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Prognostic Parameters of Acute Myeloid Leukaemia at Presentation

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ABSTRACT

Introduction: The treatment response and outcome in acute myeloid leukaemia (AML) is heterogeneous. **Aim:** To analyze the prognostic parameters of AML at presentation. **Methods:** The total sample of 44 AML patients was analyzed on the basis of age <55 and ≥55 years, sex, WBC count <50x10/^{9}/l and ≥50x10/^{9}/l, the Hb concentration <100 g/l and ≥100 g/l, PLT count <100x10/^{9}/l and ≥100x10/^{9}/l, Karnofsky score <60% and >60%, cytogenetics, CD56 expression, morphological type and types of treatment (standard and reduced induction chemotherapy, high-dose chemotherapy/stem cell transplantation – autologous and HLA matched, related, allogeneic, together and separately). **Results:** The age <55 years, Karnofsky score >60% and standard induction chemotherapy statistically correlated with the higher complete remission (CR) rates, longer relapse free survival (RFS), lower relapse rate (RR), and longer overall survival (OS) ($p<0.01$). The difference in terms of CR and RR between the sexes were not statistically significant ($p<0.05$), however women had statistically lower OS comparing to men (9.71±4.54 months vs. 38.03±9.17 months) ($p<0.01$). WBC count ≥ 50x10/^{9}/l and the Hb concentration <100 g/l statistically correlated with shorter OS ($p<0.05$), while the WBC count ≥50x10/^{9}/l statistically correlated with shorter RFS ($p<0.05$). The PLT count <100x10/^{9}/l and ≥100x10/^{9}/l was not found as prognostically significant for CR, RR, RFS, and OS ($p<0.05$). In comparison to the standard induction chemotherapy, both types of high dose chemotherapy/stem cell transplantation (HDT/SCT) (10/22), together and separately, resulted in longer RFS, lower RR, and longer OS ($p<0.05$). The frequency of cytogenetic risk was intermediate 81.6%, unfavorable 13.2%, and favorable 5.3%, respectively. CD56 + expression statistically correlated with the lower PLT count, higher RR, shorter RFS, and shorter OS ($p<0.05$). Statistical analysis of the cytogenetic risk and morphological types of AML were not possible due to the small number of patients in stratified groups. **Conclusions:** Female sex, the WBC count >50x10/^{9}/l, the concentration of Hb <100 g/l, and CD56 + expression, at presentation of AML, should be considered as parameters of adverse risk, especially in latter decisions considering post-remission treatment with HDT/SCT.

Keywords: acute myeloid leukaemia, prognostic parameter, prognosis.

1. INTRODUCTION

Acute myeloid leukaemia (AML) is the most common form of adult acute leukaemia with the incidence of 80%, and is more frequent in men comparing to the women (5:3) (1). The mean age on diagnosis is 67, out of which 54% patients are younger then 65 and 1/3 is diagnosed in age ≥75 (2). Incidence is increasing with aging, along with myelodysplasia. The treatment response and out-

come is heterogenous. The age >60 years, poor performance status determined by Karnofsky score less than 60%, MDR 1 (multi drug resistance) positive phenotype, secondary AML, complex cytogenetic abnormalities, -5, -7, 3q26 aberrations, t (6;9), 11q23 aberrations except t (9;11), "monosomal karyotype," FLT3/ITD mutations, MLL partial tandem duplication, BAALC over expression and mutations in IDH1 and/or IDH2, are considered as adverse prognostic parameters of AML (3).

The aim of the study was to analyze clinical, morphological, and cytogenetic parameters in AML patients, as well as CD56 antigenic expression on leukemic cells, with assessment of their impact on the treatment response, relapse occurrence, and survival.

