Article

Myelodysplastic syndromes: histopathology as prognostic factor

Maura Romeo[1]
Maria L.F. Chauffaille[2]
Maria R.R. Silva[3]
José Kerbauy[4]

Bone marrow biopsy allows evaluation of cellularity, abnormal localization of immature precursors and fibrosis in myelodysplastic syndrome. It has been considered important to make diagnosis and prognosis of this disorder. The object of this study evaluated the influence of histopathological parameters, such as cellularity, erythroid/myeloid ratio, abnormal localization of immature precursors and marrow fibrosis, on survival of myelodysplastic syndrome patients. Forty-six patients, admitted from April 1985 to June 1998, and diagnosed as being myelodysplastic syndrome according to French-American-British criteria, were selected. There were 20 males and 26 females, with median age of 61 years. Forty-six bone marrow smears and 36 trephine biopsies were reviewed. Mean survival of hypocellular cases was 64.8 months and of hyper and normocellular cases was 31.8 months. Patients with predominance of erythroid hyperplasia had mean survival of 50.8 months, greater than those with predominance of myeloid hyperplasia (20.3 months). There was no statistical difference in survival of patients with or without abnormal localization of immature precursors and with or without marrow fibrosis. Bone marrow biopsy is a useful tool for the identification of parameters that influence prognosis in myelodysplastic syndrome. Hypocellularity and erythroid hyperplasia were correlated with longer survival while myeloid hyperplasia with poorer survival.
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Key words*: Myelodysplastic syndrome, histopathology, prognostic*

Introduction

Myelodysplastic syndrome comprises a heterogeneous group of clonal disorders, all of which have their origin in multipotential stem cells. It is characterized by defective erythroid, myeloid and megakaryocytic maturation with normo or hypercellular bone marrow and peripheral cytopenias (1). The etiologic insults leading to the development of myelodysplastic syndrome and the latency period between the initial genomic insult and disease manifestation are largely unknown. Some myelodysplastic syndrome cases were observed post cytotoxic therapy for cancer, as well as post radiotherapy, and are called therapy related myelodysplastic syndrome. The cumulative risk of myelodysplastic syndrome increases by 0.25-2%

1 - Disciplina de Hematologia e Hemoterapia UNIFESP/EPM
2 - Professor da Disciplina de Hematologia e Hemoterapia UNIFESP/EPM
3- Professor do Departamento de Patologia Aplicada da UNIFESP-EPM
4 - Professor Titular da Disciplina de Hematologia e Hemoterapia UNIFESP/EPM

Disciplina de Hematologia e Hemoterapia UNIFESP/EPM, São Paulo, Brasil

Correspondência: *Maria de Lourdes Ferrari Chauffaille*
Disciplina de Hematologia e Hemoterapia da Universidade Federal de São Paulo/Escola Paulista de Medicina
Rua Botucatu, 740 - Prédio dos ambulatórios - 3º andar. 04023-900. São Paulo. SP. Brasil
Fone: (11) 5576-4237. Fax: (11) 5571-8806. E-mail: chauffaill@hemato.epm.com.br

per year from 1-2 years after start of therapy and continues up to 6-8 years after its cessation. There have been many reports of associations between histories of exposure to certain organic chemicals, notably benzene solvents, pesticides, and radiation, and myelodysplastic syndrome (1).

In 1982, the French-American-British classification divided myelodysplastic syndromes into five groups based on the percentage of bone marrow blasts, percentage of bone marrow ringed sideroblasts and the absolute number of monocytes in peripheral blood (2). This classification allows to set delineate prognosis and an adequate stratification of the majority of patients with these subgroups. But the French-American-British classification needs reevaluation to consider additional criteria (3). In 1991, Goasguen et al (4) proposed the first modification in the classification and defined type III blast demonstrating that this cell is important for correct classification of myelodysplastic syndromes. Besides that, histologic evaluation is not taken into account in French-American-British classification. More recently the contribution of bone marrow biopsy to the diagnosis and assessment of prognostic factors in myelodysplastic syndromes has been recognized (5-8). Bone marrow core biopsies allow evaluation of several parameters that can not be assessed from aspirated smears such as cellularity, abnormal localization of immature precursors and fibrosis (3, 9).

Objective

The aim of this study was to evaluate some histopathological aspects of bone marrow, correlate them to French-American-British subgroups and estimate their importance in patients' survival.

