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CLINICAL CHARACTERISTICS AND EVALUATION OF PROGNOSTIC FACTORS IN PATIENTS WITH MYELODYSPLASTIC SYNDROMES TREATED IN 2008-2012

CHARAKTERYSTYKA KLINICZNA I OCENA CZYNNIKÓW PROGNOSTYCZNYCH CHORYCH NA ZESPOŁY MIELODYSPLASTYCZNE HOSPITALIZOWANYCH W LATACH 2008-2012

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Summary

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders characterized by one, two or three systems peripheral cytopenia and a tendency to transform to acute myeloid leukemia. Myelodysplastic syndromes are the most common hematological malignancies in adults. The present study is one of the few retrospective analyses carried out in Poland for patients with myelodysplastic syndromes. Our study involved 178 patients hospitalized from January 2008 to the end of April 2012 in the Department of Clinical Haematology and Haematological Malignancies Diseases, University Hospital No. 2 in Bydgoszcz. The data were collected retrospectively on the basis of detailed surveys taking into account a number of demographic, clinical and prognostic factors. The analysis showed a significantly positive correlation between MDS and male sex, older age as well as the place of residence in the city. The classification of clinical data, laboratory parameters and prognostic factors showed that the majority of MDS patients represented a low-risk group; about 6% of patients experienced a transformation in acute myeloid leukemia, and the leading causes of death were infectious complications and septic shock. The data collected indicate the need for cytogenetic testing in all patients with MDS to determine the prognosis and indications for treatment.

Streszczenie

Zespoły mielodysplastyczne (*myelodysplastic syndromes* – MDS) są heterogenną grupą klonalnych chorób układu krwiotwórczego charakteryzującą się jedno-, dwu- lub trójukładową cytopenią obwodową i skłonnością do transformacji w ostrą białaczkę szpikową. Zespoły mielodysplastyczne należą do najczęstszych nowotworów układu krwiotwórczego u ludzi dorosłych. Prezentowana praca jest jedną z nielicznych retrospektywnych analiz przeprowadzonych w Polsce dotyczących chorych na zespoły mielodysplastyczne. Obserwacją objęto 178 pacjentów hospitalizowanych w okresie od stycznia 2008 roku do końca kwietnia 2012 roku w Oddziale Klinicznym Hematologii i Chorób Rozrostowych Układu Krwiotwórczego Szpitala Uniwersyteckiego nr 2 w Bydgoszczy. Dane zostały zebrane retrospektywnie na podstawie szczegółowych ankiet uwzględniających szereg czynników demograficznych, klinicznych i prognostycznych. Przeprowadzona analiza wykazała znamiennie dodatnią korelację MDS z płcią męską, starszym wiekiem i miejscem zamieszkania w mieście. Klasyfikacja danych klinicznych, parametrów laboratoryjnych i czynników prognostycznych wykazała, że większość chorych na MDS kwalifikowała się do grupy niskiego

ryzyka, u około 6% badanych wystąpiła transformacja w ostrą białaczkę szpikową, natomiast główną przyczyną zgonów były powikłania infekcyjne i wstrząs septyczny. Zgromadzone dane wskazują na potrzebę wykonywania badań cytogenetycznych u wszystkich chorych na MDS w celu ustalenia rokowania i wskazań do leczenia.

Key words: myelodysplastic syndrome, MDS register, WHO classification, prognostic factors
Słowa kluczowe: zespół mielodysplastyczny – rejestr MDS – klasyfikacja WHO – czynniki prognostyczne

INTRODUCTION

Myelodysplastic syndromes, MDS, are a heterogeneous group of clonal stem cell disorders characterized by one, two or three systems cytopenia, usually cells rich marrow with dishematopoesis features and a high risk of transformation into acute myeloid leukemia (1). Considering the MDS etiology, one can distinguish the primary and secondary MDS, preceded by a known mutagen, usually chemotherapy or radiotherapy (2). The incidence of MDS is 3-12 cases/100 000/year; it increases with age and it is higher in men.

