

Some Prognostic Factors in Myelodysplastic Syndromes Can Influence Overall Survival

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Abstract: Myelodysplastic syndromes are very heterogeneous in lot of aspects. Scientists are trying to find prognostic factors that have implication on overall survival in order to incorporate them in prognostic systems, which would enable refinement of patient's risk stratification. The aim of our study was evaluation of the prognostic significance of age, sex, blast percentage in bone marrow, cytopenias, MCV, transfusion dependency, serum ferritin, serum LDH, serum albumin, comorbidities, chromosomal abnormalities in MDS patients and their influence on overall survival, progression and transformation in acute myeloid leukemia. Our cohort consisted of 70 adult patients 33 women and 37 men, 66 pts with 'de-novo' and 4 pts with therapy-related MDS, diagnosed in the University Clinic of Hematology, "Ss Cyril and Methodius" University, Skopje, Macedonia, from January 2011 till April 2015, with the follow up period of 52 months. The univariate analysis revealed that factors associated with OS were: platelet number, blast percentage in the bone marrow, IPSS and R-IPSS. Multivariate analysis revealed that factors associated with OS were: platelets < 100x10⁹/L, IPSS - low risk and R-IPSS - intermediate risk.

Keywords: myelodysplastic syndromes, prognostic factors, overall survival

I. Introduction

Myelodysplastic syndromes are very heterogeneous in lot of aspects. Prognosis is poor with 3 years overall survival (OS) in <50% of patients. So, the most frequently asked question both from patients and physicians is how much time they have left. In order to answer that question scientists are trying to find out which prognostic factors influence OS. They focus on one, or more often on combinations of prognostic factors such as: age(1,2,3), sex(4,5), cytopenias(6,7,8), blast percentage in bone marrow (9), mean corpuscular volume (MCV) (10), serum lactate dehydrogenase (LDH) (11,12), serum albumin (13), transfusion dependency (14,15), serum ferritin (16,17), comorbidities (18,19), chromosomal abnormalities(20,21,22,23) and in the last two decades- gene mutations (24,25,26).

II. Aim of the Study

The aim of the study was evaluation of the prognostic significance of age, sex, blast percentage in bone marrow, cytopenias, MCV, transfusion dependency, serum ferritin, serum LDH, serum albumin, comorbidities, chromosomal abnormalities in MDS patients and their implication on overall survival, progression and transformation in acute myeloid leukemia.

III. Material and Methods

Our cohort consisted of 70 adult patients (>18 years), 33 women (47.1%) and 37 men (52.9%), 66 pts with 'de-novo' and 4 pts with therapy-related MDS (t- MDS), diagnosed in the University Clinic of Hematology, "Ss Cyril and Methodius" University, Skopje, Macedonia, from January 2011 till April 2015, with the follow up period of 52 months. Diagnosis was based on the criteria recommended by the International Consensus Working Group from 2007 (27). Detection of the chromosomal abnormalities in our cohort was performed with the method Multiplex Ligation - Dependent Probe Amplification. We collected 1 mL of bone marrow aspirate from each patient and put in the test tube with an anticoagulant - K₃EDTA. Deoxyribonucleic acid (DNA) was isolated with the standard phenol chloroform extraction in the Department of biomolecular sciences, Faculty of Pharmacy, Skopje, Macedonia. Then MLPA method was used. It is a multiplex polymerase chain reaction -based technique that can quantify up to 50 different genomic targets simultaneously in a single experiment through amplification of specific hybridizing probes (28). Screening of big gene deletions/duplications on different chromosome regions such as: 3, 5q (EGR1, MIR145, SPARC, MIR146A), 7q (EZH2), 8q (MYC), 11q (KMT2A), 12p (ETV6), 17 (TP53, NF1, SUZ12), 19, 20p (ASXL1) and Y is possible.

Analyses were performed with the application of P414-A1 MDS MLPA kits of MRC Holland, according to their protocol. We used the Coffalyser software, an Excel-based program able to perform data normalization steps and necessary corrections (29,30).

