ORIGINAL PAPER   Mater Sociomed. 2014 Oct; 26(5): 292-296

Influence of Prognostic Factors on Overall Survival in Myelodysplastic Syndromes

Tatjana Sotirova[1], Aleksandar Stojanovic[1], Sonja Genadieva-Stavric[1], Svetlana Krstevska[1], Dejan Spasovski[2], Trajan Balkanov[3]

University Clinic of Hematology, Ss Cyril and Methodius University, Skopje, Macedonia[1]
University Clinic for Rheumatology, Ss Cyril and Methodius University, Skopje, Macedonia[2]
Institute for Pharmacology, Ss Cyril and Methodius University, Skopje, Macedonia[3]

Corresponding author: Tatjana Sotirova, MD. University Clinic of Hematology, Ss Cyril and Methodius University, Skopje, Macedonia. Phone : +389 75 239 700; E-mail: tatjanaso@hotmail.com

ABSTRACT

Background: Accurate prediction of a patient's prognosis is useful to define the risk posed by the disease. Age, gender, peripheral blood cytopenia, proportion of bone marrow (BM) blasts, performance status, comorbidities, transfusion dependence, specific karyotype abnormalities and molecular biomarkers can refine the prediction of prognosis in MDS. **Aim:** to assess the influence of the some prognostic factors like age, gender, cytopenia, BM blast percentage, transfusion dependence, ferritin, hemoglobin (Hb), lactate dehydrogenase (LDH), albumin and specific karyotype abnormalities in myelodysplastic syndromes on overall survival (OS). **Patients and methods:** we retrospectively analyzed the cohort of 108 patients diagnosed between 1.1.2011 and 31.12.2013 at the University Clinic of Hematology, Ss Cyril and Methodius University, Skopje, Macedonia. They were evaluated for clinical and hematologic features at diagnosis and at leukemic transformation. **Results:** in the study group 62 were man and 46 women. Male to female ratio was 1.35 to 1. The differences in OS between men and women were significant (p = .03015). The mean age at diagnosis was 66,6 years. According to the age OS was 16,4 months. FAB subtypes influenced OS significantly (p = .03015). OS inversely correlated with BM blast percentage (p= .02327). Cytopenia had no impact on OS (p=.33755). Hb as a whole and groups with different levels of Hb had no influence on OS (p = .12142) and (p= .07535), respectively. The group with ferritin <500 μg/L had better OS (p=.04720). Transfusion dependence, LDH and albumin had no impact on OS. Leukemic transformation was noticed in 10 (9,3%) patients. Mortality was 36,1%. **Conclusion:** gender, FAB subtypes, BM blast percentage and the serum levels of ferritin had an influence on OS, while age, hemoglobin level, transfusion dependence, LDH and albumin had no impact on OS.
Key words: myelodysplastic syndromes, prognostic factors, overall survival.

1. INTRODUCTION

Myelodysplastic syndromes (MDSs) are a heterogeneous group of disorders characterized by dysplasia in one or more cell lines**,** followed by a progressive impairment in the ability to differentiate, manifested with peripheral cytopenia and an increasing risk of evolution into acute myeloid leukemia (AML) (1, 2).

The clinical course is variable so much effort has been focused on methods for predicting prognosis. Accurately predicting the prognosis once a malignancy has been diagnosed is of great importance to both patients and their physicians alike (1). From a patient's perspective, the prognosis helps define the severity of disease and sets expectations as to how it is likely to impact them. In contrast, prognostic information from a physician's standpoint is essentially a means of staging the disease in a manner that can be used to help direct therapy (3). For both patients and physicians, the estimation of prognosis is a continual process that does not happen just at the time of diagnosis. Reevaluating the prognosis may be useful when a patient shows signs of progression or after they have become refractory to standard treatment (3). The vast majority of cases (80% to 90%) occur 'de