2. PATIENTS AND METHODS

The study was retrospective-prospective on a total sample of 44 patients with AML who were treated in Department of Hematology, Clinic for Oncology, Hematology and Radiotherapy, University Clinical Center Tuzla. Patients were analyzed based on their age <55 and ≥55, sex, WBC count <50x10^9/l and ≥50x10^9/l, concentration of hemoglobin–Hb <100 g/l and ≥100 g/l, PLT count <100x10^9/l and ≥100x10^9/l, Karnofsky performance status <60% and >60%, cytogenetic abnormalities, CD56 antigen expression, morphological type of AML, and the type of treatment (standard and reduced induction chemotherapy, and high-dose chemotherapy combined with autologous stem cell transplantation – HDT/ASCT and HLA, matched, related allogeneic stem cell transplantation – HDT/AlloSCT) with the treatment response, duration of remission, relapse rate and overall survival. The inclusion criterion in the study was pathohistologically and immunocytochemically confirmed AML on bone marrow sample. Response to induction therapy was assessed as a complete remission achieved with the first induction cycle – CRI, complete remission achieved with the second induction cycle – CRII, partial remission – PR, and resistant disease – RD. Relapse Rate – RR included total number of patients who relapsed after CR. Relapse free survival – RFS determined the period from CR up to relapse. AML was classified in accordance with the French-American-British System of Classification (FAB classification). Bone marrow samples were used for hystological analysis and immunophenotyping. CD56 antigen expression was analyzed retrospectively using the bone marrow samples and considered positive when more than 20% of leukemic cells proved positive on specific monoclonal antibodies against CD56 and CD33 antigen. Cytogenetic analysis of bone marrow samples was conducted applying the conventional method that included the use of mitogens. Upon planting the cell culture, using various mitogens, a 72 hour long incubation in "Binder" incubator, metaphases and display of chromosome bands of mitosis of both healthy and tumor cells were analyzed after the preparation, using trypsin G-banding method. Statistical analysis was performed in GraphPad Prism version 7 (San Diego, California, USA) and SPSS version 10 for Windows. Parametric and non-parametric methods were used to determine statistical significance (D'Agostino test, Pearson omnibus test, and Kolmogorov-Smirnov normality test). Student's t-test, Mann-Whitney's test, Fisher's test, and iχ2 test were used for assessing differences between groups. ANOVA test was used for determination of relative difference in variance distribution between the variables. All tests were done with the significance level of 95% (p <0.05).

3. RESULTS

In total sample of 44 patients with AML, the mean age was 53.02±2.55 years, with a minimum of 19 years, and maximum of 82 years. The sample consisted of 56.8% (25/44) women and 43,2% (19/44) of men. Patients who were <50 years of age represented 52.3% (23/44) of the sample, comparing to the 47.7 % (21/44) of patients who were ≥ 55 years of age. The sex and the mean age were not statically different between the age groups (52.53 ±4.67 years vs. 53.4±2.82 years) (p>0.05 for all measures). De novo AML was found in 86.4% (38/44) of patients, comparing to the secondary AML in 13.6% (6/44), with the ratio of 6.35:1. The most common morphological types of AML were M5 and M1 (29.4 and 25.0 %), and M3 and M6 being the rarest (0% out of the total number). The frequency of cytogenetic risk was intermediate 81.6%, adverse 13.2%, and favorable 5.3%. In total sample, achieved CRI rates were 34.1%(15/44), CRII 15.9% (7/44), PR 6.8% (3/44), and RD 43.2% (19/44), respectively. The patients with RD were statistically older comparing to the patients with CR, whether it is achieved CRI and CRII (59.8±3.8 vs. 47.4±4.02 years) (p<0.05) or (59.8±3.8 vs. 44.4±6.81 years) (p<0.05), respectively. The total complete remission rate (CRI+CRII) was statistical-