Patients were classified according to the French-American-British (FAB) and World Health Organization (WHO) classifications and they were stratified according to the International Prognostic Scoring System – (IPSS) and Revised International Prognostic Scoring System (IPSS-R). Therapeutic approach was made according to the National Comprehensive Cancer Network (NCCN) guidelines.

Patients signed informed consent for entrance in the study. Statistical analysis was performed with statistical programs STATISTICA 7.1 and SPSS 17.0.

IV. Results

Of 70 patients, 33 women (47.1%) and 37 men (52.9%) participated in the study, aged 64.3 years (range 22-86 years). Chromosomal abnormalities were detected in 32.9% patients, while 67.1% patients had normal findings. In our cohort chromosomal abnormalities were found as follows: normal findings in 47 pts (67.1%), in 1 patient (1.4%) were found- (5q-, 7q-, 12p-, 17p-, 19p+), in 2 pts (2.9%) was found- (+8), +, in 2 pts (2.9%) was found- (12p-), in 2 pts (2.9%) was found- (5q-), in 1 patient (1.4%) was found- (11p-), in 2 pts (2.9%) were found- (5q-, 7q-), in 1 patient (1.4%) were found- (5q-, 7q-, 17p-), in 1 patient (1.4%) was found- (19p-), in 1 patient (1.4%) were found- (7q-, 20q-), in 1 patient (1.4%) were found - (5q-, 12p-), in 1 patient (1.4%) were found- (5q-, 8q-), in 2 pts (2.9%) was found- (Yp-), in 1 patient (1.4%) was found- [t(3;3)(q21,q26)], in 1 patient (1.4%) were found- (5p+, 5q-, 7p-, 7q-, 8p+, 8q+, 12p-, 19p+), in 1 patient (1.4%) were found- (17p-, 17q+), in 1 patient (1.4%) was found- (20q-), in 1 patient (1.4%) was found- [inv(9)(p12q13)] and in 1 patient (1.4%) was found - (+9).

Overall survival in our cohort was 30.2 months. We evaluated the following prognostic factors and their influence on OS:

Age

According to age patients were stratified in four age groups: <50 years with OS 28.8 months, from 51-60 years – 10.9 months, from 61-70 years – 29.3 months, >71 year – 30.9 months. According to the ‘Log-Rank’ test ($p=0.220$) the difference in OS depending on different age groups was not statistically significant.

Sex

Overall survival in women was 33.9 months and in men 25.6 months. According to the ‘Log-Rank’ test ($p=0.260$) the difference in OS depending on sex was not statistically significant.

Hemoglobin

Patients were stratified in three groups according to the hemoglobin level: <80g/L with OS – 31.9 months, from 80-110g/L with OS – 23.2 months and >110g/L with OS 30.7 months. According to the ‘Log-Rank’ test ($p=0.141$) the difference in OS depending on hemoglobin level was not statistically significant.

