Haematologica 1998; 83:358-368 review

*Recent Advances in Myelodysplastic Syndromes*

*Guest Editors: Miguel Angel Sanz, Guillermo Sanz & Teresa Vallespí*

# Prognostic factors and scoring systems in myelodysplastic syndromes

GUILLERMO F. SANZ, MIGUEL A. SANZ, PETER L. GREENBERG*

*Departments of Hematology, Hospital Universitario La Fe, Valencia, Spain; *Stanford University Medical Center and VA Palo Alto Health Care System, Palo Alto, CA, USA*

**Abstract**

***Background and Objective.*** **Great prognostic heterogeneity complicates therapy-planning and a correct evaluation of clinical trials in myelodysplastic syndromes (MDS). Thus, the development of a prognostic classification of MDS is of major clinical relevance, especially when the advanced age of most patients and the aggressiveness of the curative treatment modalities currently available are considered. This review summarizes the results of different studies focusing on prognostic factors in MDS and deals with the pros and cons of prognostic scoring systems that have been recently developed. It also discusses the prognostic factors of particular subtypes of patients and those isolated with certain treatment options.**

***Evidence and Information Sources.*** **The authors of the present review have been working in different areas of the field of MDS for several years, have contributed original papers on the prognostic factors and therapy of these disorders, and have taken part in the recent *International MDS Risk Analysis Workshop* that has resulted in the development of the *International Prognostic Scoring System* (IPSS) for MDS.**

***State of the Art and Perspectives.*** **The percentage of marrow blasts, cytogenetic pattern and number and degree of cytopenias are the most powerful prognostic indicators in MDS. Although some limitations are evident, the recently developed scoring systems, and particularly the IPSS, are extremely useful for predicting survival and acute leukemic risk in individuals with MDS and should be incorporated to the design and analysis of therapeutic trials in these disorders. A risk-adapted treatment strategy is now possible and highly recommended for MDS patients.**
**©1998, Ferrata Storti Foundation**

Key words: myelodysplastic syndromes, prognosis,

A prognostic classification of myelodysplastic syndromes (MDS) is of great importance to best suit the treatment options to the risk, as well as allowing appropriate evaluation of the impact of a given therapeutic procedure in a particular group of risk. This importance is particularly stressed if the prognostic variability and aggressive nature of the currently available curative treatment options is taken into account, especially when considering the advanced age of the majority of patients. Although the French-American-British (FAB) classification has been relatively effective for categorizing MDS patients since 1982,[1] its limitations have become evident. These limitations include the wide range of marrow blast percentages for patients in the refractory anemia with excess of blasts (RAEB) and chronic myelomonocytic leukemia (CMML) categories (5-20%, 1-20%, respectively), lack of inclusion of critical biological determinants such as marrow cytogenetics, and the degree and number of morbidity-associated cytopenias. These well-perceived problems for categorization of MDS patients have led to the development of numerous additional risk-based stratification systems.

This review summarizes our knowledge of the prognostic factors in MDS, and critically analyzes the usefulness and limitations of recently developed prognostic models for MDS. Prognostic factors in some particular settings of patients and associated with certain treatment approaches will also be discussed.

*Correspondence: Dr. Miguel A. Sanz, Servicio de Hematología, Hospital Universitario La Fe, Av Campanar 21, 46009 Valencia, Spain.*
*Phone & Fax: international +34-6-3868757 • E-mail: msanz@uv.es*

## Prognostic factors

As a result of several recent studies on prognostic factors in MDS,[2-24] a large number of patient and disease characteristics that are highly associated with survival, leukemic transformation or both have been identified. These prognostic factors are summarized in Table 1. At present, the percentage of blasts in bone marrow (BM), cytogenetic pattern and the number and degree of cytopenias are considered the main prognostic covariates in MDS.

### *Blasts in bone marrow*

Five percent of blasts in BM has consistently been found to be the worst prognosis for survival and leukemic transformation in patients.[2-9] The Spanish group showed that the addition of an extra cut-point of 10%, in addition to the generally accepted 5% and 20% FAB criteria, clearly improved the prognostic val-

©Ferrata Storti Foundation

**Table 1. Prognostic factors isolated in patients with myelodysplastic syndromes.**

| *Prognostic covariate* | *Unfavorable value/s* |
|---|---|
| *Clinical* | |
| Age | > 60 years |
| Gender | Male |
| *Hematological* | |
| In peripheral blood | |
| *Platelets* | Lower counts |
| *Hemoglobin* | Lower level |
| *PMN* | Neutropenia |
| *Leukocytes* | Leukopenia or leukocytosis |
| *Blasts* | Prosence/higher percentage |
| In bone marrow | |
| *Blasts* | Higher percentage |
| *Micromegakaryocytes* | Presence |
| Degree of dysplasia | Higher (especially dysthrombopoiesis) |
| *Marrow biopsy findings* | |
| Cellularity | Hypercellularity |
| ALIP | Presence |
| Dysthrombopoiesis | Severe |
| Fibrosis | Presence |
| *Cytogenetics** | Complex/very complex |
| | Monosmy 7/del(7q) |
| *Oncogenes* | |
| N-RAS mutation | Presence |
| p53 deletion | Presence |
| *Biochemical parameters* | |
| LDH | Higher than normal |
| *Immunophenotype* | |
| $CD34^+$ cells | Higher proportion |
| Immature/mature cells ratio | Increased |
| *Marrow culture studies* | |
| Number of colonies | Lower |
| Number of clusters | Higher |
| Colony/cluster ratio | Low |
| Leukemic pattern | Presence |
| *FAB classification* | RAEB, RAEBt |
| *Etiology of MDS* | Therapy-related (secondary MDS) |

**Favorable categories are normal karyotype, del(5q) alone, del(20q) alone, and –Y alone.*

**Table 2. Incidence of most frequent chromosomal abnormalities encountered in primary myelodysplastic syndromes.**

| *Chromosomal loss or gain* | | *Translocations* | | *Deletions* | | *Others* | |
|---|---|---|---|---|---|---|---|
| –7 | 15% | t(1;3) | 1% | 5q | 27% | Inv3 | 1% |
| +7 | 5% | t(1;7) | 2% | 7q | 4% | Iso17q | 5% |
| +8 | 19% | t(3;3) | 1% | 11q | 7% | | |
| | | t(6;9) | <1% | 12q | 5% | | |
| | | | | 13q | 2% | | |
| | | | | 20q | 5% | | |
| Overall | 39% | | 5% | | 50% | | 6% |

ue of this variable.[3] This data was later confirmed by others.[2,10]

### Cytogenetics

Although a number of series had reported the prognostic impact on survival and leukemic risk of several chromosomal abnormalities, it was only recently an independent prognostic value of karyotype was demonstrated.[2,10]

Abnormal karyotypes are found in 30% to 50% of patients with primary MDS.[25] Table 2 summarizes the most common specific chromosome abnormalities encountered. In general, cases with normal karyotype have a better prognosis than cases with one or more chromosomal aberrations. The characteristic 5q– syndrome,[26] which is associated with longer survival, is an exception.[16,27] Similarly, isolated del(20q) seems to portray a good prognosis,[10,28] although that remains disputed.[29] In young patients with hypocellular BM, partial trisomy 1q seems to confer a non-aggressive clinical course.[30] Single chromosomal abnormalities with an unfavorable prognosis include +8, iso(17q), del(12p), and particularly –7 and del(7q).[10,16,17,31] The prognostic value of other single and uncommon abnormalities is still unknown and needs to be elucidated in larger series. There is a consensus that patients with complex cytogenetic aberrations have a very poor prognosis.[2,16,17,32] The frequent finding of complex chromosomal abnormalities in patients with secondary MDS could partly explain their poor outcome.[33]

