Exp Biomed Res 2019; 2(3):103-110 DOI: 10.30714/j-ebr.2019353195

EXPERIMENTAL BIOMEDICAL RESEARCH

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Research article

A retrospective evaluation of patients with myelodysplastic syndrome

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ABSTRACT

Aim: To determine our results by examining patient's files who we followed up by myelodysplastic syndrome (MDS) diagnosis between 2005 and 2009 as retrospectively and to compare the accordance of our results with literature.

Methods: We examined 55 patient's files who got MDS diagnosis in 4 year-term. Complete blood count, biochemical analysis, peripheral spread, bone marrow aspiration, bone marrow biopsy examinations, cytogenetic and fluorescence in situ hybridization (FISH) analyses were made for all cases.

Results: Our patient's age average was 69 and when classified according to WHO criterion at the diagnosis time, % 13 (23,6) of cases got diagnosed with RA-RARS, % 29 (52,7) with RCMD-RS, %5 (9,1) with RAEB-1, % 4 (7.3) with RAEB-2, % 3 (5.5) with MDS 5q and % 1 (1.8) with secondary MDS. % 52 of the patients had normal cytogenetic structure. No relation was determined between patients' diagnosis and international prognostic scoring system (IPSS) scores. During the 4 year-term, our 13 patients died. 6 of these cases died by reason of transforming to acute myeloid leukemia (AML), and 7 patients died because of infection. Mean survival time of cases that died was 6 (1-7) months as of the diagnosis date. Whereas 8 cases were over 70 ages, 5 of our cases were under 70 ages.

Conclusion: MDS is a disease that ranges between anemia and AML and requires cytogenetic trials for diagnosis along bone marrow aspiration and biopsy for the purpose of determining the treatment regimen and prognosis. Determining the IPSS scores of patients by obtained outcomes is required. Risk of transforming to acute leukemia and susceptibility to infection are important in terms of mortality. Overage of patient population restricts the treatment regimens. Age must be an important factor for prognosis and treatment choice.

Keywords: Myelodysplastic syndrome, acute myelocytic leukemia, cytogenetic.

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Received 2018-05-25

Accepted 2019-06-15

Publication Date 2019-07-01

Introduction

Myelodysplastic syndrome (MDS) is a disease which is characterized with cytopenia in one or more lines because of abnormal cellular proliferation in bone marrow and cellular proliferation's being ineffective in peripheral blood that is seen in bone marrow. Additionally, it is a multipotent bone marrow disease that can develop primarily or secondarily [1], and the definitions about the disease have existed for almost 70 years although its MDS classification is new. In 1938, Rhoades and Barker defined refractory anemia in 60 patients without any connection with another situation. Hamilton Peterson later defined the refractory anemia cases which occur before the development of acute myeloid leukemia as preleukemic anemia in order to define this situation [2]. Block et al. [2] used the term of 'preleukemia' to describe the patients, who had one or more refractory cytopenia that also included the potential of leukemic transformation in its natural course, in 1953. For the first time in 1976, a French-American-British (FAB) group defined the diagnosis criteria for the pre-leukemic syndromes with refractory anemia, whose blast percentage was high, and chronic myelomonocytic leukemia, and this classification was revised in the year of 1982 [3]. As well as the morphological 3 classification, a separation can be made as primary or secondary MDS regarding whether it was exposed to chemotherapy, radiotherapy or toxic substances.

The classification in the FAB system is based on the number of myeloblasts in bone marrow. The FAB system is successful to a certain extent in the prediction of the disease's transformation to leukemia. Not taking into consideration such critical prognostic factors as the cytogenetic changes and previous treatment history for malign diseases, FAB classification's capability to estimate the prognosis is limited. MDS in WHO classification; Refractory anemia (RA), Refractory anemia with ring sideroblast (RARS), Refractory cytopenia (RCMD, RCMD-RS) with increased dysplasia in multiple sequences without ring sideroblasts or ring sideroblasts (RAEB-1, RAEB-2), MDS and 5q syndrome divided into subgroups.

