

Prognostic Factors in Myelodysplastic Syndromes

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ABSTRACT

Background: Myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic stem cell and are characterized by ineffective hematopoiesis with normo- or hyper cellular bone marrow and cytopenia(s). The natural evolution of the disease consists of bone marrow failure (leading to infectious and hemorrhagic episodes or anemia related complications) and transformation to acute myeloid leukemia. Because MDSs display remarkable clinical, pathologic, and cytogenetic heterogeneity, with variable evolution and survival ranging from months to years, the predictive factors of prognosis have a key role in optimal therapeutic decisions.

The purpose of this paper is to analyze prognostic factors within a group of patients diagnosed with myelodysplastic syndromes. The prognostic factors taken into account are: the number and depth of cytopenias, percentage of bone marrow blasts, cytogenetic abnormalities, intensity of anemia and transfusional dependence. These factors are related to overall survival, leukemia free survival, bone marrow failure complications, leukemic evolution, treatment decisions and the response to treatment.

Material and method: The study group comprises of 119 patients diagnosed with de novo MDS, between 2008 and 2011 in the Hematology Department of Coltea Clinical Hospital. In this monitoring period the patients were stratified according to the FAB (French-American-British) morphologic classification.

Results: This study revealed that the outcomes of patients with MDS is influenced by the percentage of bone marrow blasts at diagnosis, the number and severity of hematopoietic lineage affected by cytopenia and by the presence of chromosomal abnormalities.

Conclusions: The studied prognostic factors have predictive value in terms of survival, leukemic transformation, treatment response and development of bone marrow failure-related characteristic complications.

Keywords: IPSS, risk groups, complications

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INTRODUCTION

Patients diagnosed with myelodysplastic syndromes have a risk of disease progression to acute myeloid leukemia (AML). In some cases, MDS may gradually progress over a period of several years while in others it progresses rapidly to AML. MDS progression also occurs as bone marrow failure associated with infectious, hemorrhagic and anemia-related complications. The risk of myelodysplastic syndromes development increases with age as the disease is known to commonly affect elderly individuals over 60 years of age (1). MDS progression is assessed using the International Prognostic Scoring System (IPSS) that takes into count the percentage of bone marrow blasts, the number of cytopenias and cytogenetic abnormalities. According to these variables patients are classified into four risk subgroups: low, intermediate-1, intermediate-2 and high (2,3).

The first two subgroups, low and intermediate-1, are characterized by low risk of AML progression, prolonged survival, comorbidities accounting for 50% of deaths; in these cases the treatment aims at improving cytopenias (growth factors and transfusions).

The last two subgroups, intermediate-2 and high have a higher rate of leukemic progression and shorter survival. The treatment aims at slowing disease progression through chemotherapy and demethylating agents and even cures MDS after bone marrow transplantation.

Besides the known prognosis factors included in the IPSS, other two variables were studied: degree of anemia and RBC transfusion dependence (which reveals the severity of anemia and thus disease severity) (4,5).

There seem to be multiple anemia mechanisms in MDS: chromosomal abnormalities, mitochondrial dysfunction, acquired abnormalities of hemoglobin synthesis, abnormal expression of proinflammatory cytokines and hematopoietic growth factors (6).

The FAB classification of MDS is based on morphologic findings. Still, recurrent common chromosomal abnormalities have been identified and used in the IPSS – the most widely used prognostic scoring system. They are found in 40–70% of the de novo cases and 95% of secondary cases. These chromosomal aberrations include 5q-, 7q-/monosomy 7, trisomy 8, 20q-, deletion 12p, as well as abnormalities in 17p, 11q23, and chromosome 3 (7). Favorable

prognostic markers include: a normal karyotype, deletion 5q as an isolated anomaly, deletion 20q as an isolated anomaly, and loss of the Y chromosome. Karyotype findings associated with poor prognosis include complex karyotype and abnormalities of chromosome 7. Other cytogenetic abnormalities confer an intermediate prognosis (7,8). □

MATERIAL AND METHOD

The study group includes 119 patients diagnosed with primary and secondary MDS, according to the FAB classification, between 2008 and 2011 in the Hematology Department of Coltea Hospital, Bucharest.