Sequential cytogenetic studies are of prognostic value during follow-up. The appearance of chromosomal abnormalities in a patient with a previously normal karyotype, or the emergence of additional aberrations are associated with progression to a more aggressive FAB subtype or evolution of acute myeloid leukemia (AML) and short survival.[34,35] It may be of special value in patients with refractory anemia (RA) and RA with ringed sideroblasts (RARS).[36] However, it should be stressed that chromosomal stability does not preclude the development of AML. In fact, the majority of MDS patients do not show chromosomal changes at the time of acute leukemic transformation.[34,37]

### Cytopenias

Among peripheral blood counts, platelets and hemoglobin have a greater prognostic weight than PMN.[2,3,5,6] From the results of several studies, it is clear that the higher the severity and number of cytopenias, the worse the prognosis for survival[2,3,5-7,10] and risk of leukemic evolution.[2,3,6]

### Age

The prognostic value of age in MDS is unclear. An inverse relationship has been found between age and survival in some series.[2,3,5,6] This might reflect both a poorer tolerance to BM failure and the impact of oth-

©Ferrata Storti Foundation

**Table 3. Main scoring systems without karyotype for predicting survival in patients with myelodysplastic syndromes.**

| | *Points* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *0* | *0.5* | *1* | *1.5* | *2* | *Risk group* | *Score* |
| Bournemouth[7,48] | | | | | | | |
| Hemoglobin (g/dL) | > 10 | | ≤ 10 | | | | |
| Neutrophils ($\times 10^9$/L) | > 2.5 and ≤ 16 | | ≤ 2.5 and > 16 | | | Low risk | 0 or 1 |
| Platelets ($\times 10^9$/L) | > 100 | | < 100 | | | Intermediate | 2 or 3 |
| Marrow blasts (%) | < 5 | | > 5 | | | High | 4 |
| Spanish[3] | | | | | | | |
| Marrow blasts (%) | < 5 | | 5-10 | | 11-30 | Low (A) | 0 or 1 |
| Platelets ($\times 10^9$/L) | ≥ 100 | | 51-100 | | ≤ 50 | Intermediate (B) | 2 or 3 |
| Age (years) | ≤ 60 | | > 60 | | | High (C) | 4 or 5 |
| Goasguen[6] | | | | | | | |
| Hemoglobin (g/dL) | > 10 | | ≤ 10 | | | Low | 0 |
| Platelets ($\times 10^9$/L) | > 100 | | ≤ 100 | | | Intermediate | 1 or 2 |
| Marrow blasts (%) | < 5 | | ≥ 5 | | | High | 3 |
| Düsseldorf[5] | | | | | | | |
| Marrow blasts (%) | < 5 | | ≥ 5 | | | Low (A) | 0 |
| Platelets ($\times 10^9$/L) | > 100 | | ≤ 100 | | | Intermediate (B) | 1 or 2 |
| Hemoglobin (g/dL) | > 9 | | ≤ 9 | | | High (C) | 3 or 4 |
| LDH | ≤ 200 | | > 200 | | | | |

er old age associated disorders.[2,10] A recent study compared the mortality in a large series of MDS patients to that expected in an age- and sex-matched population.[39] The results of this study showed that the less favorable outcome for older and male MDS patients reflected a characteristic of the population rather than a more aggressive clinical course. The adverse prognosis for patients over 60 years of age was mainly noted in low-risk patients, but these patients had a lower mortality than younger patients in each risk group.[39] This study emphasizes the importance of performing both survival and mortality analysis when evaluating prognosis in MDS.

### *FAB classification*

The value of the FAB classification with regard to prognosis has several drawbacks: 1) it only distinguishes two risk groups: RA plus RARS (low-risk) and RAEB plus RAEB in transformation (RAEBT) (high-risk);[2,3,11] 2) probably due to differences in diagnostic criteria, unlikely prognosis of CMML patients has been reported; 3) in RARS, the Düsseldorf group has demonstrated clear-cut differences in the outcome between cases with pure sideroblastic anemia, which is confined to dyserythropoiesis, and patients with dysmyelopoiesis, dysthrombopoiesis or both (true RARS);[40] and 4) there are significant differences in survival and leukemic risk among patients belonging to the same FAB subtype. This proves that the FAB classification is not accurate for predicting outcome in an individual patient.

### *Other prognostic factors*

Males carried a poorer prognosis in some series.[2,3,10] This finding may be explained, to some extent by the higher life expectancy of females in industrialized countries.[10,39] The number or proportion of blasts in PB is invariably associated with prognosis, both in terms of survival[2-4,8,11,41] and risk of leukemic transformation.[2,3] In our series,[3] patients with blasts in PB had an actuarial median survival of 6 months, very similar to the expected outcome for untreated patients with AML. The close association between the proportion of blasts in PB and BM explains why the former do not have an independent value when tested in multivariate fashion.[3] Other PB characteristics occasionally related to survival are the presence of immature myeloid precursors and nucleated RBC.[3] The degree of dyshematopoiesis, especially the presence of dysmegakaryopoiesis and dysgranulopoiesis, had a prognostic impact in some series of MDS patients,[3,42,43] and may be used to segregate patients with RA[44] and RARS[40] into two risk groups. Nonetheless, subjectivity inherent to the evaluation of dyshematopoiesis limits the usefulness of this variable.[45] A German study has pointed out a strong relationship between LDH level and survival.[5] LDH level may well represent a measure of ineffective hematopoiesis and leukemic burden by reflecting an increased cell turnover. Some BM biopsy findings, such as abnormal location of immature myeloid precursors (ALIP), hypercellularity and fibrosis are related to poor outcome in MDS.[12-14] In fact, a prognostic scoring system

©Ferrata Storti Foundation

**Table 4. Main scoring systems with karyotype for predicting outcome in patients with myelodysplastic syndromes.**

| | *Points* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *0* | *0.5* | *1* | *1.5* | *2* | *Risk group* | *Score* |
| Lille[2]→ | | | | | | | |
| Marrow blasts (%) | < 5 | | 5-10 | | 11-30 | Low | 0 |
| Karyotype* | Good | | Poor | | | Intermediate | 1 or 2 |
| Platelets (x$10^9$/L) | > 75 | | < 75 | | | High | 3 or 4 |
| International (IPSS)[10] | | | | | | Low | 0 |
| Marrow blasts (%) | < 5 | 5-10 | | 11-20 | 21-30 | Intermediate 1 | 0.5-1 |
| Karyotype@ | Good | Intermediate | Poor | | | Intermediate 2 | 1.5-2 |
| Cytopenias# | 0 or 1 | 2 or 3 | | | | High | 2.5-3.5 |

*→ For leukemic risk, only blasts in bone marrow and karyotype are considered. *Good: normal, single abnormalities. Poor: complex (> 2) abnormalities; @Good: normal, del(5q) only, del(20q) only, –Y only; Poor: very complex (>2) abnormalities, chromosome 7 anomalies; Intermediate: other abnormalities. #Cytopenias: hemoglobin <10 g/dL, platelets <100×$10^9$/L, neutrophils < 1.8×$10^9$/L.*

for MDS patients built only with BM biopsy parameters was found to be valuable.[15]

The presence of N-RAS mutations has been associated with shorter survival and higher leukemic risk after stratifying for proportion of BM blasts,[18] but this finding awaits confirmation. The poor outcome of patients with p53 mutations is thought to be dependent on the higher incidence of advanced MDS FAB subtypes and complex karyotypes in these cases.[25,46] MDS secondary to chemo-radiotherapy are known to have a much shorter survival than primary MDS, probably due to their association with unfavorable chromosomal abnormalities, myelofibrosis, ALIP and CD34 positivity by immunostaining.[33-47] The independent prognostic value of all these clinical, biological and molecular characteristics remains unproved.

