

Review Article

Myelodysplastic Syndromes Experience of the Laboratory of the Military Hospital Avicenna Marrakech

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Abstract: MDS are clonal disorders of multipotent or myeloid stem cells. The disease is characterized by inefficient hematopoiesis responsible for peripheral cytopenias and contrasting with a rich marrow. The natural course of this disease is acute myeloid leukemia (AML). This is a retrospective study on the files of patients who had a haematological assessment at the laboratory of the military hospital Avicenna Marrakech between July 2014 and July 2018 for a duration of 4 years. Included in our study were all patients with documented myelodysplasia. The average age of patients is 63.63 years with extremes of 19 years and 89 years; the sex ratio was 1.3 (17 men and 13 women). NFS was abnormal in all patients, 96.66% of whom had anemia. The myelogram was performed in all patients and allowed the diagnosis of MDS in 90% of cases. Our study shows that management needs to be further improved by selecting high-risk MDS patients, potentially candidates for allogeneic hematopoietic stem cell transplantation.

Keywords: Myelodysplasia, Haemogram, Anemia, Thrombocytopenia, Neutropenia-Myelogram, Genetic Mutation

1. Introduction

Myelodysplastic syndromes (MDS) are a group of chronic and clonal hematopoietic stem cell (HSC) disorders, characterized by inefficient hematopoiesis, resulting in one or more peripheral cytopenias. It is a pre-leukemic condition with possible progression to acute myeloid leukemia (AML) in about one third of cases. [1, 2]

The diagnosis of myelodysplastic syndromes (MDS) is relatively difficult and sometimes requires time and several bone marrow examinations. [3]

The goal of MDS treatment is to prolong survival and improve quality of life. Only hematopoietic stem cell allograft is, to date, potentially curative in MDS. However, it does imply the existence of a donor, an age generally less than 65-70 years, the absence of major co-morbidities and a sufficiently high risk MDS so that the benefit is not offset by toxicity. [4, 5]

The evolution of MDS is unfavorable, similar to that of a malignant hemopathy. Median survival ranges from 9 months to more than 8 years depending on the initial risk category.

In this article, we analyze the descriptive epidemiological data of 30 patients with MDS between 2014 and 2018.

2. Patients and Methods

We report a retrospective study spread over a 4-year period from July 2014 to July 2018. Our work focused on patients who had a haematological assessment (NFS, Myelogram) at the laboratory of the Military Hospital Avicenna of Marrakech. Only patients in whom clinico-biological confrontation led to the diagnosis of primary or secondary myelodysplastic syndrome were included in this study.

Patients with dysmyelopoiesis secondary to vitamin B 12 were excluded from the study.

The collection of data was done by an exploitation file,

gathering the epidemiological, clinical, biological, therapeutic and evolutionary data of the patients.

Data capture and analysis was done using EXCEL software and a descriptive method using simple variables such as percentages and averages.

3. Results

30 cases of MDS were collected over 4 years, or 7.5 cases per year. The average age of our patients was 63.63 years (19-89 years), and 21 cases were older than 60 years (70%). We noted a male predominance with 17 men (56.66%) and 13 women (43.33%), the sex ratio between men and women is 1.3. None of our patients were treated with chemotherapy or radiotherapy or exposed to toxic drugs.

The median time from onset of symptoms to consultation was 3.5 months (1-12 months). The median time between consultation and diagnosis was 40 days (4d-9 months).

The main clinical manifestations of our patients are:

1. The anemic syndrome found in 90% of cases (n = 27).
2. The hemorrhagic syndrome in 16.66% of cases (n = 5).
3. Infectious syndrome in 33.33% (n = 10).
4. Splenomegaly in 13.33% of cases (n = 4). [Table 1]

Table 1. The different clinical manifestations of MDS.

clinical manifestations	isolated	Related	total
anemic syndrome	25 (50%)	12 (40%)	27 (90%)
hemorrhagic syndrome	0	5 (16,6%)	5 (16,6%)
splenomegaly	0	4 (13,3%)	4 (13,3%)

From a biological point of view, the blood count revealed anemia in 96.66% of cases, thrombocytopenia in 76.66% and leucopenia in 36.66%. [Figure 1]

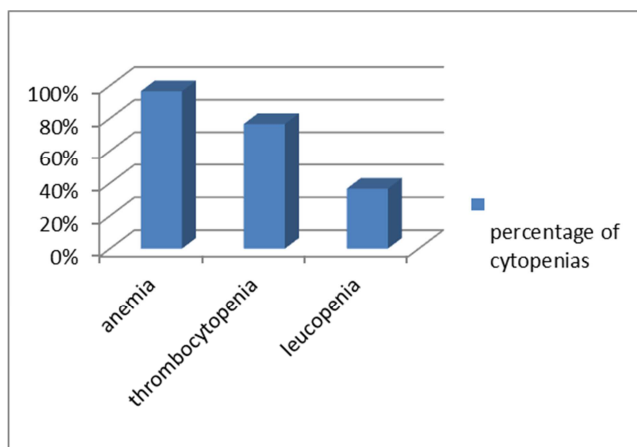


Figure 1. Percentage of cytopenias.