novo', whereas 10% to 20% of cases are secondary (4). French-American British (FAB) classification for MDS is still in use, based on morphologic findings (5). The standard prognostic tool for prognosis in MDS is the International Prognostic Scoring System (IPSS) which classifies patients into low-, intermediate-1, intermediate-2 and high-risk categories. IPSS takes into account BM blast percentage, number of cytopenia and cytogenetic abnormalities (6, 7, 8). Beside the known prognosis factors included in the IPSS, other variables that have an impact on prognosis in MDS were studied: age (4, 9, 10, 11, 12), gender (4, 11, 12), FAB subtypes (13), degree of anemia and RBC transfusion dependence (7, 8), ferritin (14, 15, 16, 17, 18), LDH (19), albumins (20), mutations (21, 22, 23) and comorbidities (24).

Diagnosis requires BM examination and cytogenetic studies, and lately molecular studies. The consensual minimum criterion for diagnosis is the presence of erythroid, granulocyte or megakaryocyte dysplasia in 10% or more of informative cells (25). One must exclude the possibility of erythroid dysplasia associated with vitamin B_{12}/ folate/copper deficiency, viral infections, chemotherapy, or lead/arsenic poisoning (26).

The incidence of MDS increases with age (median about 70 years). MDS is rare in children (4, 9, 10, 11, 36) Age had a significant effect on OS of the MDS population analyzed as a whole and stratified by subgroups–the older the age, the worse the prognosis. During the analysis on the subgroups, the effect of age was statistically relevant within RA and RARS patients, whereas it was not significant within and RAEB subgroup (36).

A significant influence of sex on OS was observed in several studies. The overall incidence of MDS is slightly higher in males than in females (1.5–2 to 1). Male patients had worse prognosis (4, 11). Considering subgroups, the effect of sex was relevant in refractory cytopenia, but did not affect the outcome in patients with RAEB (36).

According to the multivariate analysis peripheral cytopenia did not reach a statistical significance on OS in MDS patients (12). FAB subtypes can worsen the prognosis in MDS in terms of OS, with differences among subtypes. Refractory anemia had the best and RAEB-T the worst prognosis (13).

Blast count showed a significant predictive value on OS in MDS patients (36). More than 5% blasts in BM are considered as a bad prognostic factor for OS and leukemic transformation (23, 27).

Red blood cell (RBC) transfusions are a commonly used therapy to treat symptomatic anemia that affects most patients with MDS. Transfusion dependence is defined by the MDS International Study Group (2000) as requiring transfusion of at least one RBC at 8 weeks for 4 months (13). Transfusion-dependent patients had shorter survival rate than those who received less than 18 units of blood over a period of 36 months (37).

Serum ferritin level ≥500 µg/l at diagnosis was a strong independent predictor of survival. Serum ferritin was significantly correlated with OS in Chinese patients (14). These patients suffer from comorbidities such as heart failure, diabetes, infections, disorders of the thyroid gland and liver, shortening their survival (14, 15, 16, 17, 18).

Lactate dehydrogenase (LDH) is a parameter that should be recognized as a prognostic factor in MDS (19). One German study pointed out the correlation between LDH level and OS (23). Serum albumin is an independent prognostic factor that influences OS in patients with MDS. Hypoalbuminemia is a marker for shorter OS in MDS (20).

Recurrent chromosomal abnormalities have been identified in 40–70% of the 'de novo' MDS and 95% of secondary MDS. These chromosomal aberrations include 5q-, 7q-/-7, +8, 20q-, 12p-, abnormalities in 17p, 11q23 and chromosome 3 (28). Favorable prognostic markers according to IPSS include: a normal karyotype, 5q- as an isolated anomaly, 20q- as an isolated anomaly and -Y chromosome. Karyotype findings associated with poor prognosis include complex karyotype and abnormalities of chromosome 7. Other cytogenetic abnormalities confer an intermediate prognosis (1, 28). Abnormal karyotype correlates with poor prognosis and shorter OS (21, 29). According to the multivariate analysis, cytogenetics showed a significant predictive value on OS (12).