## Prognostic scoring systems

As a result of wide research on prognostic factors several scoring systems have been developed. Tables 3 and 4 offer the reader the most relevant and commonly used.

### *Scoring systems without karyotype*

In the Bournemouth score, the first proposed scoring system for MDS, patients are assigned to one of three risk groups based on the number of cytopenias present and the proportion of blasts in BM.[7] This score was built by univariate methodology, but its good performance has been confirmed by others.[3] The excessive importance of blood cytopenias in comparison with the proportion of blasts in BM is the main criticism of this system.[3] In order to give a better prediction in CMML, this system was slightly modified by adding leukocytosis as an adverse characteristic.[48] The scoring system proposed by the Spanish group uses the proportion of BM blasts, platelet count (both variables with two cut-off) and age.[3] This score was developed by multivariate methods and validated in a test set of patients. Similar to the Bournemouth score, this system is also easy to use and has demonstrated proper prediction of survival in other series.[49] Furthermore, this score was also useful in MDS patients treated with granulocyte colony-stimulating factor (G-CSF)[50] or AML-type chemotherapy.[51] The inclusion of age in this scoring system is controversial for two reasons. First, the prognostic impact of age partly reflects a general characteristic of the population.[39] Secondly, it may be troublesome for selecting therapy (i.e. older patients, who are less able to tolerate aggressive treatments, score higher than younger ones). Exclusion of age from this scoring system does not affect its predictive power (unpublished data). For leukemic transformation, no model was offered because the proportion of type I blasts in BM was sufficiently predictive of the leukemic risk, being the only variable selected by the multivariate procedure.[3] The Goasguen score[6] uses only two cytopenias (hemoglobin and platelets) and blasts in BM, and the Düsseldorf score includes these same variables and LDH serum level.[5] Although the independent weight of LDH has not been proved in other series,[3] this system has the advantage of defining a low-risk group, albeit small (16%), which portrays very good prognosis (91% two-year survival).

### *Scoring systems with karyotype: the International Prognostic Scoring System*

Several early studies utilized cytogenetics for characterizing individuals with MDS.[2,16,32,52] However, these studies had somewhat limited numbers of patients, particularly those with uncommon karyotypic abnormalities, making it difficult to clearly define the prognostic implications of a number of these aberrations. In addition, these investigations did not directly determine the possible independent prognostic abilities of the chromosomal abnormalities in comparison with other critical clinical variables, nor did they assess the relative contribution of

©Ferrata Storti Foundation

these parameters to clinical outcome.

To attempt to improve the clinical and prognostic utility of these systems and to develop a consensus prognostic risk-based analysis system, an *International MDS Risk Analysis Workshop* was convened. In this Workshop, cytogenetic, morphologic and clinical data were combined and collated from a relatively large group of patients with primary MDS from seven participating institutions whose previously reported studies utilized independent risk-based prognostic systems.[2,3,5,7,32,50,53] The combined data obtained from these patients were centrally analyzed and a global analysis performed (816 patients were evaluated for survival, 759 of whom were also evaluated for AML evolution). Critical prognostic variables were then re-evaluated using this data set to generate a prognostic system, particularly using a more refined marrow cytogenetic classification combined with relevant clinical parameters. This recently reported study[10] achieved a number of goals: 1) obtained a database from a large representative group of well-defined untreated primary MDS patients with prolonged follow-up; 2) refined the marrow cytogenetic subgroups evaluated; 3) statistically combined defined major clinical and cytogenetic parameters for evaluating clinical outcomes; 4) defined and weighted prognostic risk categories utilising multivariate analyses; 5) generated an *International Prognostic Scoring System* (IPSS) for MDS based on these findings; and 6) compared this IPSS with prior classification methods, showing it to have improved prognostic ability.

The *International Workshop* patients who had received prior short courses of low dose oral chemotherapy or hemopoietic growth factor exposure were included in the analysis, whereas those who had received intensive chemotherapy or bone marrow transplantation were excluded. Cytopenias were defined as: hemoglobin of < 10 gm/dL, ANC < 1,800/mm$^3$, and platelets < $100\times10^9$/L. Marrow morphology was evaluated by each institution utilizing the FAB classification system.[1] In this study, patients with CMML were sub-divided into *proliferative* and *non-proliferative* sub-types. *Proliferative type* CMML (i.e., patients with white blood count >$12\times10^9$/L) were excluded from this analysis as these individuals were believed to predominantly represent myeloproliferative disorders rather than MDS.[54] *Non-proliferative* CMML patients had WBCs ≤ $12\times10^9$/L as well as other features of MDS, and were included in this analysis. For marrow cytogenetic categorization, patients were divided into those with normal karyotypes or with single recurring abnormalities, double, or complex (i.e., ≥ 3 anomalies) recurring or miscellaneous (non-recurring) abnormalities. The criteria defined by the *International System for Human Cytogenetic Nomenclature* (ISCN), 1995[55] were used for identification of abnormal clones. The individual cytogenetic abnormalities were classified according to one of 12 different cytogenetic categories and subsequently, based on outcome analyses, patients were placed into *good*, *intermediate* and *poor risk* subgroups.

Univariate analysis of the MDS Workshop patients demonstrated that the major features predictive of AML evolution were FAB classification, percentage of marrow blasts (four categories: 0-5, 6-10, 11-20, 21-30%), cytogenetic pattern and number of cytopenias; for survival, the same variables, plus age and sex were found to be important. These data showed relatively poorer prognoses for patients with RAEB or RAEB-T, >10% marrow blasts, 2-3 cytopenias and for those with poor risk cytogenetics; patients > 60 years and males had poorer survival than younger or female patients. Regarding both AML evolution and survival, patients with marrow karyotypes which were normal, del(5q), del(20q) and –Y had relatively good prognoses (70%) whereas relatively poor prognoses were present in patients with complex abnormalities (i.e., ≥ 3 anomalies) or chromosome 7 or chromosomes anomalies (16%). The remaining patients were *intermediate* in outcome (14%). Of the patients in the *complex* category, the vast majority had chromosome 5 and/or 7 abnormalities in addition to other anomalies (Figure 1).