For the MDS diagnosis, it is necessary that the two initial criteria are met: persistent cytopenia: hemoglobin <11g/dl, absolute neutrophil count <1.5 x 10^9/L, platelet count <100 x 10/L, and the exclusion of other diseases that can be the cause of cytopenias or dysplasia and at least one of the criteria specific to MDS: dysplasia ≥ 10% of cells in one of the following cell lines: erythroid, granulocytic and megakaryocyte or the presence of > 15% ring-sideroblasts, the presence of 5-19% blasts in bone marrow smears, typical cytogenetic changes (3).

In 1982 the FAB classification, based on the morphology and including five myelodysplastic syndromes subtypes (RA - Refractory anemia, RARS - RA with ring Sideroblasts, RAEB - Refractory anemia with excess blasts, RAEB-t - RAEB in transition and CMML - Chronic myelomonocytic leukemia was published. In 2001 a new MDS classification according to the WHO was proposed; the RCMD subtype was introduced; Refractory cytopenia with multilineage dysplasia, with dysplasia found in more than one cell line, the RA subtype was narrowed down to the cases with dysplasia only in the erythroid line. It was distinguished between the RAEB-1 subtype (5-9 % of blasts in bone marrow) and RAEB-2 (10-19% of blasts in bone marrow), and the patients with a number of blast cells in the bone above 20% were classified as diagnosed with as acute myeloid leukemia (the MDS RAEB-t subtype was eliminated); the 5q syndrome subtype was isolated. The patients with the presence of dysplasia in only one line: granulocytic or megakaryocytic dysplasia, with the number of blasts in the bone marrow below 5% was classified as the MDS-U subtype (unclassified MDS). Chronic myelomonocytic leukemia was eliminated and classified as representing the group of myeloproliferative-myelodysplastic diseases (4). In 2008 a revised classification provided by the WHO was published (5). It differs from the previous classification: the isolation of resistant subtypes refractory neutropenia and thrombocytopenia (respectively: RN - Refractory neutropenia and RT – Refractory thrombocytopenia), which belonged to the MDS-U group, otherwise defined as MDS-U (where dysplasia occurs in less than 10% the cell line) with the presence of cytogenetic changes, eliminating the RCMD-RS form, classifying as RAEB-2 cases with the presence of Auer rods in the peripheral blood or bone marrow.

Among the prognostic indices and predictive factors of the response to the treatment presented over the recent years, it is the International MDS predictor (International Prognostic Scoring System - IPSS) published by Greenberg et al. in 1997 which is most essential. It considers the percentage of blasts in the marrow, the number of peripheral blood cytopenias and the type of cytogenetic damage (6). With that in mind, four MDS risk groups were distinguished: low, intermediate-1, intermediate-2 and high. Proposed by Malcovatiego et al. in 2007, the WPSS-WHO index considers the MDS type according to the WHO, the karyotype and the need for packed RBC transfusion, which worsens the prognosis (7). The adverse prognostic cytogenetic changes in MDS include mostly complex aberrations (≥ 3), and various abnormalities of chromosome 7th. These indices are widely used; however, they do not include some factors essential for the prognosis of patients with MDS, such as the general condition, the age or comorbidities. What is less known in Poland is the MD Anderson Prognostic Risk Model, proposed by Kantarijan et al., published in 'Cancer' in 2008. It addition to the platelet count, it includes leukocyte count, percentage of blasts, depending on the RBC concentrate transfusion and cytogenetics as well as the patient's general condition

according to the WHO and the age (8). In recent years there have been isolated a number of independent adverse prognostic factors in patients with MDS, e.g. a high LDH activity, increased red blood cell volume (> 100 fl), smoking, hypoalbuminemia, bone marrow fibrosis.

The treatment of myelodysplastic syndromes is still not satisfactory in most cases. The applicable literature reports on the survival being affected by adverse factors; the patient's age, comorbidities, an advanced MDS form, high IPSS, the dependence on the blood component transfusion as well as iron overload (9.10).

The aim of this study was to evaluate demographic data, clinical and prognostic factors in patients with myelodysplastic syndromes.