Somatic mutations are identified in more than 70% of patients with MDS, including more of the patients with normal karyotype. These mutations are major predictors of the clinical phenotype, and could also be predictors of prognosis (21, 22, 23).

The incidence of MDS increases with the age, so does the prevalence of comorbidities. About 50% of MDS patients have one or more comorbidities. Congestive heart disease, hypertension, lung diseases, diabetes, liver failure, bleeding and solid tumors are cited as the most often reasons for non-leukemic dead (24). Comorbidities are significant and independent predictors in MDS (24). Congestive heart disease and chronic obstructive lung disease are associated with shorter OS, while diabetes and cerebro-vascular diseases do not change prognosis in MDS (24).

The median OS in MDS is 2.5 years (10). Prognosis is poor for patients with MDS, with 3-year survival rates estimated at less than 50% (30). The median survival rates according to IPSS are estimated at 8, 5.3, 2.2, and 0.9 years, respectfully (23, 31).

2. AIM

The aim of this study was to assess the influence of the some prognostic factors in myelodysplastic syndromes (age, gender, cytopenia, BM blast percentage, transfusion dependence, serum levels of hemoglobin, ferritin, lactate dehydrogenase and albumin, and specific karyotype abnormalities) on OS.

3. PATIENTS AND METHODS

We retrospectively analyzed the cohort of 108 patients (62 male and 46 female) diagnosed between 1.1.2011 and 31.12.2013 at the University Clinic of Hematology, Ss Cyril and Methodius University, Skopje, Macedonia. They were evaluated for clinical and hematologic features at diagnosis and leukemic transformation. Observation time was 36 months. Diagnosis was made upon dysplastic changes in peripheral blood smear and bone marrow aspirate. Confirmation analysis included bone marrow aspirate, cytochemical stain, immunohistochemical tests, cytochemical stain of medullar iron and karyotype analysis in some cases. We evaluated some parameters that could influence OS: age, gender, cytopenia, BM blast percentage, transfusion dependence, serum levels of Hb, ferritin, LDH and albumin as well as specific karyotype abnormalities. Chromosomal analysis was performed only in 5 patients using BM aspirate, according to laboratory procedures. IPSS was not calculated in the vast majority of patients, because we could not perform cytogenetic analysis in all patients. Most patients (pts) received supportive care: transfusion of RBC and platelets, red cell and granulocyte growth factors (21 pts), vitamins, corticosteroids, iron chelatation therapy (7 pts), some received chemotherapy (4pts) and few patients allogeneic transplantation (3 pts). OS was estimated in months including the period from the date of diagnosis to the time of death / time of last visit. Leukemic transformation was noticed in 10 (9,3%) patients. Mortality was 36,1%. Infectious and hemorrhagic complications as well as BM failure were considered causes of MDS-related deaths.

4. RESULTS

Mean age at diagnosis was 66,6 years (range 18-89) (SD 14.2). Mean OS depending on age was 16,4 months, and it was not statistically significant (p= .46375). In our study, 62 (57.4%) patients were men, 46 (42.6%) women. Male to female ratio was 1.35 to 1. Women had better OS than men (p = .00819). (Figure 1). According to the FAB classification patients were classified as follows: 75 patients as having refractory anemia (RA; 69.4%), 1–RA with ringed sideroblasts (RARS; 0.9%), 21–RA with excess of blasts (RAEB; 19.4%), 3–RAEB in transformation (RAEB-T 2.8%), and 8 as having chronic myelomonocytic leukemia (CMML 8.2%). (Table 1)
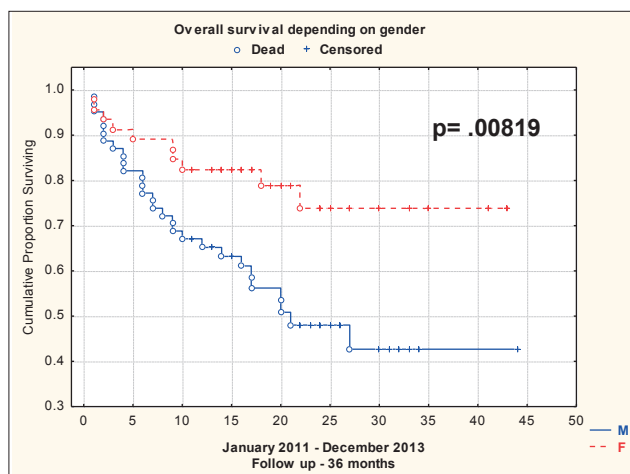
Figure 1. OS depending on gender