The diagnosis of MDS was made after the peripheral blood and bone marrow testing revealed dysplastic changes. Confirmatory diagnostic tests included in certain cases bone marrow biopsy, karyotype analysis, cytochemical stain, immunohistochemical tests, cytologic and cytochemical study of medullar iron.

All patients were diagnosed with primary MDS. IPSS was calculated for a small percentage of patients only because in most cases we could not perform cytogenetic tests. Chromosomal analysis was performed for 13 patients using marrow aspirate and according to laboratory procedures (a minimum of 11 metaphases analyzed).

Most patients received supportive care: transfusion (packed red blood cells and platelets), red cell and granulocyte growth factors, vitamins, cortisone, iron chelators and some patients received chemotherapy. Infectious and hemorrhagic complications, bone marrow failure and leukemic transformation are considered causes of MDS-related deaths. Overall survival was estimated in months including the period from the date of diagnosis to time of death / time of last visit.

The clinical data was collected from the original patients' charts (Table 1).

Follow-up period lasted for 36 months. More than half of the 119 analyzed patients were diagnosed with low risk subtypes (RA and RARS) (Figure 1). Of all patients, 33 (27%) progressed to AML. A number of 83 (70%) patients died due to MDS-related causes, while 22 (30%) of the patients died of AML.

Statistical analysis

The statistical analysis was performed on the personal computer, using SPSS 16.0 soft-

ware for Windows. For the parameters or variables used in this paper, the range, mean and standard deviation, coefficient of variation and standard error were presented. We used the Kolmogorov-Smirnov and Shapiro-Wilk tests, rejecting that the assumption of normality was determined by values of $p < 0.05$. The determinations of correlations between different studied variables was based on the Pearson correlation coefficient in all cases where the variables had a normal distribution, and a certain correlation was considered statistically significant if $p < 0.05$. □

RESULTS

Anemia is the main clinical manifestation in myelodysplastic syndromes. More than half of the patients diagnosed with *de novo* low-risk or high risk MDS had hemoglobin levels < 10 g/dl (83.2%) at diagnosis.

The patients were grouped in two categories according to the severity of anemia: moderate anemia (Hb 7-10 g/dl) and severe anemia (Hb < 7 g/dl). Overall survival at 36 months was higher in patients with moderate anemia and lower for severe anemia respectively, with a $p=0.032$ (Figure 2). Few patients presented with Hb > 10 g/dl and were not included in the analysis.

Therapeutic failure was seen in the group of patients with Hb values < 10 g/dl but significantly different in the group of patients with severe anemia and Hb < 7 g/dl ($p=0.044$). In the mild anemia group the therapeutic failure rate was 32.8% of patients while in severe anemia patients it reached 28.6%. There is a significant difference among patients with severe anemia (**Pearson chi-square=6.32 p=0.004**) (Figure 3).

Transfusion dependence. Red blood cell (RBC) transfusions are a commonly used therapy to treat symptomatic anemia that affects most patients with myelodysplastic syndromes. Transfusion dependence is defined by the MDS International Group (2000) study as requiring transfusion of at least one packed red blood cells at 8 weeks for 4 months (9).

Packed red blood cells transfusion-dependent patients have a shorter survival rate than those who received less than 18 units of blood over a period of 36 months with a significant difference ($p=0.0001$).

Average survival of patients who are transfusion dependent is 10.74 months while the ave-

rage survival in non-transfusion dependent patients is 23.83 months, the difference being statistically significant ($F = 5.73, p = 0.0001$) (Figure 4).

Percentage of bone marrow blasts

Overall survival and leukemia free survival correlated with the percentage of marrow blasts wasn't significantly different.