Materials and methods

Bone marrow and peripheral blood smears from 51 myelodysplastic syndrome patients admitted from April 1985 to June 1998 were selected. From these, 5 were excluded due to inadequate smears. All cases were evaluated by 2 Hematologists and classified according to French-American-British criteria (2). Peripheral blood and bone marrow smears were reviewed since most cases had been admitted before blast type III description. At least 500 cells were counted to establish the real blast number (3 types of blasts were considered, I, II and III) (4) and differential counts for bone marrow smears. The percentage of ringed sideroblasts was counted in Perl's stained smears. At least 100 cells were counted in peripheral blood smears taking into account the absolute number of monocytes and percentage of blasts. Bone marrow biopsy was obtained from posterior iliac crest with a Jamshid needle. Histologic evaluation was made in 36 cases since the remaining presented inadequate material or no biopsy. Three sections stained with Hematoxylin-Eosin, Giemsa and Gömöri's silver were analyzed in each case by a skilled Pathologist taking into account the following aspects: 1. cellularity, assessed by visual examination and graded into three groups: normocellular - 30-50% of intertrabecular space occupied by hematopoietic tissue; hypercellular - more than 50% of intertrabecular space occupied by hematopoietic tissue, and hypocellular - less than 30% of intertrabecular space occupied by hematopoietic tissue (6); 2. Abnormal localization of immature precursors (10); 3. cellularity of erythroid and myeloid series considering predominance of erythroid hyperplasia or of myeloid hyperplasia; 4. Fibrosis: divided into grade I, absent or slight increase of thin reticulin fibers which can only be recognized in Gömori's silver impregnation; grade II, moderate increase of reticulin fibers with an over-crossing network; grade III, severe increase of reticulin fibers (6).

Statistical methods

Histopathologic data and French-American-British groups were statistically correlated using chi-square tests or the Fischer exact test.(11) Survival curves were calculated by Kaplan-Meier method (1958) (12). Log-rank test was used for survival curves comparison.

Results

Forty-six patients, 20 males (43.5%) and 26 females (56.5%) had bone marrow and peripheral blood evaluated by morphology. Median age was 61 years (varying from 20 to

85 years). Mean follow-up time was 21.5 months (from 0.2 to 96 months). According to French-American-British classification there were: 20 refractory anemia (43.5%), 7 refractory anemia with ringed sideroblasts (15.2%), 11 refractory anemia with excess of blasts (23,9%), 4 refractory anemia with blasts in transformation (8.7%) and 4 chronic myelomonocytic leukemia (8.7%).

Four cases were re-classified after blast III count: 2 refractory anemia and 1 refractory anemia with ringed sideroblasts into refractory anemia with excess of blasts and 1 refractory anemia with excess of blasts was re-classified as refractory anemia with excess of blasts in transformation, respectively.

Patients were divided into two groups for survival analysis: first group with 27 patients with refractory anemia and refractory anemia with ringed sideroblasts (group I) with 65.6 months of mean survival; second group with 19 patients with refractory anemia with excess of blasts, refractory anemia with excess of blasts in transformation and chronic myelomonocytic leukemia (group II) with mean survival time of 12.6 months (P=0.0001) (Figure 1). Twelve (26.1%) patients died due to cytopenia, 11 to infection (23.4%) and 1 to myocardial infarction and anemia (2.6%). Ten patients transformed into acute myeloid leukemia in a period varying from 1 to 80 months.

Histologic evaluation: Cellularity - bone marrow biopsies were hypercellular in 23 (63.8%) patients, normocellular in 4 (11.1%) and hypo in 9 (25%). Five cases had a heterogeneous cellular distribution. Hypocellular marrows were more frequently seen in group I (40% x 6.25%) and the hyper in group II (81.25% x 50%) (P= 0.065). Mean survival of hypocellular cases was 64.8 months and normo/hyper ones 31.9 months (P=0.14).