MATERIAL AND METHODS

The study was conducted among 178 patients: 96 men and 82 women, with the median age of 69 in men and in women – 63, hospitalized with myelodysplastic syndromes in the Department of Clinical Haematology and Haematological Malignancies Diseases, University Hospital No. 2 in Bydgoszcz from January 2008 till the end of April 2012. The data were collected retrospectively on the basis of detailed surveys prepared for the Polish Register of patients with MDS in 2008: the basic survey considered the sex, age, the date of the first MDS diagnosis, the place of residence, the exposure to toxic agents, the cancer history, peripheral blood counts (% blasts, ANC), an MDS subtype according to the WHO 2008, cytogenetics, IPSS, packed red blood cells/ platelet concentrate transfusion dependence, serum ferritin. The supplementary survey, the autoimmune diseases and follow-up survey, the treatment with iron chelators, the transformation into acute myeloid leukemia, death (date, cause), the loss of observations. The MDS diagnosis was based on current clinical and laboratory criteria. The clinical disease stage was determined according to the 2008 WHO MDS classification and based on prognostic factors according to IPSS.

RESULTS

Patients qualified for the analysis included a group of 96 men (54%) and 82 women (46%) with the median age of 69 in men and 63 in women. The group below 50 years included 21 (12%) patients (8 men and 13 women) and above 70 years of age as many as 79 (44%) patients (51 men and 28 women); the other patients, 78 (44%) were between 50 and 70 years of age. Fig. 1.

Most patients resided in the city - 132 (74%). Considering the study population exposure to harmful factors, it has been demonstrated that 19 (11%) patients were exposed to chemical toxins (including 10 people who have been in contact with plant protection agents); 36 (20%) patients were smokers; 21 (12%) of those interviewed reported to suffer from malignancy (usually it was a prostate cancer- 5 persons, colorectal cancer- 4, kidney cancer- 3, lung cancer- 2, one case of breast cancer, cervix, testis, skin, thyroid, sarcoma of the ribs and chronic lymphocytic leukemia each), in the past, chemotherapy was used in 7 patients, and radiotherapy in 5 patients and in 10 (6%) patients with MDS diagnosed the autoimmune disease coexisted.

The distribution of MDS subtypes according to the WHO was as follows: RA- 4 (2%) individuals, RN- 9 (5%), RT- 14 (8%), RARS- 19 (11%), RCMD- 39 (22%), RAEB1- 31 (17%), RAEB2- 13 (7%), MDS-U- 44 (25%) and CMML- 5 (3%). Fig. 2.

Cytogenetics was performed in 28 (16%) patients, of which 13 people represented the group of low risk (LR), 9 in the intermediate risk I (IR-I) group, and 6 in the group of intermediate risk II group (IR-II), according to the IPSS.

At the time of the diagnosis, the following were recorded: the average value of HGB- 11 g/dl, PLT- 179 G/l, ANC - 3.0 g/l. Having excluded five patients with CMML from the analysis, the mean values of blood count parameters evaluated were the following: HGB - 11 g/dl, PLT- 176 G/l, ANC - 2.4 g/L. 37 (21%) patients depended on packed red blood cells transfusion and 9 (5%) – on the platelet concentrate substitution; elevated serum ferritin> 1000 µg/l was observed in 19 (11%) patients.

In the entire group of 178 patients diagnosed with MDS, there were identified 10 (6%) transformations into acute myeloid leukemia, including five patients diagnosed with the RAEB2 subtype and 25 (14%) deaths; in 22 cases the cause of death was the infection leading to septic shock, in two patients diathesis and stroke occurred, one patient committed suicide. Among the dead there were reported more advanced MDS subtypes according to the WHO: RAEB2 - 8 persons, RAEB1 - 7, RCMD - 2, RARS - 2, MDS-U - 5 and CMML – 1.

Over the 52 months there were lost 91 (51%) patients from outpatient observations, including 25 deaths. The other surviving patients were referred for

follow-up in the outpatient hematological clinic or adjunctive treatment of transfusion of blood components in the place of residence or at another hospital in Bydgoszcz.

DISCUSSION

In this study for the entire group of 178 MDS patients, an analysis of demographic, clinical and prognostic factors was carried out. The study revealed that the men - 96 (54%) and the people older than 70 years of age prevailed; 79 (44%) patients (51 men and 28 women). Urban residents were more likely to suffer; 132 (74%). Similar findings come from the database of other haematological centers, such as the of the Düsseldorf Haematological Register (1975-2001, n-1886), SEER+NAACCR (2001-2003, n-24798) and from the Polish Register (2008, n-966).