Baseline characteristics			
Gender	n (%)	Male	67 (56.3)
		Female	52 (43.7)
Age (years)	n +/- std. dev	71	+/-10.13
Demography	n (%)	Rural	86 (72.3)
		Urban	33 (27.7)
FAB	n (%)	RA	50 (42)
		RAEB	21 (17.6)
		RAEBt	20 (16.8)
		RARS	21 (17.6)
		CMML	7 (5.9)
Hb	n (%)	10-12	20 (16.8)
		7-10	57 (47.9)
		< 7	42 (35.3)
Percentage of bone marrow blasts	mean +/- std. dev	6.31	+/-1.78
Number of BM dysplastic lineages	n (%)	0	1 (0.8)
		1	34 (28.6)
		2	40 (33.6)
		3	44 (47)
Cytogenetic groups	n (%)	Good	9(7.6)
		Intermediate	2(1.7)
		Poor	2(1.7)

TABLE 1. Clinical, demographic and biologic/cytogenetic data.

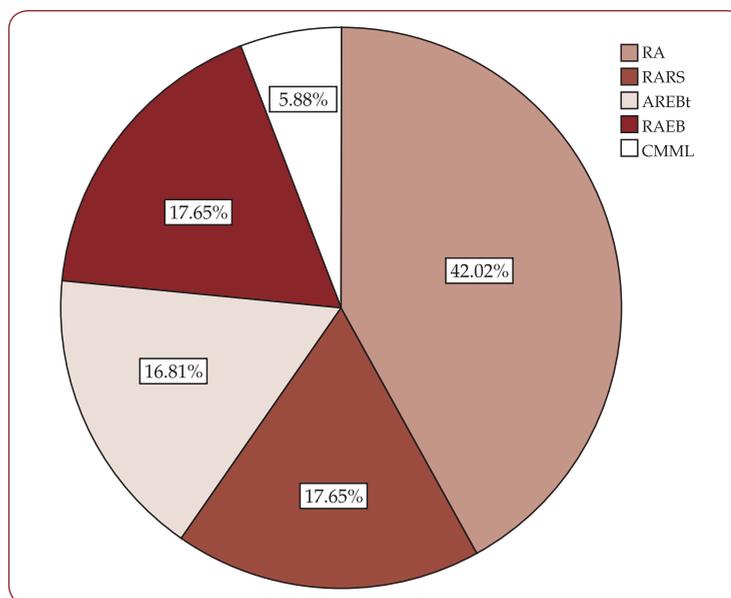


FIGURE 1. Distribution of patients according to the FAB classification (RA-refractory anemia; RARS-refractory anemia with ringed sideroblasts; RAEB-refractory anemia with excess of blasts; RAEBt-refractory anemia with excess of blasts in transformation; CMML-chronic myelomonocytic leukemia).

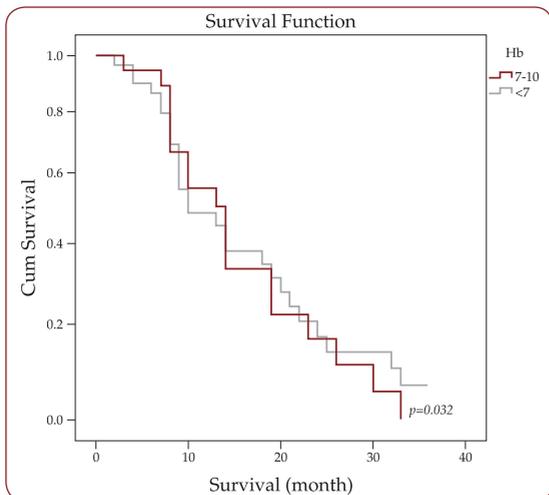


FIGURE 2. Survival (in months) in patients classified according to hemoglobin levels.

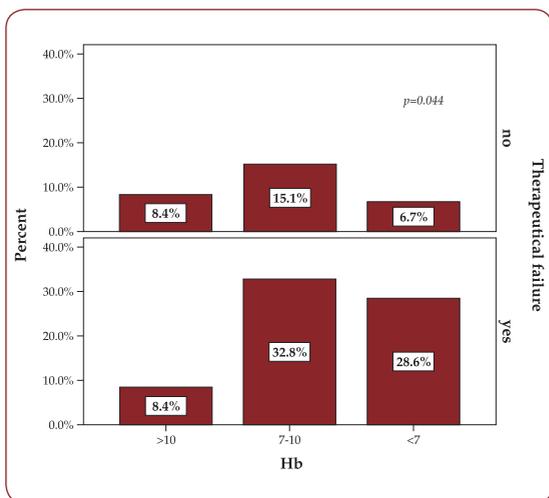


FIGURE 3. Correlation between severity of anemia and therapeutic failure.