Using proportional hazards regression multivariate analysis, the most significant independent variables for determining outcome for both survival and AML evolution were marrow blast percentage, number of cytopenias, and cytogenetic subgroup (i.e., *Good, Intermediate, Poor*). Risk scores for each significant variable were generated with weighting relative to the statistical power (i.e., utilizing coefficients from the proportional hazards regression analysis) and an *International Prognostic Scoring System* (IPSS) for MDS was developed. The risk scores for marrow blast percentage, cytogenetic subgroup and number of cytopenias were evaluated and the weighted scores are shown in Table 4. By combining the risk scores for these three major variables, patients were stratified into four distinctive risk groups regarding both survival and AML evolution, with their risk scores being: Low = 0, Intermediate-1 (INT-1) = 0.5-1.0, Intermediate-2 (INT-2) = 1.5-2.0, High = ≥ 2.5. Figure 2 shows the Kaplan-Meier curves depicting survival and freedom from AML times for patients in these prognostic sub-groups. Much less precise discrimination between the four subgroups occurred when either cytopenias or cytogenetic subtypes were omitted from the classification.

By evaluating a relatively large group of patients, this study permitted risk-related analysis of a greater number of cytogenetic subgroups regarding survival and AML evolution, particularly for those chromosomal abnormalities which were relatively uncommon. Regarding the specific abnormalities defined prognostically, this study demonstrated that patients with del(20q) only, del(5q) only, –Y or normal karyotypes had improved outcomes. These findings regarding del(20q) as the sole abnormality are similar to those

Ospedale Storti Foundation

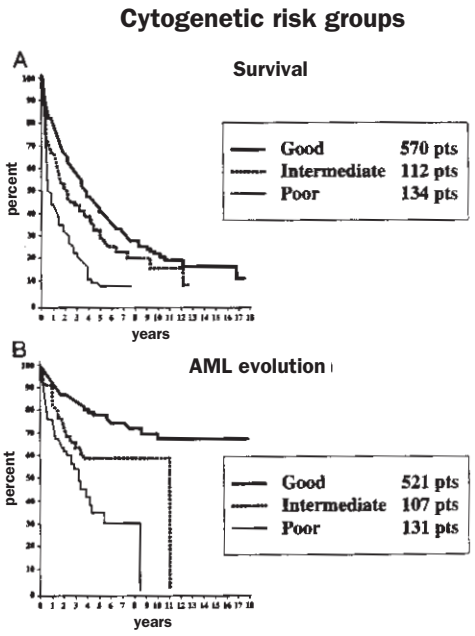


**Figure 1. Survival (top) and freedom from AML evolution (bottom) of myelodysplastic syndrome patients related to their risk-based categorical cytogenetic subgroups: good, intermediate and poor. Good = normal, del(5q) only, del(20q) only, –Y only; poor = complex (ie, ≥ 3 anomalies), chromosome 7 abnormalities; intermediate = other abnormalities (Kaplan-Meier curves). Reprinted with permission from reference #10.**

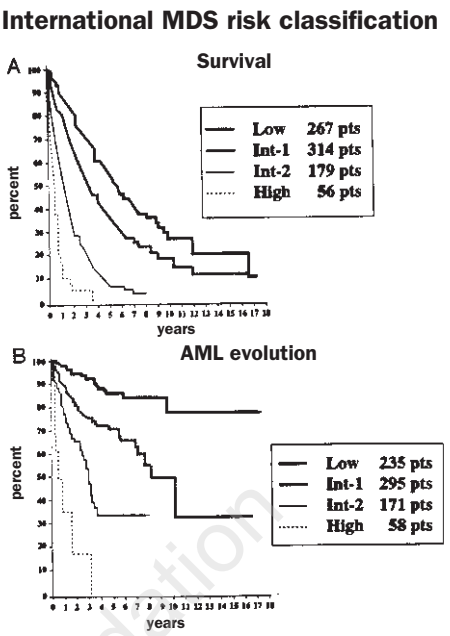


**Figure 2. Survival (top) and freedom from AML evolution (bottom) of myelodysplastic syndrome patients related to their classification by the *International Prognostic Scoring System* (IPSS) for MDS: Low, INT-1, INT-2, high (Kaplan-Meier curves). Reprinted with permission from reference #10.**

recently reported for a smaller group of MDS patients.[28] Of note are the results of a recent report in which most MDS patients with a del(20q) had complex karyotypes, an advanced MDS stage or AML, and a poor prognosis.[29] Together, these data suggest that the del(20q) may be associated with a favorable outcome when noted as a sole abnormality, but with a less favorable prognosis in the setting of a complex karyotype. As described below, this phenomenon is analogous to that observed with the del(5q).

Patients with del(5q) as the sole karyotypic abnormality have previously been well defined as having relatively good prognoses, whereas poor prognoses were found when it was combined with other anomalies.[26,42,52,56] Loss of the Y chromosome in elderly males has been described in the marrow of patients with hematologic malignancies, but this abnormality has also been noted in marrow samples from hematologically normal elderly males.[57] Thus, this finding alone does not indicate the presence of a myeloid clonal hemopathy. However, once the diagnosis is established by other means, our findings indicated that this feature conferred an improved clinical outcome. Conversely, chromosome 7 anomalies and complex cytogenetic abnormalities (variously defined) have previously been associated with poor prognoses.[16,42,52,58] In this series, the vast majority of patients in this group had abnormalities of chromosomes 5, 7 or both, together with other abnormalities. Multiple clones were common in this group, reflecting genetic instability. The presence of abnormalities of chromosomes 5 and 7 has been associated with poor outcomes in MDS and AML.[2,16,32,42,52,58] Other anomalies were associated with intermediate risk. This study demonstrated similar karyotypic prognostic findings of these cytogenetic abnormalities in MDS patients to those reported in several smaller groups of MDS patients, many of whom were included in this analysis.[2,32] The data from this study confirm these findings and extend their prognostic utility by using a more extensive karyotypic analysis and by combining such biological parameters with clinical features to provide a risk scoring system. These cytogenetic correlative findings also suggest that genomic instability and biologically important genes may be present on these chromosomes which alter survival and the potential for leukemic evolution in MDS patients.

The importance of karyotypic analysis has been further demonstrated. When cytogenetics were omitted from the MDS Workshop analysis, relatively poorer discrimination of clinical outcome occurred.[59] In this analysis, a substantial proportion of IPSS INT-1 and INT-2 patients would have been inaccurately categorized as low risk had cytogenetics not been included.

©Ferrata Storti Foundation

In addition, cytogenetics are potentially helpful in distinguishing patients who are likely to have evolving AML, rather than the more indolent MDS. A number of studies indicate that certain types of cytogenetic abnormalities, particularly recurring translocations, are rarely seen in MDS,[2,16,32,42,60-63] but are not uncommon in AML,[64-66] i.e., trisomy 21, t(8;21) or 11q abnormalities. Examination of the *International Workshop* data also indicated a very low incidence of these abnormalities in MDS.[10,67] However, prior reports of some patients considered to have *MDS* had these cytogenetic abnormalities.[68,69] These features suggest that some of these patients may have represented evolving AML rather than MDS. Consistent with this thesis is the recent report indicating that t(8;21) *myelodysplasia* is an early presentation of M2 AML, with rapid clinical progression.[70] Further studies are needed to determine the biological mechanisms underlying the relatively indolent pace of MDS and its distinction from AML.

