Perspectives in the prognostication of myelodysplastic syndromes

Since the first precise definition of myelodysplastic syndromes (MDS) in 1982,[1] prognostication of this disease has been a matter of debate. It very quickly became clear that the prognosis of MDS patients cannot be assessed by a single parameter, although the prognostic impact of the FAB classification, which is based on bone marrow morphology, is still impressive. This reflects the fact that the percentage of marrow blasts is the variable with the greatest impact on prognosis.

Other parameters, such as cell counts, morphologic features, lactate dehydrogenase concentrations, gender and age were used to construct scoring systems in order to define risk groups differing in terms of survival as well as evolution to acute myeloid leukemia. Cytogenetic findings were added into the scoring systems later. To improve the clinical and prognostic use of these systems, a consensus risk-based score, the International Prognostic Scoring System (IPSS)[2] was developed by seven working groups, each of which had already proposed a scoring system for risk assessment in MDS. The IPSS, which combines information on marrow blasts, cell counts and cytogenetic findings, has become the gold-standard for the assessment of prognosis. This score is now widely used in clinical decision-making and within clinical trials.

However, there are some problems not satisfactorily addressed by the IPSS. One is the prognostication of dysplastic chronic myelomonocytic leukemia (CMML). The majority of patients with CMML present with a normal karyotype, do not have trilineage cytopenia and does not present with more than 20% marrow blasts.[3] Another is the fact that since the introduction of the WHO classification, CMML and refractory anemia with excess blasts in transformation (RAEB-T) are no longer considered MDS. This may influence the feasibility of the IPSS, too. A further restriction to proper risk assessment is the large number of cytogenetic findings, whose prognostic meaning is still un-known. For example, the MDS registry of Düsseldorf contains data on 926 patients who were karyotyped at diagnosis. About 16% of these are categorized as having an intermediate risk karyotype according to the IPSS, although the actual prognostic meaning of such relatively rare cytogenetic find-ings remains unclear.

The article by Solé and co-workers of the Spanish Cooperative Cytogenetic group in this issue of the journal opens up new perspectives in different ways.[4]

Solé *et al*. started by looking at a large group of cytogenetic findings, whose prognostic meaning has been uncertain until now, attempting to decipher cytogenetic findings in order to gather more information about their impact on prognosis. In a first step, the authors confirmed the usefulness of the cytogenetic categories of the IPSS, but in the next step, they identified additional, less frequent cytogenetic aberrations, associated with different prognoses: patients with del(11q) or del(12p) had a median survival of at least 3.8 years and thus should be reclassified as being in the good risk group. On the other hand, i(17q) was associated with a poor risk. Patients with this cytogenetic abnormality (n=10) exhibited a median survival of less than 1 year. Furthermore, Solé *et al*. propose an intermediate group, comprising patients with +8, r3q21q26, t(11q), and del (17p) and a new group, termed *unknown,* for other single or double aberrations, most of which are rare cytogenetic events. Introducing this new category is reasonable, because of a trend towards a poorer prognosis when compared to the intermediate risk group. These findings lead to an refinement of the cytogenetic risk categories established by the IPSS. The newly defined risk group *unknown* is smaller than the original intermediate risk group of the IPSS and is segregated from it into a higher risk category. Its designation emphasizes that our knowledge of the majority of cytogenetic findings is still limited and should be improved by further analysis of larger patient co-horts.

In a last step these new findings are included in two new scoring systems assessing survival and AML progression, leading to 4 different risk groups with different clinical outcomes. We have validated these scoring systems by applying them to data in the Düsseldorf MDS registry. The scoring systems successfully separated 735 non-treated patients (Figures 1 and 2), providing prognostic information with an exactness similar to the IPSS.

However, not all problems of prognostication are solved by this new score. Using age as a prognostic parameter is a still debated controversy. Younger MDS patients generally have a better prognosis than older patients, but this difference is restricted to low-risk MDS.[5]

A further limitation to all cytogenetic-based scoring systems is the fact that the number of patients who are karyotyped at the time of diagnosis is relatively low outside MDS centers: only 20% of the MDS patients in the Düsseldorf MDS registry who had diagnostic bone marrow biopsies outside MDS centers had been karyotyped. This means that neither the IPSS nor the new Spanish score can be assessed in all patients. Prognostication of these patients must be performed using scores that are not based on cytogenetics.[6-8] Furthermore younger MDS patients are karyotyped more frequently than older patients. The mean age of patients in the MDS registry Düsseldorf who have been karyotyped at diagnosis is 10 years lower (62 years) than that of patients who have not been karyotyped (72 years) (p=0.005). This leads to a better prognosis in patients who are karyotyped (p=0.0005).