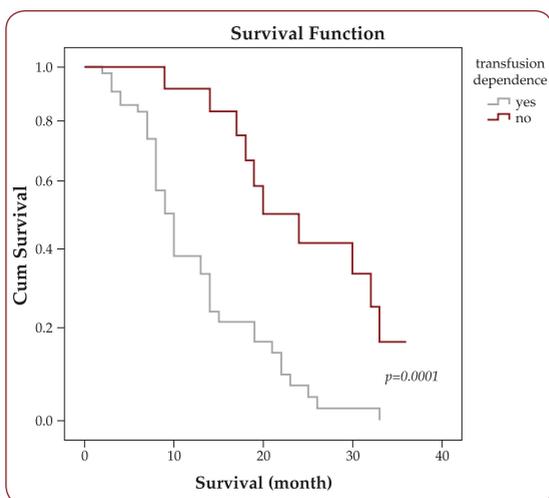


FIGURE 4. Correlation between transfusion dependence and overall survival.

The graphic shows a significant association between the presence of bone marrow blasts

and leukemic evolution in patients with more than 5% bone marrow blasts. A percentage of 12.1% patients with <5% marrow blasts experienced leukemic transformation. In patients who presented with a percentage of marrow blasts between 5-10% leukemic evolution rate was 21.2% while in the group of patients with 11-30% BM blasts a higher proportion had leukemic transformation (36.4%). In conclusion we noticed significant differences within the group of patients with percentage of marrow blasts ranging between 6-10% and 11-30%, respectively (**Pearson chi square = 12.2 p = 0.016**) (Figure 5).

The graphic shows a significant association between the presence of bone marrow blasts and mortality in the group of patients with more than 10% BM blasts. In the group of patients with <5% marrow blasts mortality was 25.5%. In patients who presented with a percentage of marrow blasts between 5-10% mortality was higher (32.7%). In patients with 11-30% BM blasts mortality was higher (32.7%). In conclusion we noticed differences between groups of patients with percentage of marrow blasts ranging between 11-30% (**Pearson chi square = 6.9 p=0.03**) (Figure 6)

The number of cytopenias shows a direct relation with the worse prognosis for survival and quality of life.

Overall survival and leukemia free survival correlated with the number of cytopenias (defined according to the IPSS criteria) didn't show statistical significance.

In patients with unilineal cytopenia or without cytopenia, overall survival was 36 months

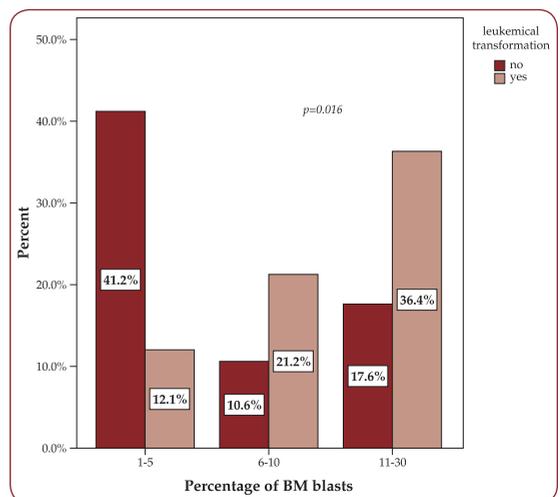


FIGURE 5. Correlation between percentage of BM blasts and leukemic evolution.

but leukemia free survival could not be assessed. Bilineal cytopenia or pancytopenia patients had an overall survival of 32 and 26 months respectively while leukemia free survival could not be assessed.