As age at diagnosis was shown to be an important variable for survival in the International Workshop, patients and the vast majority of primary MDS patients are elderly, age-stratified morbidity and mortality figures were utilized in the IPSS regarding their clinical outcomes. Data regarding age-related outcomes of the individuals in the IPSS showed that marked differences were apparent in survival for patients in the low and INT-1 subgroups, but not in the INT-2 or high subgroups (Figure 3); for the patients in the former subgroups poorer prognosis were demonstrated in the relatively elderly cohorts of patients (i.e., > vs. ≤ 60 years, > vs. ≤ 70 years). Coexisting diseases in the elderly patients contribute substantially to their poorer survival. These data are similar to those recently reported which further indicates the prognostic importance of age for survival in patients with MDS.[39] Thus, to provide insights into disease-specific vs. age-related impact on survival, age-stratified and normalized evaluations are needed to aid decision-making regarding patient management.

**Table 5. Prognostic factors after AML-type chemotherapy in patients with myelodysplastic syndromes.**

| *Characteristic* | *Favorable value* |
|---|---|
| Age | Younger |
| ECOG performance score | ≤ 2 |
| Gender | Female |
| Interval diagnosis-treatment | Shorter |
| FAB subtype | RAEBT |
| Auer rods | Presence |
| Cytogenetics | Normal |
| p53 deletion | Absence |
| *mdr* phenotype | Absence |

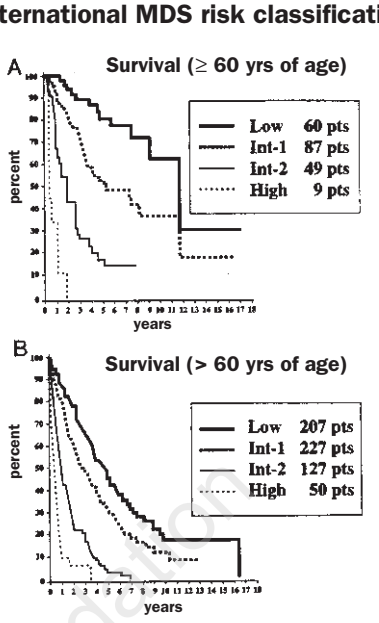


**Figure 3. Survival, based on ages ≤ 60 years old (top) vs > 60 years old (bottom), of myelodysplastic syndrome patients related to their classification by the *International Prognostic Scoring System* (IPSS) for MDS: Low, INT-1, INT-2, High (Kaplan-Meier curves). Reprinted with permission from reference #10.**

The IPSS was compared to other MDS prognostic systems to determine their relative discriminatory abilities for assessing disease natural history. Thus, patients were analyzed for clinical outcomes based on their categorization using the FAB (i.e., based on marrow blast percentage),[1] Spanish (marrow blasts, age, platelet count),[7] and Lille (platelet count, marrow blasts, karyotype)[4] prognostic risk systems, in addition to the IPSS. The IPSS effectively discriminated between the defined subgroups of these other categorisation systems. For each of the other systems, the IPSS was able to effectively separate patients in those subgroups into more precise subgroups. For example, for the Lille system, which utilized marrow karyotype, but had only three subgroups (high, intermediate and low risk), its high risk patients were redistributed between the IPSS INT-1, INT-2 and high groups; the Lille intermediate group were separated into the IPSS high, INT-2, INT-1, and to a lesser degree into low patients, whereas its low risk patients were separated into INT-1, INT-2 and low groups. Compared with the prognostic abilities of the Lille (as well as the FAB and Spanish) systems, both for survival and AML evolution, the IPSS demonstrated statistically greater discriminating power.

Thus, these data indicated that the IPSS provided

©Ferrata Storti Foundation

an improved method for predicting survival and AML evolution in MDS compared to prior systems. This effect was due to several features of the *International Workshop* model: the more refined cytogenetic categorizations, inclusion of cytopenias, improved subdivision of marrow blast percentages, the four defined outcome sub-groups and the separate stratification for age. This classification system should improve the ability to define clinical outcome in MDS and provide a framework for future studies determining the possible role of molecular determinants (e.g., oncogenes, tumor suppressor genes, cytokine expression and responsiveness) for evaluating prognosis in this disorder. This system will likely prove useful for the design and analysis of therapeutic trials in MDS as well as aiding in management of these patients.

### *Limitations of prognostic scoring systems*

All of the above scoring systems are extremely useful in defining the outcome for patients with MDS and the designing accurate analyzation of therapeutic trials in MDS. Nonetheless, they have some important limitations. The first is inherent to the characteristics of the patients and the aggressive nature of the treatment modalities that are required for a complete cure of the disease. In general, the choice of treatment will depend on age and performance status rather than on prognosis. Secondly, the scoring systems, with the possible exception of the Düsseldorf score and the IPSS, are not good enough to identify the small subset of very-low-risk patients that will rarely require treatment.[49] Thirdly, the appearance of new effective therapies may render obsolete these systems. Also, the proportion of blasts in BM alone is almost as good as any of the published scoring systems for predicting the risk of leukemic transformation. Finally, the prognostic value of the number and severity of cytopenias is minor in Japanese patients.[71] Thus, the use of a score for clinical decision-making extracted from a series of Western patients would be misleading in a Japanese patient.

Scoring systems that use karyotype have additional limitations. Even in highly specialized centers, cytogenetics are not available in nearly 30-50% of patients. The results of chromosomal analysis may lead to misclassification of patients as well. In some instances a poor-prognosis abnormality may pass unnoticed and, consequently, the case being erroneously assigned to a wrong prognostic category. Lastly, single chromosomal abnormalities that are classified at present as having intermediate prognosis may well prove in the future to be of good or poor prognosis.

## Prognostic factors in childhood MDS

The prognostic scoring systems outlined above are thought to be inadequate in childhood MDS.[72-74] A scoring system for pediatric MDS, that includes as adverse factors HbF >10%, platelet count $\leq 40\times10^9$/L and complex karyotype has been recently proposed.[74] In juvenile myelomonocytic leukemia, age at diagnosis between 6 and 24 months, thrombocytopenia, hepatosplenomegaly, and high blast cell and normoblast counts in PB are predictors of a poor outcome.[73]

## Prognostic factors in chronic myelomonocytic leukemia

The prognostic factors in CMML are those that reflect the severity of the maturation arrest of hematopoietic precursors, such as proportion of blasts in PB and BM, hemoglobin level and platelet count, or the degree of myeloid proliferation, such as leukocyte and monocyte counts, presence of immature myeloid and erythroid precursors in PB, splenomegaly and lysozimuria.[75-78] Certain chromosomal anomalies may also be relevant.[76] The most important prognostic factor for acute leukemic transformation is the proportion of blasts in BM.[76]

## Prognostic factors related to treatment outcome

Some series have shown better results after low-dose cytarabine in patients with a normal platelet count, absence of ringed sideroblasts, hypocellular bone marrow, less than two chromosomal abnormalities, and RAEBT.[79]

Several factors have been associated with a higher complete remission (CR) rate after intensive antileukemic chemotherapy (Table 5). Among them, the most important appear to be younger age, RAEBT subtype, a short interval between diagnosis and treatment, presence of Auer rods, and a normal karyotype.[80-84] In fact, the combination of RAEBT and younger age[83] or a normal karyotype[82] defines a particularly favorable subset of MDS patients, with CR rates similar to those obtained in patients with de novo AML. Data from a recent study support that a diagnosis of RAEB or RAEBT does not constitute per se a deterrent to standard AML therapy.[85]

Allogeneic bone marrow transplantation (BMT) remains the only therapeutic approach with a demonstrated curative potential in MDS. Patients with excess of blasts in marrow (RAEB and RAEBT) clearly have a higher relapse risk (RR) and a lower disease-free survival (DFS) after allogeneic BMT than patients with a lower proportion of marrow blasts.[86-89] The presence of chromosomal abnormalities adversely affects both the RR[89,90] and DFS.[89,91,92] Thus, the IPSS should also have a major prognostic relevance in patients with MDS who undergo allogeneic BMT. Younger patients have a higher DFS not only due to a lower transplant-related mortality,[86,89] but also due to a lower RR.[86,88] A shorter disease duration before allogeneic BMT has also been related to a better outcome.[86,89,93,94] In allogeneic BMT from unrelated donors, younger age, RAEB or AML before BMT and use of TBI-containing regimens were associated with RR, and advanced age and longer disease duration negatively affected TRM,

©Ferrata Storti Foundation

but no factor was clearly associated with DFS.[95]

It can be noted that many of the prognostic characteristics after different treatment modalities are the same that are operative in untreated MDS patients.