Idiopathic MDS is an old age disease. Its average age to occur is around 68. There is a mild male gender dominance in the disease. The incidence in the general population is 35-100/million people. It reaches 120-500/million people in the elderly. It is rare in children, but monocytic leukemia can be observed. Treatment-dependent MDS is not dependent on age, and the recurrence rate for the patients who took intense combined treatment models for cancer treatment is 15% [4].

In MDS, the course of the disease depends on the severity of the cytopenias and the number of blasts. In RA and RARS, which are included in the low-risk MDS group, the cytopenia becomes more severe in a long chronic process. As the result, the complications, belonging to cytopenia or treatment (transfusion hemochromatosis), occur. The transformation of these cases to acute myeloid leukemia (AML) is fewer, and the average of survival is longer [5].

The most important factors that affect the prognosis are age, the percentage of myeloblast in the bone marrow, the number of the cell lines, in which cytopenia is seen, and cytogenetic disorders. In an international study, made on prognosis in myelodysplasia, a prognostic scoring system (International prognostic scoring system - IPSS) was crated [6].

MDS must be planned according to the subgroup, in which the patient's treatment is found, and the prognostic score. Along with increasing the survival time which is the actual treatment purpose, the treatment goals must include delaying the transformation of leukemia, increasing the response rate, decreasing the transfusion need, decreasing infections and control, and increasing life quality with hematological correction. In the patients, who are younger and have a suitable health condition, the only known treatment method for long-term survival is allogeneic bone marrow transplantation. The treatments, except for this, must be supportive cares. In the present study, we aimed to retrospectively review the files of patients with MDS between 2005 and 2009 and compare our results with the literature.

Methods

Between the dates of January 2005-September 2009, the files of 55 adults, who had been diagnosed with MDS according to WHO classification by the Department of Adult Hematology of the Faculty of Medicine of Ondokuz Mayıs University, were retrospectively examined. Complete blood count, biochemical analysis, peripheral spread, bone marrow aspiration, bone marrow biopsy examinations, cytogenetic and fluorescence in situ hybridization (FISH) analyses were made for all cases. The patients' hometown, age, cytopenia rate at the moment of diagnosis, organomegaly, bone marrow blast percentage, cytogenetic and FISH analysis results, bone marrow biopsy results and IPSS score were recorded. The patients' cytogenetic and FISH analyses were studied by the Department of Child Genetics of Ondokuz Mayıs University. The obtained data was analyzed with statistics software of SPSS 15 (Statistical Package Social Science) for Windows. The statistical analyses were made with the chi-square test. The statistical significant limit was accepted as $p<0.05$ value.

Results

The total of 55 patients, 23 (41.8%) of whom are women and 32 (58.2%) men, were taken into evaluation. The average age of the patients were found to be 69 (43-82). There was not a significant relationship between the age and gender of the patients ($p>0.05$). 54% of the patients applied from Samsun, 21% from Ordu, and the rest of them applied from Rize, Artvin and Giresun as 25% of them applied from the provinces of Sinop and Amasya, mostly.

At the moment of application, Hemoglobin (Hb) was under 10 gr/dl in 54 (98.2%) cases, neutropenia was existing (the number of neutrophil under 1500/mm^3) in 28 (50.9%) cases, thrombocytopenia (the number of thrombocyte was under 100 thousand/mm3) in 35 (63.6%) cases, and pancytopenia in 24 (43.6%) cases When the performed examination and scans were examined, only hepatomegaly was found in 8 (14.5%) cases, only splenomegaly in 4 (7.3%) cases and hepatosplenomegaly in 5 (9.1%) cases. The number of cases without hepatosplenomegaly was 38 (69.1%).

When our patients, diagnosed with MDS, were classified according to the WHO criteria, 13 (23.6%) cases were diagnosed as RA-RARS, 29 (52.7%) as RCMD-RS, 5 (9.1%) as RAEB-1, 4 (7.3%) as RAEB-2, 3 as (5.5%) as MDS 5q, and 1 (1.8%) as Secondary MDS. During making diagnoses for the patients, ring sideroblast percentages could not be counted because bone marrow was not painted with iron dye in our hematology laboratory. Our RA and RARS cases were examined under RA,

together. The same was true for RCMD and RCMD-RS diagnoses.