FAB classification	Number	%
RA	75	69.4
RARS	1	0.9
RAEB	21	19.4
RAEB—T	3	2.8
CMML	8	8.2

Table 1. Distribution of patients according to the FAB classification

Statistically significant differences in OS were found among patients with RA, RAEB, RAEB-T and CMML (p = .03015). (Figure 2)

Cytopenia had no influence on OS (p=.09340). In our group 23 patients (21.3%) presented with one cytopenia, 46 patients (42.6) with bicytopenia and 39 patients (36.1%) with pancytopenia. There was no statistically significant difference in OS among patients with different cytopenia (p = .33755).

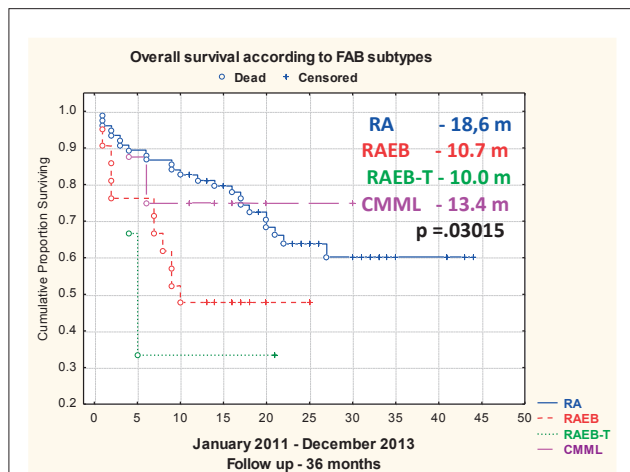
Figure 2. OS depending on FAB subtypes

Percentage of BM blasts correlated with OS (p=.02327). Mean OS in the group with < 5% blasts was 17,8 months, in the group with blasts 5-9%–17.7 months, with blasts 10-19%–9.7 months and in the group with 20-30% blasts – 9.5 months. The differences among groups were statistically significant (p<0.05).

Mean Hb level in our cohort was 85,1 g/L (range 41-150). Hb had no impact on OS (16.4 months) (p=.12142). The patients were grouped in three categories according to the severity of anemia: severe anemia (Hb <70 g/L), moderate anemia (Hb 70-100 g/L) and patients with Hb >100 g/L. OS was highest in patients with Hb >100 g/L–21.6 months, in moderate ane-

mia–14,8 months and in severe anemia–15.2 months, being not statistically significant (p=0.07535).

Mean level of serum ferritin in our group was 3826.1μg/L. Serum ferritin had no impact on OS – 16,5 months (p=.13178). But, groups with ferritin <500 μg/L (17 months) and >500 μg /L (16 months) had significant differences in OS (p= .04720). (Figure 3).