Our data indicate an interesting correlation between the number of cytopenias and the infectious complications. Patients who presented with pancytopenia (22.8%) experienced fewer infectious complications. Among the patients with one cytopenia, 45.6% had infectious complications. A percentage of 31.6% of bicytopenia patients had infectious complications. In conclusion, we noticed that the number of cytopenias is associated with the development of infectious complications with a significant difference within the lot with pancytopenia (**Pearson chi square=8.81 p=0.032**) (Figure 7).

The presence of cytopenias is associated with disease progression in bicytopenia and pancytopenia with a significant difference (**Pearson chi square=8.76 p=0.033**). Among the patients with one cytopenia 35.4% experienced progressive disease. In the group of patients with bicytopenia, 45.1% had progressive disease while in the pancytopenia group 18.3% of patients had progressive disease (Figure 8).

Cytopenias are associated with therapeutic failure in cases of bicytopenia and pancytopenia. In the lot of patients with one cytopenia, therapeutic failure was 34.9%. In bicytopenia patients the therapeutic failure rate was higher (44.6%) while in the group with pancytopenia therapeutic failure was seen in 19.3% of patients. Pancytopenia was associated with therapeutic failure with significant difference (**Pearson chi square=10.06 p=0.018**) (Figure 9).

Cytogenetic evaluation

Cytogenetic evaluation is important in the assessment of MDS as the presence of chromosomal abnormalities is included in the IPSS and specific findings have important prognostic significance. Three cytogenetic risk categories were identified: low risk (normal karyotype or loss of Y chromosome as a single anomaly), high risk (presence of trisomy 8 or abnormalities of chromosome 7, or complex karyotype), and intermediate risk (all other abnormalities). We were unable to perform cytogenetic analysis in all cases of the lot, the other analyses were inconclusive, and only 13 cases could be analyzed. For the patients who underwent cytogenetic tests, 3 (20%) did not show analy-

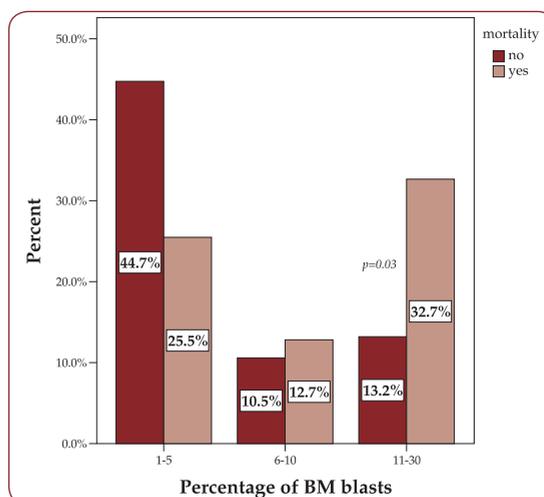


FIGURE 6. Correlation between the percentage of BM blasts and mortality.

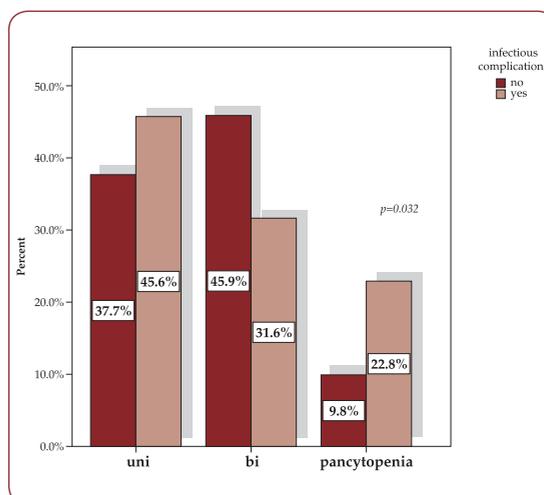


FIGURE 7. Correlation between the number of cytopenias and infectious complications.