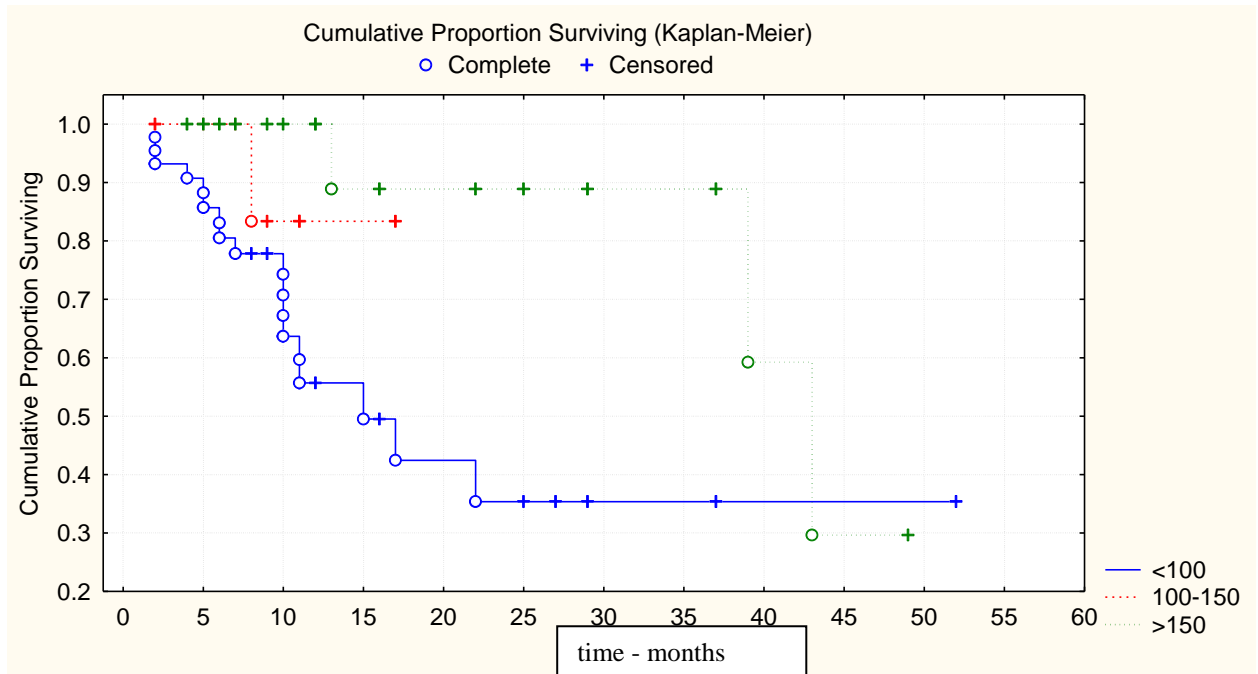
Absolute neutrophil count (ANC)

According to the ANC patients were divided in three groups: <500 – 8 pts (11.4%) with OS – 11.8 months, from 500-1000 – 18 pts (25.7%) with OS - 26.8 months and >1000 – 44 pts (62.9%) with OS – 33.4 months. According to the ‘Log-Rank’ test ($p=0.104$) the difference in OS depending on ANC number was not statistically significant.

Platelets

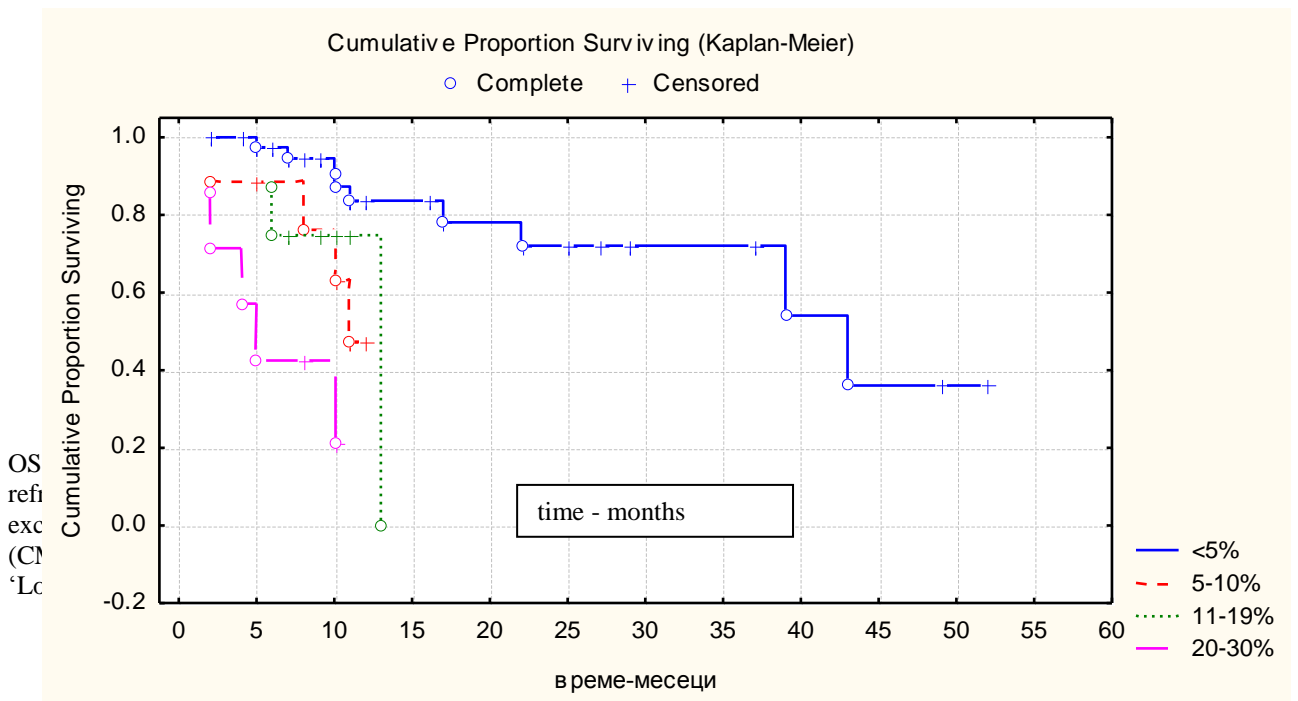
According to the platelet number patients were divided in three groups: <100x10⁹/L – 44 pts (62.95%) with OS – 25.4 months, from 100-150x10⁹/L – 9 pts (12.8%) with OS 15.5 months and >150x10⁹/L – 17 pts (24.3%) with OS – 40.3 months (Graph 1) According to the ‘Log-Rank’ test ($p=0.026$) the difference in OS depending on platelet number was statistically significant.