## Conclusions

The vast research focusing on prognostic factors over the last two decades has resulted in the publication of several prognostic scoring systems, among them the IPSS, that accurately predict outcome in the individual patient with MDS. The IPSS, or other scoring systems with a proven prognostic value in independent series,[96] should be used in the clinical practice both for selecting the best risk-based therapy and for designing and analyzing clinical trials. Unfortunately, in many instances other characteristics such as advanced age, poor performance status or presence of unrelated disorders will limit the applicability of prognostic scoring systems. Nevertheless, their use should be regarded as a great step beyond for the selection and delivery of a better and more rationale therapy in MDS.

### *Contributions and Acknowledgments*

*The three authors equally contributed to this article.*

### *Disclosures*

*Conflict of interest: none.*

*Redundant publications: no substantial overlapping with previous papers.*

### *Manuscript processing*

*Manuscript received December 4, 1997; accepted January 26, 1998.*

## References

1. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982; 51:189-99.
2. Morel P, Hebbar M, Lai JL, et al. Cytogenetic analysis has strong independent prognostic value in *de novo* myelodysplastic syndromes and can be incorporated in a new scoring system: a report on 408 cases. Leukemia 1993; 7:1315-23.
3. Sanz GF, Sanz MA, Vallespí T, et al. Two regression models and a scoring system for predicting survival and planning treatment in myelodysplastic syndromes: a multivariate analysis of prognostic factors in 370 patients. Blood 1989; 74:395-408.
4. Coiffier B, Adeleine P, Gentilhomme O, Felman P, Treille-Ritouet D, Bryon PA. Myelodysplastic syndromes. A multiparametric study of prognostic factors in 336 patients. Cancer 1987; 60:3029-32.
5. Aul C, Gatterman N, Heyll A, Germing U, Derigs G, Schneider W. Primary myelodysplastic syndromes: analysis of prognostic factors in 235 patients and proposals for an improved scoring system. Leukemia 1992; 6:52-9.
6. Goasguen JE, Garand R, Bizet M, et al. Prognostic factors of myelodysplastic syndromes-A simplified 3-D scoring system. Leuk Res 1990; 14:255-60.
7. Mufti GJ, Stevens JR, Oscier DG, Hamblin TJ, Machin D. Myelodysplastic syndromes: a scoring system with prognostic significance. Br J Haematol 1985; 59:425-33.
8. Tricot G, Vlietinck R, Boogaerts MA, et al. Prognostic factors in the myelodysplastic syndromes: importance of initial data on peripheral blood counts, bone marrow cytology, trephine biopsy and chromosomal analysis. Br J Haematol 1985; 60:19-32.
9. Coiffier B, Adeleine P, Viala JJ, et al. Dysmyelopoietic syndromes. A search for prognostic factors in 193 patients. Cancer 1983; 52:83-90.
10. Greenberg P, Cox C, Lebeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997; 89:2079-88.
11. Kerkhofs H, Hermans J, Haak HL, Leeksma CHW. Utility of the FAB classification for myelodysplastic syndromes: investigation of prognostic factors in 237 cases. Br J Haematol 1987; 65:73-81.
12. Mangi MH, Mufti GJ. Primary myelodysplastic syndromes: diagnostic and prognostic significance of immunohistochemical assessment of bone marrow biopsies. Blood 1992; 79:198-205.
13. Sultan C, Sigaux F, Imbert M, et al. Acute myelodysplasia with myelofibrosis: a report of eight cases. Br J Haematol 1981; 49:11-6.
14. Ríos A, Cañizo MC, Sanz MA, et al. Bone marrow biopsy in myelodysplastic syndromes: morphological characteristics and contribution to the study of prognostic factors. Br J Haematol 1990; 75:26-33.
15. Maschek H, Gutzmer R, Choritz h, Georgii A. Life expectancy in primary myelodysplastic syndromes: a prognostic score based upon histopathology from bone marrow biopsies in 569 patients. Eur J Haematol 1994; 53:280-7.
16. Yunis JJ, Lobell M, Arnesen MA, et al. Refined chromosome study helps define prognostic subgroups in most patients with primary myelodysplastic syndromes and acute myelogenous leukaemia. Br J Haematol 1988; 68:189-94.
17. Billström R, Thiede T, Hansen S, et al. Bone marrow karyotype and prognosis in primary myelodysplastic syndromes. Eur J Haematol 1988; 41:341-6.
18. Paquette RL, Landau EM, Pierre RV, et al. N-ras mutations are associated with poor prognosis and increased risk of leukemia in myelodysplastic syndrome. Blood 1993; 82:590-9.
19. Greenberg PL. *In vitro* culture techniques defining biologic abnormalities in the myelodysplastic syndromes and myeloproliferative disorders. Clin Haematol 1986; 15:973-93.
20. Raymakers R, De Witte T, Loziasse J, et al. *In vitro* growth pattern and differentiation predict for progression of myelodysplastic syndromes to acute nonlymphocytic leukaemia. Br J Haematol 1991; 78:35-41.
21. Oscier DG, Worsley A, Darlow S, Figes A, Williams JD, Hamblin TJ. Correlation of bone marrow colony growth in the myelodysplastic syndromes with the FAB classification and the Bournemouth score. Leuk Res 1989; 13:833-9.
22. Tennant GB, Bowen DT, Jacobs A. Colony-cluster ratio and cluster number in cultures of circulating myeloid progenitors as indicators of high-risk myelodysplasia. Br J Haematol 1991; 77:296-300.
23. Kristensen JS, Hokland P. Monoclonal antibody ratios in malignant myeloid diseases: diagnostic and prognostic use in myelodysplastic syndromes. Br J Haematol 1990; 74:270-6.
24. Mittelman M, Karcher DS, Kammerman LA, Lessin LS. High Ia (HLA-DR) and low CD11b (Mo1) expression may predict early conversion to leukemia in myelodysplatic syndromes. Am J Hematol 1993; 43:165-71.