Erythroid hyperplasia versus myeloid hyperplasia: Erythroid hyperplasia was present in 24 of 36 (66.6%) patients and myeloid hyperplasia in 12 of 36 (33.3%). Ninety percent of group I patients had erythroid hyperplasia and 37.5% of group II, 10% of group I had myeloid hyperplasia and 62.5% of group II, demonstrating a correlation between erythroid hyperplasia and refractory anemia and refractory anemia with

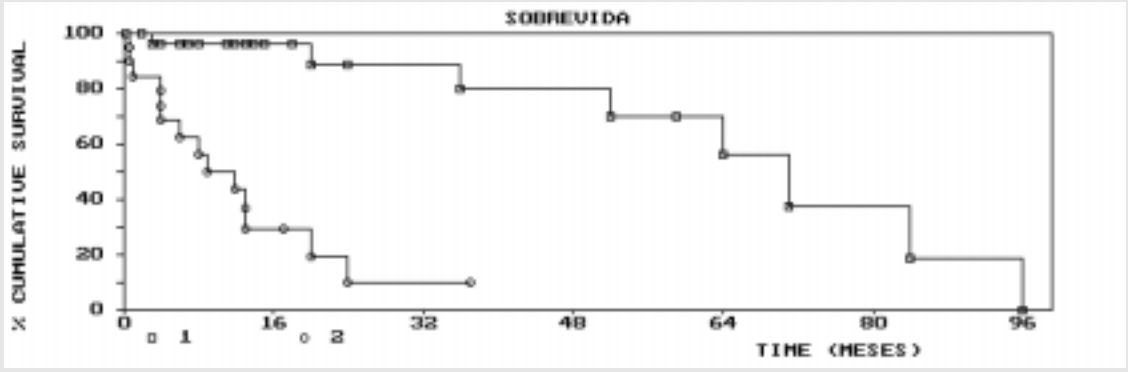

Figure 1. *Survival curves from group 1 and group 2 patients.*

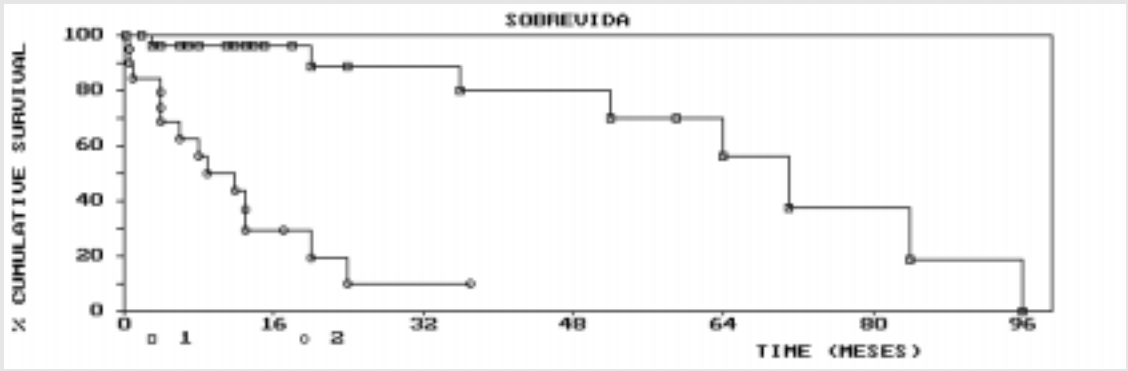

Figure 2. *Survival curves from patients with erythroid hyperplasia and myeloid hyperplasia.*

ringed sideroblasts, and of myeloid hyperplasia with refractory anemia with excess of blasts, refractory anemia with excess of blasts in transformation and chronic myelomonocytic leukemia (P=0.003). Mean survival of patients with erythroid hyperplasia was 50.8 months versus 20.3 months of that with myeloid hyperplasia (P=0.05) (Figure 2).

Fibrosis: Fibrosis was absence or discrete (I) in 66.6% of biopsies and moderate to severe (II and III) in 33.3%. Grade I fibrosis was present in 68.4% of group I and 64.7% of group II. Grade II was observed in 21% group I and 29.4% of group II and grade III in 10.5% of group I and 5.8% of group II (P=0.77). Mean survival time of patients with grade I fibrosis was 43.7 months versus 34.3 months for grade II / grade III.

Abnormal localization of immature precursors: 50% of group II patients and 40% of group I were positive for abnormal localization of immature precursors (P=0.793). Mean survival of group I patients with abnormal localization of immature precursors was 46 months and without, 77.3 months (P=0.17). Independent of French-American-British classification patients without abnormal localization of immature precursors had 46.7 months survival versus 34.3 months in cases with abnormal localization of immature precursors (P=0.63).