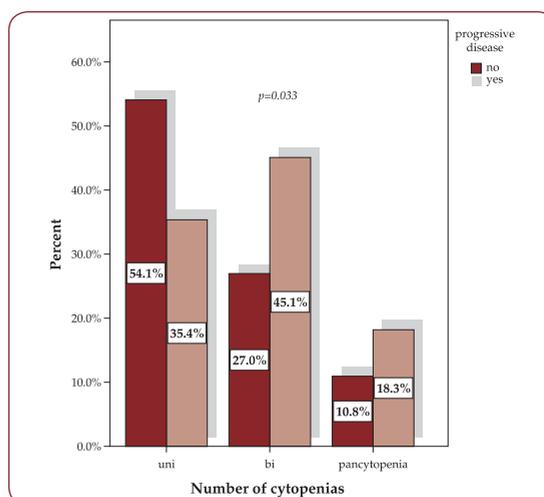


FIGURE 8. Correlation between number of cytopenias and progressive disease.

zable metaphases. Three patients with analyzable metaphases had normal karyotype at

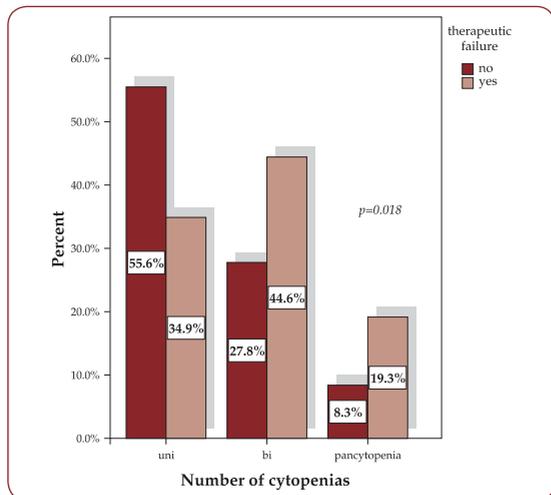


FIGURE 9. Correlation between of the number of cytopenias and therapeutic failure.

diagnosis. The following cytogenetic abnormalities were found: del 20q (3 patients), del5q (2 patients), -Y (1 patient), del 7q (1 patient), complex karyotype (1 patient), +8 (2 patients). Cytogenetic abnormalities were classified according to IPSS in good (69.3%), intermediate (15.3%) and poor (15.3%).

We could not describe curves for survival and leukemic transformation correlated with karyotype changes due to the small number of patients in whom cytogenetic analysis was performed.

Among the patients with intermediate and poor cytogenetic risk, an equal proportion (15.4%) presented leukemic evolution. Less patients within the group with good karyotype presented leukemic transformation (7.7%) (Figure 10).

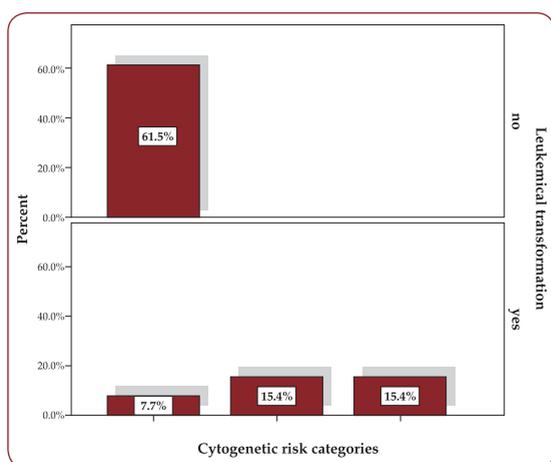


FIGURE 10. Correlation between cytogenetic risk categories and leukemic transformation (0-low risk; 1-intermediate risk; 2-high risk).

Acute myeloblastic leukemia transformation

	AML transformation		
	yes	no	p
The number of BM dysplastic lineages mean (std. dev)	13.51±2.31	14.27±2.36	0.22
Percentage of BM blasts mean (std. dev)	2.77 (0.78)	1.89 (0.8)	0.047
Cytogenetic groups			
good	1 (89)	8 (11)	
medium	2 (100)	0 (0)	0.01
poor	2 (100)	0 (0)	

TABLE 2.

The risk of AML transformation correlates with the percentage of bone marrow blasts, the cytogenetic abnormalities and the number of BM dysplastic lineages changes, with significant difference (Table 2).