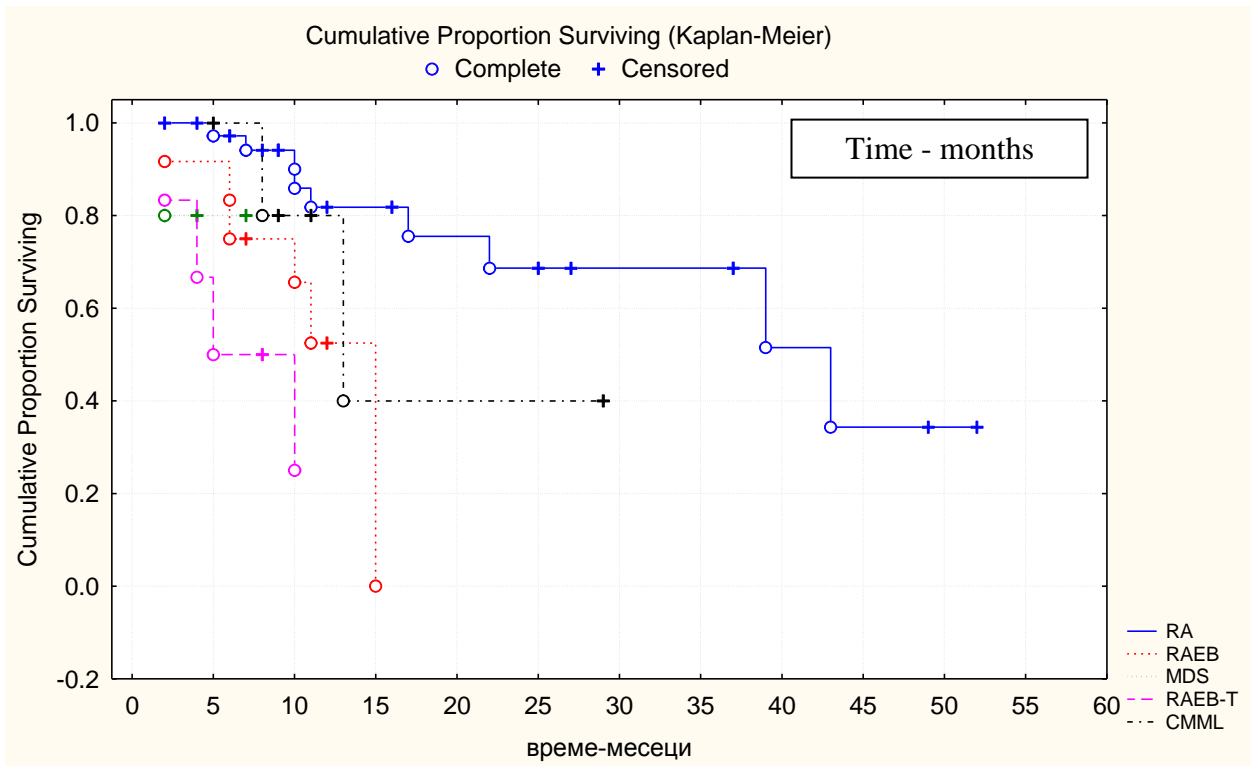
Graph 1. OS depending on platelet number