Discussion

Some authors believe that French-American-British classification is useful to identify two main myelodysplastic syndrome groups: refractory anemia and refractory anemia with ringed sideroblasts with good prognosis and refractory anemia with excess of blasts, refractory anemia with excess of blasts in transformation and chronic myelomonocytic leukemia, with poor prognosis (13). The contribution of bone marrow biopsy to the diagnosis and assessment of prognostic factors has been recognized (1, 7, 14).

The present study aimed to evaluate some histopathological aspects, correlate them to the French-American-British classification and estimate their importance in patients' survival. A review of all peripheral blood and bone marrow smears was made since most cases had been admitted before the blast type III description (4).

Patients were divided into two groups, group I (refractory anemia and refractory anemia with ringed sideroblasts) and group II (refractory anemia with excess of blasts, refractory anemia with excess of blasts in transformation and chronic myelomonocytic leukemia), with mean survival time of 65 and 12 months respectively, similar to published series (15, 16). Median age (61 yr) was similar to Tricot et al. (1985) (9) but lower than Maschek et al (1994) (6) (61 x 71.5). Transformation into acute myeloid leukemia was also similar to literature data (17). Mortality due to infection was the main cause of death (23%) as has already been shown (18). The unexpected higher incidence of hypocellular cases (25%) (7,19) was probably due to the fact that some patients were retired farming workers and had been exposed to pesticide. More epidemiological studies are needed to reveal the real incidence of myelodysplastic syndrome in rural population. Longer survival of hypocellular cases (64.8 months) versus hyper (31.8 months) has been shown before (7).

Although we had observed 33% of moderate to severe fibrosis we could not demonstrate a relation between the grade of fibrosis and the French-American-British groups. Lower survival was observed in the severe/moderate fibrosis cases however some controversies in the correlation of the presence of fibrosis and poor prognosis exist (6, 20).

The frequency of abnormal localization of immature precursors positive cases in group I (46.5%) was similar to other series (9) while lower in group II (60%) (7). Mean survival of group I without abnormal localization of immature precursors (77.3 months) was higher than patients with these aggregates (46 months). Morphological definition of abnormal localization of immature precursors is nowadays considered a weak parameter since some of the aggregates identified as abnormal localization of immature precursors do not belong to granulocytic lineage when immunohystochemistry reactions are performed (21). Therefore methods that allow an exact identification of these cells should be routinely introduced in order to detect the transformation earlier (7).

Conclusion

Type III blast identification was of fundamental importance to the re-classification of 4 cases whose evolution was poorer than initially considered demonstrating the importance of this cell to FAB/ French-American-British subtypes.

Bone marrow biopsy revealed to be an important tool helping to make diagnosis and to define prognosis in myelodysplastic syndrome.

Síndromes mielodisplásicas: a histopatologia como fator prognóstico

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Resumo

A biópsia de medula óssea propicia a avaliação da celularidade global, dos precursores imaturos de localização anormal e de fibrose nas sídromes mielodisplásicas. O método tem sido considerado importante também para o diagnóstico e prognóstico da síndrome.

O objetivo deste estudo foi o de observar a influência de parâmetros histológicos como a celularidade, a relação eritróide-mielóide, a presença de precursores imaturos de localização anormal e fibrose medular na sobrevida de pacientes com a síndrome.

De abril de 1985 a junho de 1998, 46 pacientes diagnosticados segundo os critérios do grupo Franco, Americano, Britânico foram estudados. A casuística era composta de 20 pacientes do sexo masculino e de 26 do sexo feminino com idade média de 61 anos. Foram revisados 46 esfregaços de aspirado de medula óssea e 36 cortes histológicos de biópsia de medula óssea. A sobrevida média dos casos de hipocelularidade foi de 64,8 meses e dos casos que eram hiper ou normocelulares foi de 31.8 meses. Pacientes com a predominância de hiperplasia tiveram sobrevida média de 50,8 meses, que foi superior aos que apresentavam hiperplasia mielóide (20,3 meses). Não houve diferença estatística na sobrevida dos pacientes que apresentaram ou não fibrose medular.

A biópsia de medula óssea deve ser considerada útil na identificação de parâmetros que influenciam no prognóstico da síndrome mielodisplásica.

A hipocelularidade e a hiperplasia eritrocitária está relacionada com a sobrevida maior, enquanto a hiperplasia mielóide com a sobrevida mais curta.

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Palavras-chave: *Síndrome mielodisplásica, histopatologia, prognóstico*

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