©Ferrata Storti Foundation

25. Fenaux P, Morel P, Lai JL. Cytogenetics in myelodysplastic syndromes. Semin Hematol 1996; 33:127-38.
26. Van Den Berghe H, Vermaelen K, Mecucci C, et al. The 5q- anomaly. Cancer Genet Cytogenet 1985; 17: 189-255.
27. Third MIC Cooperative Study Group. Recommendations for a morphologic, immunologic and cytogenetic (MIC) working classification of the primary and therapy-related myelodysplastic disorders. Report of the workshop held in Scottsdale, Arizona, USA, on February 23-25, 1987. Cancer Genet Cytogenet 1988; 32:1-10.
28. Wattel E, Laï JL, Hebbar M, et al. *De novo* myelodysplastic syndrome (MDS) with deletion of the long arm of chromosome 20: a subtype of MDS with distinct hematological and prognostic features? Leuk Res 1993; 17:921-6.
29. Campbell LJ, Garson OM. The prognostic significance of deletion of the long arm of chromosome 20 in myeloid disorders. Leukemia 1994; 8:67-72.
30. Fonatsch C, Haase D, Freund M, Bartels, Tesch H. Partial trisomy 1q. A nonrandom primary chromosomal abnormality in myelodysplastic syndromes? Cancer Genet Cytogenet 1991; 56:243-53.
31. Heim S, Mitelman F. Chromosome abnormalities in the myelodysplastic syndromes. Clin Haematol 1986; 15:1003-21.
32. Toyama K, Ohyashiki K, Yoshida Y, et al. Clinical implications of chromosomal abnormalities in 401 patients with myelodysplastic syndromes: a multicentric study in Japan. Leukemia 1993; 7:499-508.
33. Pedersen-Bjergaard J, Philip P, Larsen SO, Jensen G, Byrsting K. Chromosome aberrations and prognostic factors in therapy-related myelodysplasia and acute nonlymphocytic leukemia. Blood 1990; 76:1083-91.
34. Tricot G, Boogaerts MA, De Wolf-Peeters C, Van Den Berghe H, Verwilghen RL. The myelodysplastic syndromes: different evolution patterns based on sequential morphological and cytogenetic investigations. Br J Haematol 1985; 59:659-70.
35. White AD, Culligan DJ, Hoy TG, Jacobs A. Extended cytogenetic follow-up of patients with myelodysplastic syndrome. Br J Haematol 1992; 81:499-502.
36. Ghaddar HM, Stass SA, Pierce S, et al. Cytogenetic evolution following the transformation of myelodysplastic syndrome to acute myelogenous leukemia associated with a preleukemic syndrome. J Clin Oncol 1989; 7:1637-45.
37. Benitez J, Carbonell F, Sanchez-Fayos J, Heimpel H. Karyotypic evolution in patients with myelodysplastic syndromes. Cancer Genet Cytogenet 1985; 16:157-67.
38. Sanz GF, Sanz MA. Prognostic factors in myelodysplastic syndromes. Leuk Res 1992; 16:77-86.
39. Morel P, Declercq C, Hebbar M, Bauters F, Fenaux P. Prognostic factors in myelodysplastic syndromes: critical analysis of the impact of age and gender and failure to identify a very-low-risk group using standard mortality ratio techniques. Br J Haematol 1996; 94: 116-9.
40. Gattermann N, Aul C, Schneider W. Two types of acquired idiopathic sideroblastic anemia (AISA). Br J Haematol 1990; 74:45-52.
41. Foucar K, Langdon RM, Armitage JO, Olson DB, Carroll TJ. Myelodysplastic syndromes: a clinic and pathologic analysis of 109 cases. Cancer 1985; 56:553-61.
42. Jacobs RH, Cornbleet MA, Vardiman JW, Larson RA, Le Beau MM, Rowley JD. Prognostic implications of morphology and karyotype in primary myelodysplastic syndromes. Blood 1986; 67:1765-72.
43. Varela BL, Chuang C, Woll JE, Bennett JM. Modifications in the classification of primary myelodysplastic syndromes. Hematol Oncol 1985; 3:55-63.
44. Rosati S, Mick R, Xu F, et al. Refractory cytopenia with multilineage dysplasia: further characterization of an "unclassifiable" myelodysplastic syndrome. Leukemia 1996; 10:20-6.
45. Sanz GF, Sanz MA, Vallespí T, del Cañizo MC. Two types of acquired idiopathic sideroblastic anaemia. Br J Haematol 1990; 75:633-4.
46. Wattel E, Preudhomme C, Hecquet B, et al. p53 mutations are associated with resistance to chemotherapy and short survival in hematologic malignancies. Blood 1994; 84:3148-57.
47. Orazi A, Cattoretti G, Solino D, et al. Therapy-related myelodysplastic syndromes: FAB classification, bone marrow histology, and immunohistology in the prognostic assessment. Leukemia 1993; 7:838-47.
48. Worsley A., Oscier DG, Stevens J, et al. Prognostic features of chronic myelomonocytic leukaemia: a modified Bournemouth score gives the best prediction of survival. Br J Haematol 1988; 68:17-21.
49. Wattel E, Hecquet B, Grahek D, et al. Long term survivors in myelodysplastic syndromes: a report on 63 cases and comparison with short and intermediate survivors. Leuk Res 1993; 17:733-9.
50. Greenberg P, Taylor K, Larson R, et al. Phase III randomized multicenter trial of G-CSF versus observation for myelodysplastic syndromes (MDS). Blood 1993; 82(suppl 1):196a.
51. Bernstein SH, Brunetto VL, Davey FR, et al. Acute myeloid leukemia-type chemotherapy for newly diagnosed patients without antecedent cytopenias having myelodysplastic syndrome as defined by French-American-British criteria: a Cancer and Leukemia Group B study. J Clin Oncol 1996; 14:2486-94.
52. Pierre RV, Catovsky D, Mufti GJ, et al. Clinical cytogenetic correlations in myelodysplasia (preleukemia). Cancer Genet Cytogenet 1989; 40:149-61.
53. Oscier D. Myelodysplastic syndromes. Bailliére's Clin Haematol 1987; 1:389-426.
54. Bennett JM, Catovsky D, Daniel MT, et al. The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Br J Haematol 1994; 87:746-54.
55. ISCN (1995). An International System for Human Cytogenetic Nomenclature. Mitelman F, ed. Basel: S. Karger, 1995.
56. Sokal G, Michaux JL, Van den Berghe H, et al. A new hematologic syndrome with a distinct karyotype: the 5q- chromosome. Blood 1975; 46:519-33.
57. United Kingdom Cancer Cytogenetics Group (UKCCG). Loss of the Y chromosome from normal and neoplastic bone marrows. Genes Chromosom Cancer 1992; 5:83-8.
58. Samuels BL, Larson RL, LeBeau MM, et al. Specific chromosomal abnormalities in acute nonlymphocytic leukemia correlate with drug susceptibility *in vivo*. Leukemia 1988; 2:79-83.
59. Greenberg P, Cox C, Bennett J. International Prognostic Scoring System and other prognostic scoring systems for myelodysplastic syndromes. Blood 1997; 90:4233-4.
60. Second International Workshop on Chromosomes in Leukemia. Chromosomes in preleukemia. Cancer Genet Cytogenet 1980; 2:108.
61. Borgstrom GH. Cytogenetics in myelodysplastic syndromes. Scand J Haematol 1986; 45(suppl):74-7.
62. Suciu S, Kuse R, Weh, et al. Results of chromosome studies and their relation to morphology, course and prognosis in 120 patients with *de novo* myelodysplastic syndrome. Cancer Genet Cytogenet 1990; 44:15-26.
63. Solé F, Prieto F, Badia L, et al. Cytogenetic studies in