Another problem of all scoring systems, including the IPSS, is that they have been developed on the basis of untreated patients and therefore do not provide predictive information for patients who undergo specific treatment. Treatment outcome after intensive chemotherapy, stem cell transplantation, and new promising alternatives such as demethylating agents or lenalidomide is not predictable with the IPSS. Of the prognostic variables in patients undergoing intensive chemotherapy only the karyotype remains predictive for treatment outcome.[9,10] Agents such as decitabine have been shown to produce a better response rate in high-risk MDS[11] and lenalidomide appears to be the first agent producing an exceptionally high response rate in a single cytogenetic subgroup, with the best responses occurring in the 5q- syndrome.[12] So, in the future it might be necessary to develop predictive scores more than prognostic scores for different therapeutic approaches, because the number of patients who

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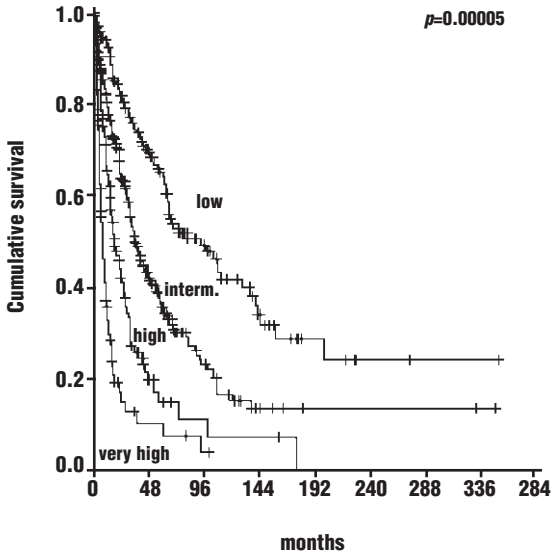

Figure 1. GCEGH scoring system assessed on 735 MDS patients from the Düsseldorf registry (survival).

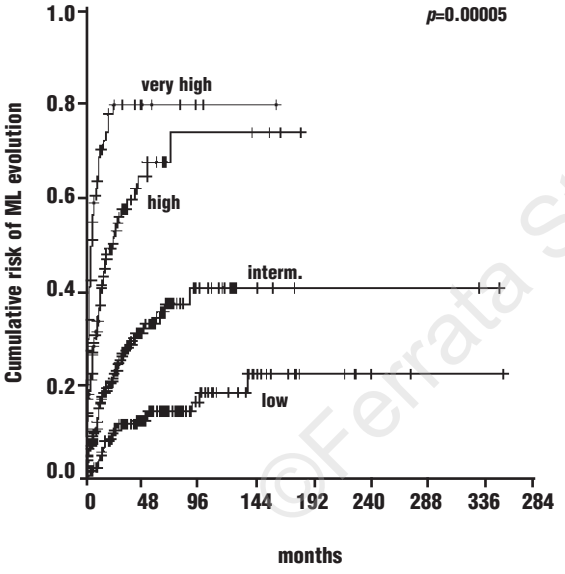

Figure 2. GCEGH scoring system assessed on 735 MDS patients from the Düsseldorf registry (AML evolution).

undergo specific treatments will increase in the future.

Like the IPSS, the new Spanish Score was developed based on the FAB classification. However, the WHO classification is being increasingly used and has become the new standard for morphologic classification in MDS.[13] Thus, a score taking into account the degree of dysplasia in the bone marrow must be developed, because the prognostic impact of the WHO classification has clearly been demonstrated[14] and the same cytogenetic aberration may result in different prognostic categories depending on morphologic features.[15] In the future the large group of chromosomal aberrations with unknown prognostic significance should be deciphered through large studies. The German-Austrian MDS prognosis group has already made such an attempt, collecting more than 2,100 karyotyped cases of MDS.[16] Additional parameters such as fibrosis, cellularity, presence of peripheral blasts, genomic data, proteomics, and clonality have to be validated to assess their value in predicting clinical outcome. Dynamic scores, taking into account time dependent variables might also be useful. New prognostic parameters are especially clearly needed for CMML. A classification and prognostic tool for treatment-related MDS is also desired. The outcome in this MDS subgroup is generally poor and currently used classification sys-tems are not feasible to separate different risk groups. Besides that, it is unclear whether prognostic tools that are useful for western-type MDS are also feasible for eastern-type MDS patients, because there are important differences in clinical and hematologic behavior between eastern and west-ern MDS.[17]

There will be pros and cons to every classification and score as long as our knowledge about the biology of MDS remains limited. New insights into the pathogenesis of MDS and further analysis of large MDS databases will help to improve our current knowledge on MDS prognosis.

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