Blast percentage in bone marrow (BM)

According to the blast percentage in bone marrow patients were divided in four groups: <5% – 45 pts (64.3%) with OS – 37.2 months, from 5-10% – 9 pts (12.9%) with OS – 10 months, 11-19% – 8 pts (11.4) with OS – 11.3 months and 20-30% – 7 pts (10%) with OS – 6.1 months. (Graph 2) According to the ‘Log-Rank’ test ($p=0.000$) the difference in OS depending on the blast percentage in bone marrow was statistically significant.

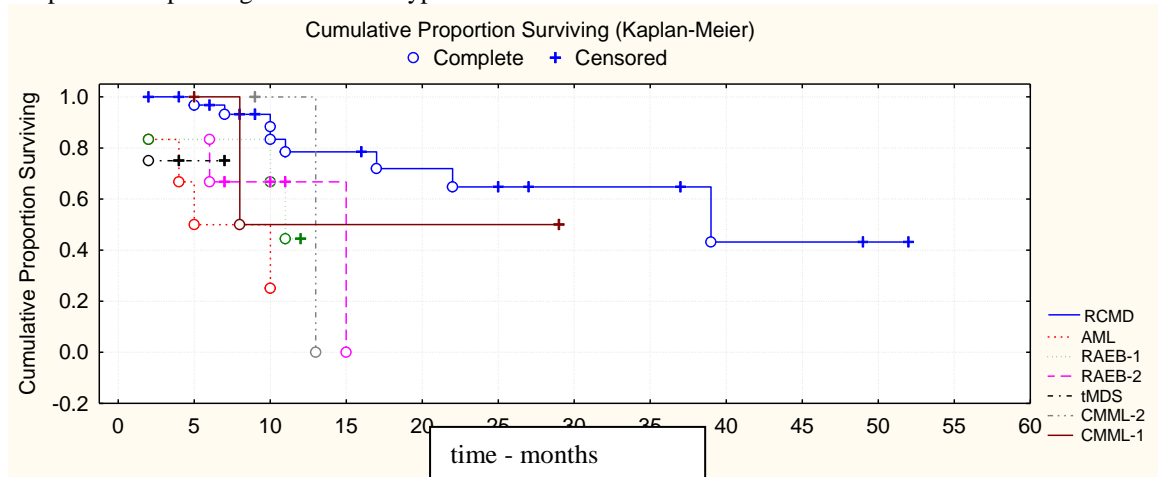




WHO Classification

According to WHO almost half of the patients, 34pts (48.6%) belong to the subtype refractory cytopenia with unilineage dysplasia(RCUD) with OS – 6.8 months, 2 pts (2.9%) to 5q- syndrome, 5 pts (7.9%) to refractory cytopenia with multilineage dysplasia (RCMD) with OS – 35.5 months, 1pts (1.4%) to RARS, 6 pts (8.6%) to RAEB-1 with OS 5.7 months, 6 pts (8.6%) to RAEB-2 with OS – 12 months, 2 pts (2.9%) to CMML-1, 3 pts (4.3%) to CMML-2 with OS – 18.5 months, 6 pts (8.6%) to AML with OS – 11 months, 4 pts (5.7%) to t-MDS with OS – 13 months, and 1 pts (1.4%) to unspecified MDS (u-MDS). (Graph4) According to the ‘Log-Rank’ test($p=0.015$) the difference in OS depending on WHO subtypes was statistically significant.

Graph4. OS depending on WHO subtypes



Mean corpuscular volume (MCV)

According to the mean corpuscular volume patients were divided in three groups: <80fL – 2 pts (2.9%) with OS – 27 months, from 80-100fL – 34 pts (48.6%) with OS – 24.5 months and >100fL – 33 pts (47.1%) with OS – 35.5 months. According to the 'Log-Rank' test ($p=0.487$) the difference in OS depending on MCV was not statistically significant.