Transfusion dependence is defined by the MDS International Group (2000) study as requiring transfusion of at least one packed red blood cells (RBC) at 8 weeks for 4 months (13) OS depending on transfusion as a whole was 16.2 months, being not statistically significant (p= .16298). OS in the group without RBC was 16.5 months, in the group that received ≤ 18 RBC had OS 15.4 months, and the group that received >18 RBC had OS 19.8 months. Mean transfused doses in this cohort were 13.2 RBC (St.dev.-16.8). Transfusion dependent patients with >18 doses RBC had shorter survival than patients who required ≤ 18 doses RBC, being not statistically significant (p=.72185).
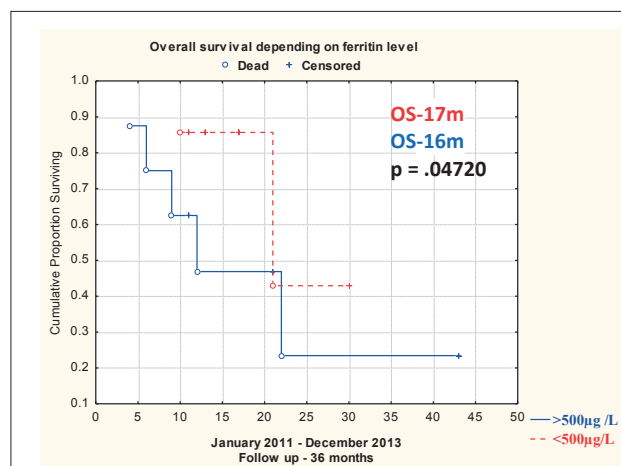

Figure 3. OS in groups with different serum ferritin levels

Mean serum level of LDH was 809 IU/L. There was no statistical significance in OS between the two groups with different LDH (<423 IU/L and >423 IU/L) (p = .48310).

Mean albumin level in the study group was 39g/L. Albumins had no influence on OS – 20 months (p= .25087). There was no statistical significance in OS between the two groups with different levels of albumins (<40 g/L and >40 g/L) (p=.18986).

When testing mutual influence of several parameters on OS, we found that age, gender, FAB subtypes, bone marrow blast percentage, hemoglobin level and transfusion dependence had statistically significant impact on OS (p=.01628).

We were unable to perform cytogenetic analysis in all patients. From those 5 patients who underwent cytogenetic tests, 3 had normal karyotype, one patient had +8 and one inv16. We could not show survival curves due to the small number of patients in whom cytogenetic analysis was performed.

5. STATISTICAL ANALYSIS

The statistical analysis was performed using statistical package SSPS 16.0. For the parameters or variables used in this paper, the range, mean and standard deviation were presented. Differences among variables were evaluated by the Chi-square test. The determinations of correlations between different variables was based on the Pearson correlation coefficient in all cases where the variables had a normal distribution, and a certain correla-

tion was considered statistically significant if p <0.05. Overall survival was defined as the time interval between diagnosis date and death date. Patients who were alive were censored at the last follow-up date. The probabilities of OS were estimated using the method of Kaplan and Meier. Cox proportional hazards regression models were used to assess the association between prognostic factors and OS.

6. DISCUSSION

Our results considering age (66.6 years) correspond with those in the literature (12). Age in this group did not affect OS neither as a whole nor stratified by subgroups, similar with some studies (36). Considering gender, men had worse OS than women, corresponding with the data in the literature (4, 11, 32). FAB subtypes had a significant effect on OS. Considering subtypes, the worst results were observed in RAEB-T, than in CMML, RAEB and RA subtype, similar with those in the literature (13). There was only one patient with RARS and he was not taken in consideration. Cytopenia had no impact on OS, corresponding with some data in the literature (12). But, others showed opposite results (8, 27, 33, 34). OS correlated inversely with BM blast percentage, showed in other studies (23, 27). Hemoglobin as a whole and stratified into subgroups did not show any impact on OS (12). Transfusion dependence could be an independent prognostic factor for bad prognosis (2, 17, 35), although in our study group the influence on OS was not significant. Serum ferritin level ≥500 µg/L at presentation is an independent poor predictor for OS (14). The group with ferritin <500 µg/L had better OS. LDH is a factor sited as having predictive value (19), although we could not prove that. Hypoalbuminemia is an independent poor prognostic factor in MDS patients (20), but in our study group it was not significant.

Cytogenetics in other studies showed a significant predictive value on OS (36) and patients were accordingly stratified in groups with different IPSS score (3, 27, 29). Only 5 patients were analyzed for cytogenetic abnormalities, three of them with good prognosis, and two of them (+8, inv16) with intermediate prognosis.