©Ferrata Storti Foundation

112 cases of untreated myelodysplastic syndromes. Cancer Genet Cytogenet 1992 ; 64:12-20.
64. Kaneko Y, Naseki N, Takasaki N, et al. Clinical and hematologic characteristics in acute leukemia with 11q23 translocations. Blood 1986; 67:484-91.
65. Berger R, Flandrin G, Bernheim A, et al. Cytogenetic studies in 519 consecutive de novo acute nonlymphocytic leukemias. Cancer Genet Cytogenet 1987; 29:9-21.
66. Second MIC Cooperative Study Group. Morphologic, immunologic and cytogenetic working classification of the acute myeloid leukemias. Cancer Genet Cytogenet 1988; 30:1-15.
67. Greenberg P, Le Beau MM, Fenaux P, et al. Application of the International Prognostic Scoring System for MDS. Blood 1997; 90:2844-6.
68. Cortes J, Kantarjian H, O'Brien S, et al. Clinical and prognostic significance of trisomy 21 in adult patients with acute myelogenous leukemia and myelodysplastic syndromes. Leukemia 1995; 9:115-7.
69. Cortes J, O'Brien S, Kantarjian H, et al. Abnormalities in the long arm of chromosome 11 (11q) in patients with *de novo* and secondary acute myelogenous leukemias and myelodysplastic syndromes. Leukemia 1994; 8:2174-8.
70. Taj A, Ross F, Vickers M, et al. t(8;21) myelodysplasia, an early presentation of M2 AML. Br J Haematol 1995; 89:890-2.
71. Oguma S, Yoshida Y, Uchino H, et al. Clinical characteristics on Japanese patients with primary myelodysplastic syndromes: a co-operative study based on 838 cases. Leuk Res 1995; 19:219-25.
72. Bader-Meunier B, Mielót F, Tchernia G, et al. Myelodysplastic syndromes in childhood: report of 49 patients from a French multicenter study. Br J Haematol 1996; 92:344-50.
73. Locatelli F, Zecca M, Pession A, Maserati E, De Stefano P, Severi F. Myelodysplastic syndromes: the pediatric point of view. Haematologica 1995; 80:268-79.
74. Passmore SJ, Hann IM, Stiller CA, et al. Pediatric myelodysplasia: a study of 68 children and a new prognostic scoring system. Blood 1995; 85:1742-50.
75. Del Cañizo MC, Sanz G, San Miguel JF, et al. Chronic myelomonocytic leukemia-clinicobiological characteristics: a multivariate analysis in a series of 70 cases. Eur J Haematol 1989; 42:466-73.
76. Fenaux P, Beuscart R, Lai JL, et al. Prognostic factors in adult chronic myelomonocytic leukaemia: an analysis of 107 cases. J Clin Oncol 1988; 6:1417-24.
77. Catalano L, Improta S, de Laurentiis M, et al. Prognosis of chronic myelomonocytic leukemia. Haematologica 1996; 81:324-9.
78. Rigolin GM, Cuneo A, Roberti MG, Bardi A, Castoldi G. Myelodysplastic syndromes with monocytic component: hematologic and cytogenetic characterization. Haematologica 1997; 82:25-30.
79. Hellström-Lindberg E, Robert K-H, Gahrton G, et al. A predictive model for the clinical response to low-dose Ara-C: a study of 102 patients with myelodysplastic syndrome or acute leukaemia. Br J Haematol 1992; 81:503-11.
80. De Witte T, Muus P, De Pauw B, Haanen C. Intensive antileukemic treatment of patients younger than 65 years with myelodysplastic syndromes and secondary acute myelogenous leukemia. Cancer 1990; 66:831-7.
81. Aul C, Schneider W. Treatment of advanced myelodysplastic syndromes: trend toward more aggressive chemotherapy? Haematol and Blood Transfusion: Acute Leukemias II 1990; 33:382-6.
82. Fenaux P, Morel P, Rose C, Lai JL, Jouet JP, Bauters F. Prognostic factors in adult *de novo* myelodysplastic syndromes treated by intensive chemotherapy. Br J Haematol 1991; 77:497-501.
83. Michels S, Saumur J, Arthur D, Robinson L, Brunning R. Refractory anemia with excess of blasts in transformation. Hematologic and clinical study of 52 patients. Cancer 1989; 64:2340-6.
84. Seymour JF, Estey EH. The prognostic significance of Auer rods in myelodysplasia. Br J Haematol 1993; 85:67-76.
85. Estey E, Thall P, Beran M, Kantarjian H, Pierce S, Keating M. Effect of diagnosis (refractory anemia with excess of blasts, refractory anemia with excess of blasts in transformation or acute myeloid leukemia [AML]) on outcome of AML-type chemotherapy. Blood 1997; 90:2969-77.
86. Anderson JE, Appelbaum FR, Lloyd D, et al. Allogeneic bone marrow transplantation for 93 patients with myelodysplastic syndrome. Blood 1993; 82:677-81.
87. De Witte T, Gratwohl A. Bone marrow transplantation for myelodysplastic syndromes and secondary leukaemias. Br J Haematol 1993; 84:361-4.
88. Sutton L, Chastang C, Ribaud P, et al. Factors influencing outcome in *de novo* myelodysplastic syndromes treated by allogeneic bone marrow transplantation: a long-term study of 71 patients. Blood 1996; 88:358-65.
89. Anderson JE, Thomas DE. The Seattle experience with bone marrow transplantation (BMT) for myelodysplasia (MDS). Leuk Res 1997; 21 (suppl 1):51a.
90. Anderson JE, Appelbaum FR, Schoch G, et al. Allogeneic bone marrow transplantation for myelodysplastic syndromes with advanced disease morphology: a phase II study of busulfan, cyclophosphamide, and total-body irradiation and analysis of prognostic factors. J Clin Oncol 1996; 14:220-6.
91. Sepherd JD, Fung HC, Forrest DE, et al. Allogeneic bone marrow transplantation for adults with primary myelodysplastic syndromes: evaluation of prognostic factors. Leuk Res 1997; 21 (suppl 1): 52a.
92. Sierra J, Carreras E, Rozman C, Champlin R, Rowlings P, Horowitz M. Bone marrow transplantation for myelodysplasia: the IBMTR data. Leuk Res 1997; 21 (suppl 1):51a.
93. Anderson JE, Appelbaum FR, Schoch G, et al. Allogeneic marrow transplantation for refractory anemia: a comparison of two preparative regimens and analysis of prognostic factors. Blood 1996; 87:51-8.
94. Alessandrino EP, Astori C, Van Lint MT, et al. Myelodysplastic syndrome or leukemia developing after MDS treated by allogeneic bone marrow transplantation: outcome of 90 adult patients. Leuk Res 1997; 21 (suppl 1):52a.
95. Anderson JE, Anasetti C, Appelbaum FR, et al. Unrelated donor marrow transplantation for myelodysplasia (MDS) and MDS-related acute myeloid leukaemia. Br J Haematol 1996; 93:59-67
96. Balduini CL, Guarnone R, Pecci A, Centenara E, Ascari E. International Prognostic Scoring System and other prognostic systems for myelodysplastic syndromes. Blood 1997; 90:4232-3.

©Ferrata Storti Foundation