Lactate dehydrogenase (LDH)

According to the serum lactate dehydrogenase level patients were divided in two groups: <248U/L – 16 pts (22.9%) with OS – 37.2 months, and ≥ 248 U/L – 48 pts (68.6%) with OS – 30.7 months and missing data – 6 pts (8.5%). According to the 'Log-Rank' test ($p=0.728$) the difference in OS depending on LDH level was not statistically significant.

Albumin

According to the serum albumin level patients were divided in three groups: <35g/L – 6 pts (8.6%) with OS – 11 months, from 35-40g/L – 7 pts (10%) with OS – 8.9 months and >40g/L – 32 pts (45.7%) with OS – 29.4 months. According to the 'Log-Rank' test ($p=0.295$) the difference in OS depending on albumin level was not statistically significant.

Ferritin

According to the ferritin level patients were divided in three groups: <500ng/ml – 29 pts (41.4%) with OS – 32.7 months, from 500-1000ng/ml – 9 pts (12.9%) with OS – 19 months and >1000ng/ml – 4 pts (5.7%) with OS – 28.3 months, while in 28 pts (40%) the data were missing. According to the 'Log-Rank' test ($p=0.250$) the difference in OS depending on ferritin level was not statistically significant.

Blood transfusion

According to the number of packed red blood cells (PRBCs) patients were divided in two groups: <18U – 33 pts (47.1%) with OS – 28.2 months, and ≥ 18 – 11 pts (15.7%) with OS – 26.5 months and the data were missing in 26 pts (37.2%). According to the 'Log-Rank' test ($p=0.908$) the difference in OS depending on the number of PRBCs was not statistically significant.

Chromosomal abnormalities

Chromosomal abnormalities were detected in 23 pts (32.9%): 5p+, 5q-, 7p-, 7q-, 8p+, 8q+, 11p, 12p-, 17p-, 17q+, 19p+, 19p-, 20q-, etc., while 47 pts (67.1%) had normal findings. According to the presence or absence of chromosomal abnormalities patients were divided in two groups. Those who had some chromosomal abnormalities had OS – 25.7 months, while those who had not – 34.2 months. According to the 'Log-Rank' test ($p=0.144$) the difference in OS depending on presence or absence of chromosomal abnormalities was not statistically significant.