The etiology and pathogenesis of myelodysplastic syndromes, expressed in clonal hematopoietic stem cell damage, indicate the search for causal factors in the history of the patient. In the population of the studied MDS patients it was reported that 19 (11%) patients were exposed to chemical toxins (including 10 people who have been in contact with plant protection agents). Malignant tumors are more common in patients over 60 years of age, and MDS occurs predominantly in this age range, and so it is difficult to determine whether there is a positive correlation between these two diseases, in addition to significantly higher incidence of cancer of the lymphatic system reported in literature. In our study there was no significant correlation in this range - 21 (12%) of those interviewed reported also that they suffered from cancer, chemotherapy was used in 7 patients, and radiotherapy – in 5 patients.

Advanced forms of myelodysplastic syndromes are characterized by a short survival time and a high risk of transformation to acute myeloid leukemia (RAEB according to the WHO classification) (11). In the present study the distribution of MDS subtypes according to the WHO was as follows: RA- 4 (2%) patients, RN- 9 (5%), RT- 14 (8%), RARS- 19 (11%), RCMD- 39 (22 %), RAEB1- 31 (17%), RAEB2- 13 (7%), MDS-U- 44 (25%) and CMML- 5 (3%). The Polish Register of Patients with MDS in the observation period: 03.2008 to 05.2009, reported that in the group of 966 patients, there were comparable percentages of individual subtypes shown (12). In the studied group we found 10 (6%) transformations in acute myeloid leukemia, including five patients with the RAEB2subtype and 25 (14%) deaths - in 22 cases the cause of death was infection leading to septic shock. Among the dead, there were reported more advanced MDS subtypes according to the WHO.

Cytogenetics was evaluated only in 28 (16%) patients, of which 13 people were found in the group of low risk (LR), 9 in the group of intermediate risk I (IR-I), and 6 in the group of intermediate risk II (IR-II), according to the IPSS. In view of the increasing number of new reports on the crucial role of cytogenetic studies in difficult diagnosis and prognosis of patients with MDS, we are confident about the validity of the performance of such studies in all the patients with suspected MDS.

In patients with myelodysplastic syndromes ineffective erythropoiesis occurs and in the majority of them anemia of varying degree is diagnosed. A significant proportion of patients require frequent transfusions of packed red blood cells (transfusion dependence), and the frequency of transfusion is different; an average of 2 packed red blood cells units every 2-6 weeks (packed red blood cells transfusion of 2 units / month provides approximately 5 g of iron per year) (13). Another important cause of iron overload in patients suffering from MDS is its increased absorption from the gastrointestinal tract. Elevated serum ferritin levels (> 1000 μg/l), which is an acute phase protein and indirectly determines the concentration of iron in the body, is associated with shortened survival, contributing primarily to cardiac complications. According to the Polish Register of Patients with MDS, the mean HGB was 9.1 g/dl, 44% of the patients depended on the packed red blood cells transfusion and an elevated serum ferritin (> 1000 μg/l) was found in 32%. Our findings showed, respectively, the average value of HGB - 11 g/dl, depending on the substitution of packed red blood cells - 37 (21%) patients, and elevated serum ferritin (> 1000 μg/l) – in 19 (11%) patients. Taking into account the fact that during the 52 months as many as 91 (51%) patients were lost from the follow-up outpatient observations, the data on the number of transfused packed red blood cell units and markers of iron overload is likely to be underestimated and requires the verification of the MDS patient monitoring system.

CONCLUSIONS

1. The analysis of demographic factors showed a significant positive correlation between

MDS and the male sex, older age as well as the place of residence of patients in the city.

2. The present study showed that most patients with MDS were found in the low- risk group, whereas in the high-risk patients higher mortality caused mainly by infectious complications was observed.
3. Own observations of patients with MDS indicate the need for cytogenetic testing in all the diagnosed patients in order to determine the prognosis and indications for treatment and to improve the monitoring of the myelodysplastic syndromes.

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