When the patients' diagnoses and organomegaly frequency are compared, a significant relationship between them could not be found ($p>0.05$).

In the evaluation of our patients' bone marrow biopsies, the bone marrow symptoms were found in 31 (56.4%) cases, normocellular in 9 (16.4%) cases, hypercellular in 9 (16.4%) cases, insufficient in 3 (5.5%) and leukemic infiltration in 3 (5.5%) cases. 2 of 3 patients, who were concluded as leukemic infiltration, had RAEB-1, and the remaining 1 case had the diagnosis of RAEB-2.

When the cytogenetic results of the patients were examined, a significant relationship could not be found between the cytogenetic results, age and gender ($p>0.05$). When the cytogenetic examination of the patients was evaluated, cytogenetic anomaly was found in 29 (52.7%) cases. Isolated 5q deletion was found in 5 (9.1%) of our cases. Trisomy was found in 4 (7.2%) of our cases in total as isolated in 2 cases and together with complex chromosomal anomalies in 2 cases. Monosomy 7 was found at the rate of 3.6%. Isolated monosomy 7 was not found.

When the patients' cytogenetic results and cytopenia rates were compared, a significant relationship could not be found. The patients, who had complex chromosomal anomalies, mostly applied with pancytopenia.

When the chromosome anomalies of our patients were taken into consideration according to the WHO classification, it was observed that the cytogenetical anomaly frequency was more often in the cases, diagnosed with RCMD-RS. The existence of complex cytogenetical anomalies could not be associated according to the MDS subgroup. Being only a diagnoses criteria, del 5q anomaly was displayed in MDS 5q in an isolated manner. Again similarly, del 7q was found in our Secondary MDS case. The primary diagnosis of our Secondary MDS patient was Non Hodgkin Lymphoma, and transformed into MDS after chemotherapy. As we stated it before, del 7q was seen in Secondary cases at high rates.

When the IPSS scores of the patients were compared with their current diagnoses, a significant relation could not be found ($p>0.05$).

When the IPSS scores of the patients were compared with mortality, a significant relation was found ($p<0.05$). While there was not any mortality in all of the patients in the low risk group, there were mortalities in 6 (23%) cases in Medium-1 risk group, 3 (60%) in Medium-2 group, in 1 (100%) in High risk group. Because the cytogenetic result of our 3 cases were not known, their IPSS score could not be determined. In comparison to our total number of patients, the mortality rate was determined as 23.6% with 13 cases.

The total of 8 cases under monitoring turned into AML, 3 of them were Mid-1 when their IPSS scores are considered, whereas the IPSS scores could not considered for the remaining 4 patients, 1 of whom was determined to be in the high risk group, as their cytogenetic result could not be obtained. There was no significant relationship between MDS subgroups and AML and no significant relationship was found in our RA-RARS cases. Our 3 cases, diagnosed with RCMD-RS, 2 cases, diagnosed with RAEB-1, and 3 cases, diagnosed with RAEB-2, transformed into AML. Here, 75% of our RAEB-2 patients, constituting high blast number, transformed into AML ($p>0.05$).

Within this period that we took into examination, 6 of our 13 cases died by transforming into AML, and the remaining 7

patients died out of infection. The average life expectancy of deceased patients were found to be 6 (1-17) months since the date of diagnosis. While 8 cases were above the age of 70, 5 of our cases were under 70.

When the mortalities of the patients are compared according to the MDS subgroups, a significant relationship could not be found. 2 of our 5 cases, who was diagnosed with RAEB-1 and died, transformed to AML, and the remaining 3 cases died out of infection.