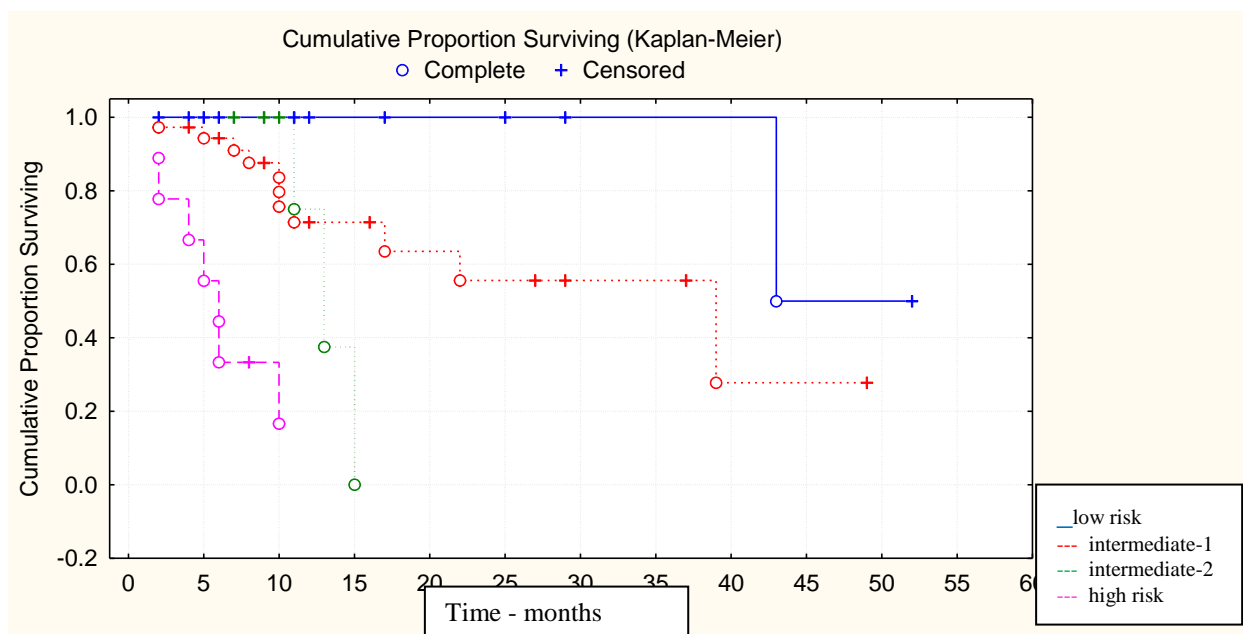
Comorbidities

Comorbidities were present in 21 pts (30.0) with OS – 32.4 months, while in 49 pts (70.0%) they were absent, with OS – 25.8 months. Most frequent comorbidities were hypertension, hypothyreosis, chronic renal failure, gastritis, etc. According to the 'Log-Rank' test ($p=0.477$) the difference in OS depending on the presence or absence of comorbidities was not statistically significant.

IPSS

According to IPSS, distribution was as follows: low risk - 16 pts (22.9%) with OS – 47.5 months, intermediate 1 – 37 pts (52.9%) with OS – 29.9 months, intermediate 2 – 8 pts (11.3%) with OS – 13.3 months and high risk - 9 pts (12.9%) with OS – 6.1 month. (Graph 5) According to the 'Log-Rank' test ($p=0.000$) the difference in OS depending on the IPSS was statistically significant.

Graph 5. OS depending on the IPSS



R-IPSS

According to R-IPSS, distribution was as follows: very low risk - 5 pts (7.1%), low risk 22 pts (31.4%) with OS - 39.5 months, intermediate risk - 24 pts (34.3%) with OS - 36.8 months, high risk - 10 pts (14.3%) with OS - 15.4 months and very high risk - 9 pts (12.9%) with OS - 6.8 months. According to the 'Log-Rank' test ($p=0.144$) the difference in OS depending on the R-IPSS was not statistically significant.

AML transformation

AML transformation was noted in 17 pts (24.3%). According to FAB subtypes: RAEB - 41.2%, inRAEB - 29.4%, inCMML - 23.5%, inRAEB-T - 5.9%. According to WHO subtypes: RCMD - 44.4%, inRAEB-1 - 33.3%, inRAEB-2 - 11.8%, CMML-1 - 11.8%, CMML-2 - 11.8% and in AML - 11.1%. OS in patients after AML transformation was 9.3 months. Most common reasons for death after AML transformation were cerebral hemorrhage (83.3%) and cardiopulmonary failure (16.7%).

Univariate and multivariate analysis

In the cohort of 70 patients we evaluated the relation among prognostic factors and OS. The univariate analysis revealed only 4 from 17 factors as predictors of the event and associated with OS: platelet number, blast percentage in the BM, IPSS and R-IPSS. Platelets $< 100 \times 10^9/L$ increase the event in comparison with other platelets. Blast percentage in the bone marrow < 5 , IPSS and R-IPSS (very low and low risk) reduced the event in comparison with the others. Multivariate analysis for OS revealed that predictors of the event were: platelets $< 100 \times 10^9/L$, IPSS - low risk and R-IPSS - intermediate risk.

V. Conclusion

In our cohort the univariate analysis revealed that factors associated with OS were: platelet number, blast percentage in the BM, IPSS and R-IPSS. Multivariate analysis revealed that factors associated with OS were: platelet number, IPSS - low risk and R-IPSS - intermediate risk.

In the recent years great emphasis is put on mutations. More than 900 mutations are discovered and scientists put them in different combinations aiming to see their influence on OS in MDS. That would lead to their incorporation in prognostic systems, enabling refinement of patient's risk stratification. So far, no mutation is included in prognostic systems, although several mutations are found to worsen OS. Still, we need more studies for proper risk stratification.

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