Limitations in our study include retrospective analysis, insufficient data on cytogenetic analysis and impossibility to stratify patients according to IPSS score, lack of data on comorbidities, insufficient data on ferritin, LDH and albumins, that probably reflected on the results making some of them different than those cited in the literature.

CONFLICT OF INTEREST: NONE DECLARED.

REFERENCES

1. Cazzola M. Risk assessment in myelodysplastic syndromes and myelodysplastic/ myeloproliferative neoplasms. Haematologica. 2011; 96: 349-351.
2. Cazzola M, Malcovati L. Myelodysplastic syndromes-coping with ineffective hematopoiesis. N Eng J Med. 2005; 352: 536-538.
3. Bejar R. Clinical and Genetic Predictors of Prognosis in Myelodysplastic Syndromes. 2014; 99(6): 956-964.
4. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982; 51: 189-199.
5. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997; 89: 2079-2088.
6. Giagounidis A, Leto di Priolo S, Ille S, et al. A European survey on the detection and management of iron overload in transfusion-dependent patients with MDS. Ann Hematol. 2011; 90: 667-673.
7. Pardanani A, Tefferi A. Prognostic relevance of anemia and transfusion dependency in myelodysplastic syndromes and primary myelofibrosis. Haematologica. 2011; 96: 8-9.
8. Codispoti KET, Depalma L. Myelodysplastic syndrome in elderly patients: correlation of CBC with cytogenetic and FISH analysis. Int J Lab Hematol. 2010; 32: 443-448.
9. Scott Bl, Deeg HJ. Myelodysplastic syndromes. Annual Review of Medicine. 2010; 61: 345-358.
10. Sanz GF, Sanz MA, Greenberg P. Prognostic factors and scoring systems in myelodysplastic syndromes. Haematol. 1998; 83: 358-368.
11. Malcovati L, Della-Porta MG, Strupp C, Ambaglio I, Kuendgen A, Nahtkamp K. et al. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndromes and its integration into the WHO Classification-based Prognostic Scoring System (WPSS). Haematologica. 2011; 96(10): 1433-1440.
12. Vallespi T, Torrabadella M, Julia A. et al. Myelodysplastic syndromes: a study of 101 cases according to the FAB classification. Br J Haematol. 1985; 61(1): 83-92.
13. Li B. Xu Z. Gale R.P. Qin T. Zhang Y. Xiao Z. Serum Ferritin Is an Independent Prognostic Factor in Chinese with Myelodysplastic Syndromes Classified as IPSS Intermediate-1. Acta Haematol. 2013; 129: 243-250.
14. Pullarkat V. Objectives of iron chelation in myelodysplastic syndromes: more than meets the eye? Blood. 2009; 114(26): 5251-5255.
15. Goldberg SL. et al. Incidence and Clinical Complications of Myelodysplastic Syndromes among United States Medicare Beneficiaries. J Clin Oncol. 2010; 28: 2847-2852.
16. Takatoku M. et al. Retrospective nationwide survey of Japanese patients with transfusion-dependent MDS and aplastic anemia highlights the negative impact of iron overload on morbidity/mortality. Eur J Hematol. 2007; 78: 487-494.
17. Genadieva-Stavric S, Georgievski B, Stojanovski Z, Krstevska-Balkanov S, Pivkova A, Trajkova S, Genadieva-Dimitrova M, Serafimovski V. Iron overload in patients with transfusion dependent myelodysplastic syndrome. Prilozi. 2011; 32(1): 295-304.
18. Wimazal F, Sperr WR, Kundi M. et al. Prognostic significance of serial determinations of lactate dehydrogenase (LDH) in the foolow-up of patients with myelodysplastic syndromes. Ann Oncol. 2008; 19: 970-976.
19. Komrokji RS. et al. Hypoalbuminenemia is an independent prognostic factor for overall survival in myelodysplastic syndromes. Am J Haematol. 2012; 87: 1006-1009.
20. Bejar R. Clinical and genetic predictors of prognosis in myelodysplastic syndromes. Haematologica. 2014; 99: 956-964.
21. Rocquain J, Carbuccia N, T rouplin V, et al. Combined mutations of ASXL1, CBL, FLT3, IDH1,IDH2, JAK2, KRAS, NPM1, NRAS, RUNX1, TET2 and WT1 genes in myelodysplastic syndromes and acute myeloid leukemias. Biomed Central Cancer. 2010; 10: 401-408.
22. Grenberg PL. The Multifaceted Nature of Myelodysplastic Syndromes: Clinical, Molecular and Biological Prognostic Features. J Natl Compr Canc Netw. 2013; 11: 877-885.
23. Naqvi K, Garcia-Manero G, Sardesai S, Oh J, Vigil CE, Pierce S, Lei X, Shan J, Kantarjian HM, Suarez-Almazor ME. Association of comorbidities with overall survival in myelodysplastic