Anemia was normocytic in 51.72% of cases (n = 15), macrocytic in 40% of cases (n = 12) and microcytic in 6.66% of cases (n = 2). In 100% of cases the anemia was arterenerative with a low reticulocyte level reaching up to 3500 elt / mm³. Bicytopenia was found in 36.66% of patients (n = 11), made of anemia + thrombocytopenia in all cases. Pancytopenia was found in 36.66% of cases (n = 11).

The blood smear was performed in all our patients, it was pathological in 53.33% of patients (n = 16): anisocytosis, poikilocytosis, giant platelets, dysgranulopoiesis, dyserythropoiesis, polymorphonuclear morphological abnormalities etc...

20% of the patients (n = 6) had peripheral blood blasts, the average blast content was 6.66% (3-12%).

The myelogram was performed in all patients and was used to diagnose the disease in 90% of cases (n = 27). Bone marrow was hypercellular in 63.33% of patients (n = 19), normocellular in 23.33% of patients (n = 7), and hypocellular in 13.33 patients (n = 4).

Morphological abnormalities were present in all patients and involved one or more lines (dyserythropoiesis, dysmegacaryopoiesis, dysgranulopoiesis). The level of bone marrow blasts was less than 5% in 70% of cases, 5% to 10% in 17% of cases, 11% to 20% in 13% of cases, and in no case was it greater than 20%. [Figure 2]

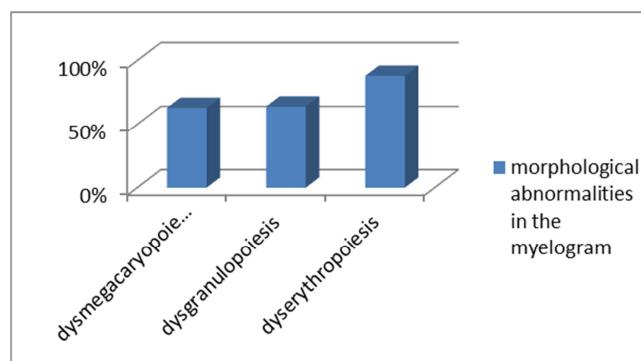


Figure 2. Morphological abnormalities present in the myelogram.

In 10% of our patients (n = 3) the sternal puncture was white, and the diagnosis was made on a second myelogram performed following a suction puncture during an osteomedullary biopsy.

The cytogenetic study was performed in 16 patients (53.33%). Among these 16 patients, the medullary karyotype was normal in 6 patients (37.5%), and abnormal in 10 patients (62.5%).

The cytogenetic abnormalities found are:

1. Del (5q) in 12.5% of cases (n = 2).
2. Monosomy 7 in 6.25% of cases (n = 1).
3. Complex in 18.75% of cases (n = 3).

According to the WHO 2008 classification of MDS, in our series the cases are distributed as follows:

1. Refractory cytopenias with multilineage dysplasia (CRDM) represent 26.66% of cases.
2. Refractory cytopenias with unilateral dysplasia (CRDU) represent 20% of cases.
3. Refractory anemia with excess blast accounts for 33.33% of cases; in 16.66% of cases it is refractory anemia with excess blast type 1 (AREB 1) and in 16.66% of cases it is refractory anemia with excess blast type 2 (AREB 2).
4. Chronic myelomonocytic leukemia (CMML) accounts for 10% of all cases
5. Myelodysplastic syndrome 5q represents 6.66% of cases.

6. Unclassifiable myelodysplastic syndrome represents 3.33% of cases.

We calculated the IPSS and IPSS-R score in patients with a marrow karyotype (16 patients).

The IPSS is 0 in 25% of the cases ($n = 4$), making it possible to classify the SMD at low risk, between 0.5 and 1 in 37.5% of the cases ($n = 6$) so SMD intermediate 1, between 1.5 and 2 at 25% of cases ($n = 4$) is an intermediate MDS 2, whereas it is greater than 2.5 in 12.5% of cases ($n = 2$), so MDS is classified as high risk. [Figure 3]

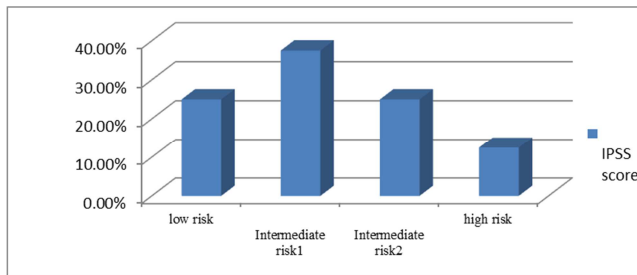


Figure 3. Distribution of Cases by IPSS Score.

Transfusion support was the mainstay of treatment in most patients, 20% of patients were placed on erythropoietin and 13.33% under iron chelators. 16.66% of patients had received aracytin-based chemotherapy. And hypomethylating agents were prescribed in 16.66% of cases.

The evolution was marked by the death of 6 patients, while 13 patients are still followed and 11 were lost to follow-up.

