and to plan effective risk-adapted treatment strategy.

Significant advances in our ability to predict survival and leukemic evolution in MDS have been made since the formal definition of these disorders by the FAB cooperative group. The WHO classification has a significant prognostic value, and the prospective validation of this proposed classification carried out by the Düsseldorf MDS registry strongly supports use of this classification in clinical practice, together with diagnostic instruments able to increase the accuracy of morphological analysis in the diagnostic work-up of MDS patients, such as flow cytometric immunophenotyping.[14,15] Refining disease-related prognostic factors within WHO subgroups and integrating them into new prognostic models is warranted in order to implement effective risk-adapted treatment strategies in MDS.

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