Infectious complications

	Infectious complications		
	yes	no	p
Number of cytopenia 0	0 (0)	4 (100)	
n (%)			
1	26 (53)	23 (47)	
2	18 (39)	28 (61)	0.032
3	13 (68.4)	6 (31.6)	
Percentage of BM blasts mean (std. dev)	2 (100)	0 (0)	0.003

TABLE 3.

DISCUSSIONS

The MDS comprises a group of diseases with dysplastic features, which are between two extremities: refractory anemia and preleukemia.

Aging is an important risk factor for the development of these diseases. In this study the median age of patients was 71 years old. Other study reports that the median age ranges from 65 to 70 years old and the majority of patients with myelodysplastic syndromes are older than 55 years of age (10).

The main clinical manifestation in myelodysplastic syndromes is anemia. More than half of the patients diagnosed with *de novo* low-risk or high risk MDS had hemoglobin levels <10 g/dl (83.2%) at diagnosis. More than 80% of the patients with MDS had anemia at the beginning or during the course of their disease and often require red blood cell (RBC) transfusion

support (11). Overall survival at 36 months was higher in patients with moderate anemia and lower for severe anemia respectively. The therapeutic failure was notice in group of patients with Hb values less than 7 g/dl reflecting that severe anemia is a negative prognostic factor.

Several retrospective studies have shown that patients who become RBC transfusion-dependent have a significantly shorter overall survival than those who are not dependent on transfusions (12). This decreased survival may partially be due to iron overload and/or to intrinsically more severe bone marrow disease than in nondependent patients.

In this study we noticed that the number of cytopenias is associated with development of infectious complications, therapeutic failure and disease progression. The chronicity of cytopenias associated with MDS causes morbidity and mortality even in the absence of disease evolution to acute leukemia.

The overall 3-year survival rate was 32%; lower for females than for males.

Overall survival of patients with bone marrow blasts less than 10% is better than those which presented higher than 10% bone marrow blasts, with significant difference.

In this study, during the course of the disease, 33 (27%) patients underwent leukemic evolution which is similar to the others study results (13). The risk of AML transformation correlates with the percentage of bone marrow blasts (>5%), the cytogenetic abnormalities and the number of BM dysplastic lineages changes, with significant difference.

Considering that there were great variations in survival and leukemic evolution among patients belonging to the same FAB subtype, the integration of IPSS and FAB criteria allowed identification of worse prognostic subgroups within patients with RA, RARS and RAEB (14).

The FAB classification is useful for diagnosis, risk assessment and management and this is the reason for which it is still currently used. □

CONCLUSIONS

- Severe anemia represents a negative prognostic factor in the evolution of MDS. This study revealed that anemia has a deep impact on survival of patients

with MDS mainly low-risk subtypes. In high-risk subtypes anemia has significance in the clonal progression of the disease.

- Low-risk patients, who may have prolonged survival, have received blood transfusions for many years and may be exposed to a greater risk of iron overload, leading to heart and liver failure and endocrine glands dysfunctions. This explains our results which suggested that transfusion dependent patients have a shorter survival and not all these patients have received treatment with iron chelators.
- Percentage of blasts in bone marrow aspirate has a strong prognostic value. Our results revealed that the percentage of marrow blasts is highly predictive for leukemic transformation although there weren't significant differences between groups with 6-10% and 11-30% marrow blasts respectively. These results indicate that patients with 5-30% marrow blasts have a similar evolution.
- In the low-risk groups the percentage of marrow blasts is insignificant. Poor prognosis of patients is given by the unfavorable cytogenetic profile and increased number of cytopenias.
- Also, this study revealed that there is a direct relationship between the number and severity of cytopenias and poor prognosis related to survival and AML transformation. Infections and bleedings continue to be the main causes of death in patients with MDS and most patients die before the disease turns into AML (Tabel 3). This type of evolution was observed in 35% of patients while 17% experienced AML transformation before death.
- A karyotype patient at diagnosis coincides with chromosomal changes reported in large studies.
- In MDS the clinical course is variable, with or without treatment and thus, much effort has been focused on methods for predicting prognosis. The purpose is to obtain survival benefit, delay of leukemic transformation or improvement of cytopenias.

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