syndrome: development of a prognostic model. J Clin Oncol. 2011; 29(16): 2240.

24. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009; 114: 937-951

25. Tefferi. Myelodysplastic syndromes – Many New Drugs, Little Therapeutic Progress. Mayo Clin Proc. 2010; 85(11): 1042-1045.

26. Jabbour E, Takahashi K, Wang X, Cornelison AM, Abruzzo L, Kadia T, Borthakur G, Estrov Z, O'Brien S, Mallo M, Wierda W, Pierce S, Wei F, Chen R, Kantarjan H, Garcia-Manero G. Acquisition of cytogenetic abnormalities in patients with IPSS defined lower-risk myelodysplastic syndrome is associated with poor prognosis and transformation to acute myelogenous leukemia. Am J Hematol. 2013; 88(10): 831-837.

27. Haase D. Cytogenetic features in myelodysplastic syndromes. Ann Haematol. 2008; 87(7): 515-526.

28. Bejar R, Levine R, Ebert BL. Unraveling the molecular pathophysiology of myelodysplastic syndromes. J Clin Oncol. 2011; 29: 504-515.

29. Rollison DE, Howlader N, Smith MT, et al.Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. Blood. 2008; 112: 45-52.

30. Germing U, Hildebrandt B, Pfeilstocker M, et al. Refinement of the international prognostic scoring system (IPSS) by including LDH as an additional prognostic variable to improve risk assessment in patients with primary myelodysplastic syndromes (MDS). Leukemia. 2005; 19: 2223-2231

31. Nösslinger T, Tüchler H, Germing U, Sperr WR, Krieger O, Haase D, Lübbert M, Stauder R, Giagounidis A, Valent P. Prognostic impact of age and gender in 897 untreated patients with primary myelodysplastic syndromes. Ann Oncol. 2010; 21 (1): 120-125.

32. Gonzalez-Porras JR, Cordoba I, Such E, Nomdedeu B, Vallespi T, Carbonell F, Luño E, Ardanaz M, Ramos F, Pedro C, Gomez V, de Paz R, Sanchez-Barba M, Sanz GF, Del Cañizo AC, Spanish Myelodysplastic Syndrome Registry. Prognostic impact of severe thrombocytopenia in low-risk myelodysplastic syndrome. Cancer. 2011; 117(24): 5529.

33. Cheson BD. The Myelodysplastic Syndromes. The Oncologist. 1997; 2(1): 28-39.

34. Itzykson R, Thépot S, Quesnel B, Dreyfus F, Beyne-Rauzy O, Turlure P, et al. Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine. Blood. 2011; 117(2): 403-411.

35. Malcovati l, Della Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, Passamonti F, Arcaini L, Maffioli M, Bernasconi P, Lazzarino M and Cazzola M. Prognostic Factors and Life Expectancy in Myelodysplastic Syndromes Classified According to WHO Criteria: A Basis for Clinical Decision Making. JCO. 2005; 23(30): 7594-7603.

36. Triantafyllidis I, Ciobanu A, Stanca O, Lupu AR. Prognostic factors in Myelodysplastic syndromes, Maedica (Buchar). 2012; 7(4): 295-302.