Discussion

In our study, 41.8% of 55 patients were women, and 58.2% men. In literature and the conducted studies, the MDS incidence in male patients was seen to be a little more in comparison to women, in general. In our study, the ratio of men/women was 1.3. The youngest of our patients was at the age of 43 and the oldest one was 81. The average age was found to be 69. In the sources, when MDS epidemiology is examined it is seen that the average age is 68 and it was seen frequently in these decades [4]. In a 10-years-long retrospective study that was made by Maura et al. [7], 40 patients were evaluated and the ratio of men/women was found to be 0.6/1. Again in this study, the average age was found to be 64.1. In another study that was made by Sendi et al. [8], 117 MDS patients were examined, and the average age was found to be 58 and the ratio of men/women to be 1.7. In an 18-years-long study that was made by Li et al. [9], 351 MDS patients were examined, and the average age was found to be 45 and the ratio of men/women to be 2/1. A relationship for the organomegalies, which were determined with the physical examination and scanning methods, of our patients, diagnosed with MDS, could not be found with MDS subgroups. In our study, while the rate of isolated splenomegaly was 7.3%, if we count our patients with hepatosplenomegaly this ratio increases to 16.4%. In a study which Steensma et al. [10] made, 218 patients were taken into evaluation, and the splenomegaly rate was found to be 16%. In bone marrow examination, normocellular was found in 31 cases, hypercellular in 9 cases, hypocellular in 9 cases, and leukemic infiltration in 3 cases, and it was found to be insufficient in 3 cases. If it is evaluated regarding the total, normal or hypercellular bone marrow was found in 40 cases, and a hypocellular bone marrow was determined in 16.4% of the cases. In literature, the hypocellularity is around 20% in MDS patients [4]. This rate is suitable with the value of 20% given in the literature.

When we examined the MDS subgroups; in the comparison of the WHO data [4] and our patient population, the RAEB-1 and RAEB-2 incidence was found to be 9% in our data while it was 40% in the WHO data. The existence of a significant difference in comparison to other subgroups can be related to the low number of our cases. As a reason of this difference, it is thought that RAEB cases with high risk of leukemia may be transformed into leukemia until the time of diagnosis due to socioeconomic reasons. While the RAEB 1-2 rates were close to the WHO rates in the study, made by Romeo et al. [7] the RCMD-RS rate was lower than our study and the WHO data.

When the cytogenetic anomalies of our patients were studied, an anomaly was determined in 52.7% of the cases. When we look at the literature, the cytogenetic anomaly incidence changes between 30 and 50% in the studies that were made on the MDS patients [8,11,12]. In the study, which was made by Romeo et al. [7] with 40 people, the cytogenetic anomaly was determined to be at 35%, in the one, which was made by Sendi et

al. [8] with 117 people, at 55%, and in the one, which was made by Li et al. [9] with 351 people, at 67.5%.

When the relationship between the cytogenetic analysis results and gender, a significant relationship could not be found. When the chromosome anomalies of our patients were taken into consideration according to the WHO classification, it was observed that the cytogenetical anomaly frequency was more often in the cases, diagnosed with RCMD-RS. The existence of complex cytogenetical anomalies could not be associated according to the MDS subgroup. Being only a diagnosis criterion, del (5q) anomaly was shown in MDS 5q as isolated. Again similarly, del 7q was found in our Secondary MDS case. The primary diagnosis of our Secondary MDS patient was Non Hodgkin Lymphoma, and transformed into MDS after chemotherapy. As we stated it before, del 7q was seen in Secondary cases at high rates. In the MDS cases, del 5(q), monosomy 7, trisomy 8, del 8, 20q-, -Y and del (7q) anomalies are observed. By this reason, the anomalies that belong to chromosome 5 and 7 can be interpreted as the AML transformed by MDS in the AML cases. There are not any cytogenetic anomaly unique for the subtype of the cases [11,12]. In our population, the anomalies belonging to the 5th, 7th and 8th chromosomes were observed more frequently. In the study, made by Mauro et al., the chromosome 5q anomaly was found to be at the rate of 20%, monosomy 7 to be 15% and trisomy 8 to be 5%. In the study, made by Halima et al., the chromosome 5q anomaly was found to be at the rate of 14%, monosomy 7 to be 7% and trisomy 8 to be 4% [7,8].