4. Discussion

Myelodysplastic syndromes are heterogeneous diseases of the hematopoietic stem cell characterized by myeloid dysplasia and excessive apoptosis of hematopoietic precursors. [6] Homeostasis, production of oxygen free radicals, permeabilization of the mitochondrial membrane, activation of caspases). [6] Studies show that a wide variety of chromosomal and gene abnormalities may contribute to the dysplastic and apoptotic phenotype of MDS by inhibiting cell survival signals (cytokine receptor signaling, DNA repair, ribosome biogenesis), and / or proapoptotic signals relayed by the endoplasmic reticulum and mitochondria (disruption of Ca^{2+} homeostasis, production of oxygen free radicals, permeabilization of the mitochondrial membrane, activation of caspases). [6]

SMDs account for 13% of all Hematological Disease diagnoses and the first haemopathy of the subject over 65, affecting men with a sex ratio of 1.5-2 / 1 [7]. The mean frequency of MDS in our series was 7.5 cases per year, with a male predominance and a mean age of 63.63 years.

MDS are mainly revealed by peripheral cytopenias (especially anemia), symptomatic or incidental discovery. But other manifestations, rheumatological, dermatological or systemic, may be in the foreground, making diagnosis more difficult. [8] In our study, the main clinical sign of MDS is represented by anemic syndrome.

Biologically, the blood count is most often found in normo-

or macrocytic arterative anemia, which may be associated with thrombocytopenia and / or neutropenia. [9] Indeed, in our series anemia was present in 96.66% of cases, it was normochrom in 51.72% of cases and macrocytic in 40% of cases. She was arterenerative in 100% of cases.

The different clinical and laboratory abnormalities are not specific and the diagnostic confirmation comes from the spinal cytological analysis after realization of a myelogram. [8]

A SMD is defined as the presence of a significant dysplasia, representing at least 10% of the cells of a line. It is called unilateral or multilineage (if 2 or 3 lines are affected). The threshold of 20% of medullary blasts is retained to differentiate SMD with excess blasts (5-19% blasts) of AML. MDS are classified according to WHO 2008 criteria, revised in 2016 [8]. These criteria also distinguish a subpopulation of SMD with sideroblasts, revealed by Perls staining. The presence of ring sideroblasts is pathological when it represents at least 15% of the cells. This threshold is lowered to 5% in case of mutation of associated SF3B1. Type III sideroblasts may occur in generally low numbers during secondary sideroblastic anemias (deficiency of copper, zinc, alcoholism, azathioprine, etc.) [10, 11].

In our series, the myelogram made it possible to pose the diagnosis of MDS in 90% of the cases. Dyserythropoiesis predominates in 86.6% of cases. This is similar to the Ehsan et al study in Pakistan [12], where dyserythropoiesis is 89%, and dysmegacaryopoiesis 50%.

In recent years, cytogenetic abnormalities have taken a major place in the estimation of prognosis and the therapeutic decision. The karyotype analysis is therefore essential for the diagnosis of MDS. The abnormalities found in our series are Del (5q) in 12.5% of cases, monosomy 7, chromosome 20 anomaly, trisomy 8, trisomy 6, monosomy 19 present in 6.25% of cases for each; karyotype was complex in 18.75% of cases. This is consistent with the literature data [13].

Several prognostic scores have been proposed but the main one used is the IPSS (International Prognostic Scoring System) score, published in 1997. However, more recent data on the prognostic importance of cytogenetics have led to a revision of this score (IPSS-R).

In our series, the IPSS was low risk in 25% of cases, intermediate1 in 37.5% of cases, intermediate 2 in 25% of cases, high risk in 12.5% of cases. In the IPSS-R the SMD is classified very low in 12.5% of the cases, low in 37.5% of the cases, intermediate in 18.75% of the cases, high in 25% of the cases, and very high in 6.25% of the cases. Our results are consistent with literature, and close to many studies, including the study of Schanz et al [14].

The therapeutic management is different between SMD-LR and SDM-HR. While the treatment of SMDLR, which accounts for 2/3 of patients, consists mainly of correcting cytopenias, the treatment of MDS-SMD will target blast proliferation and chromosomal instability to control the leukemic clone. In the study by Ben hassan et al [15], treatment was symptomatic in 57% of cases, androgen therapy

in 9% of cases, a single bone marrow allograft and therapeutic abstinence in 27.5% of patients.

During the evolution several patients developed complications to type of: hemorrhagic complications in 30% of the patients, infectious complications in 26.66% of the patients, the transformation to acute myeloid leukemia in 6.66% of the patients, and the secondary haemochromatosis, consequence of the iterative transfusions in 13.33% of patients. 20% of the cases in our series were deaths. Massimo *et al* [16] reported a death rate of 41%, of which 32% by transformation and 9.2 by cardiovascular complications.

5. Conclusion

The management of MDS is significantly optimized through the use of new therapeutics. Our study shows that care needs to be further improved by selecting high-risk MDS patients, potentially candidates for allogeneic hematopoietic stem cell transplantation.

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