Again in our study, while 2 of the 8 cases, which subsequently transformed into AML, were found to have a normal cytogenetic structure, 1 of them to have a -Y and t (3-21) anomaly, 1 of them to have Del5q and t (1.7) anomaly, the remaining 4 cases' cytogenetic examination could not be determined due to insufficient metaphase. Because the number of cases is scarce and the cytogenetic examination of 4 cases could not be determined, a prognostic cytogenetic anomaly could not be found in terms of transformation to AML. While calculating the IPSS score in MDS, the blast percentage in the bone marrow, the cytopenia rate and chromosomal anomaly values must be known. The obtained scores are classified as low, medium and high risk groups. When the MDS subgroups were compared with the IPSS scores, a significant relation could be found.

In terms of mortality, RAEB 1-2 has a higher risk among the subgroups in comparison to RCMD-RS and RA-RARS groups. In our story, the IPSS scores were concentrated in the low risk group for RA-RAS, in the medium risk group for RCMD-RS and in the medium-high risk group for RAEB-1-2. When the MDS subgroups were compared with the IPSS scores, a significant relation could be found. In our RA-RARS cases, no transformation ALM was seen in 4 years of monitoring. Our 3 cases, diagnosed with RCMD-RS, 2 cases, diagnosed with RAEB-1, and 3 cases, diagnosed with RAEB-2, transformed into AML. Here, 75% of our RAEB-2 patients, constituting high blast number, transformed into AML. When we compared to the literature, along with the fact that our findings are similar, that the percentage increased to 75 percent in RAEB-2 cases can be explained with the low number of cases. In the study, which was made by Breccia et al. [8], the transformation rates to AML was found to be 27% for RAEB-1 and 44% for RAEB-2. In the study, which was made by Kazuma et al. [8], while the transformation of RAEB-1 to AML was 37.5% the

transformation rate of RAEB-2 to AML was found to be 50%. When the mortalities of the patients are compared according to the MDS subgroups, a significant relationship could not be found. However, when we examine RAEB 1 and 2 under a single subject by removing Secondary MDS and MDS 5q diagnoses from MDS subgroups because of the low number of cases, a significant relationship was determined between mortality and MDS subgroups. In terms of its relationship with mortality, the higher the blast rate got in bone marrow (as the diagnosis revised from RA-RARS to RAEB-2), the higher mortality became. According to the Literature, mortality is in the order of RAEB-1-2, RCMD, RARS, RA in order [4]. In the study, in which Breica et al. [14], compared RAEB-1 and RAEB-2, RAEB-1's mortality was found to be 44% while RAEB-2's mortality was found to be 67%. The relationship between mortality and IPSS score was found to be insignificant in our study. Because the cytogenetic result was not certain, the IPSS score could not be determined in some cases, and it could be because of the low number of cases. Along with this, such a relationship cannot be established due to the different responds that the patients given to treatments.

As the result, the age average and gender ratio of the patients were found to be proportional to other studies in MDS. When the MDS subgroups are examined, their occurrence frequencies are similar to the literature. In our patients, the percentage of the chromosomal anomalies, which are seen the most frequently in MDS, is in compliance with other studies. Although it is presented in other studies that the existence of complex cytogenetic anomalies increases mortality, the fact that 12 patients' cytogenetic results were insufficient in our study caused not being able to show this relationship. The patients' transformation to AML was associated with their diagnoses. This relationship is in correlation with other studies. Mortality is related to the ratio of blasts in bone marrow and the rate of cytopenias that developed in connection. It can be suggested that the age factor can also be included into the score system in determining the prognosis with IPSS. Whatever the blast percentage is in bone marrow, the age of the patients is factor in effecting the prognosis, including cytogenetic anomaly. Age is an important factor in selection of the treatment to be chosen.

Informed Consent: *Informed consent was obtained from all individual participants included in the study.*

Conflicts of interest: *There are no conflicts of interest.*

Funding sources: *None.*

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