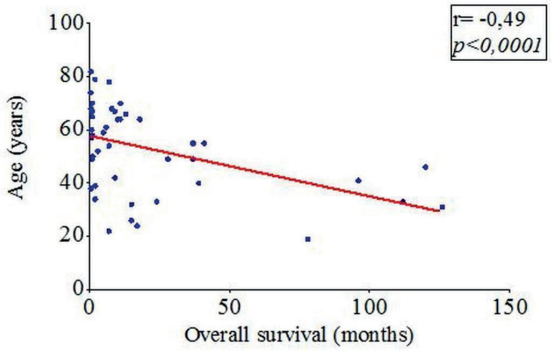
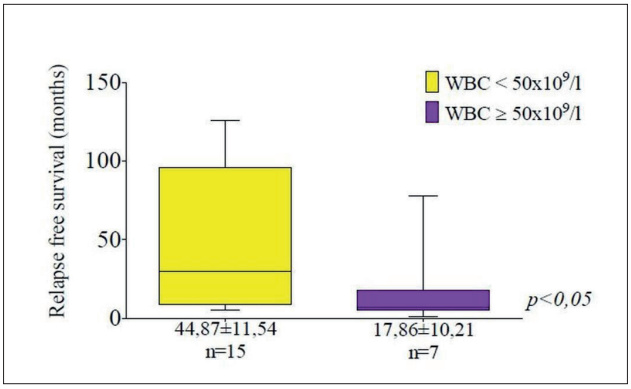


Figure 1. Correlation of age and overall survival in AMLpatients



Figrue 2. Relapse free survival compared to the WBC count

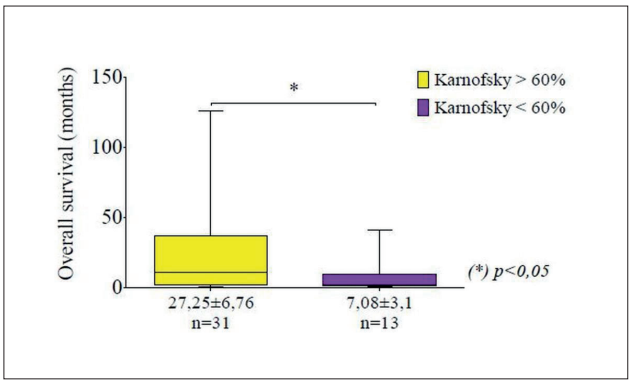


Figure 3. Overal survival compared to the Kornofsky score

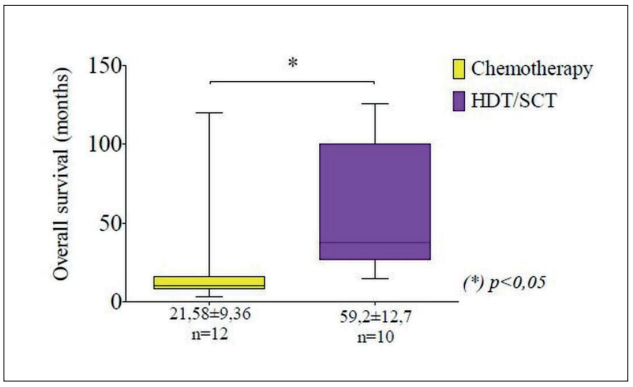


Figure 4. Overal survival compared to the type of treatment

ly higher, while the adverse response rate (PR+RB) was statistically lower in patients >55 years of age (66.6% vs. 34.8%) (33.3% vs. 65.2%) (p<0.05). The RFS was statistically longer in patients younger then 55 of age, comparing to patients who were ≥ 55 years of age (49.29±12.52 months vs. 13.5±3.75 months) (p<0.01). Patients who relapsed were statistically older comparing to those who without relapse (53.08±4.4 years vs. 36.89±3.6 years) (p<0.01). OS was statistically longer in group of <55 years of age, comparing to patients ≥55 years of age (35.22±9.42 months vs. 8.12±2.28 months) (p<0.01). The lower the age was, the longer CR was (Spearman's correlation coefficient in total was: -0.3624; 95% CI: -0.6872 to 0.08321; p<0.05) (Figure 1). The CRI rates and favorable response rates (CRI+CRII) were statistically higher in men comparing to women (CRI: 42.1% vs. 28%, CRI +CRII: 57.89% vs. 44%) (p<0.05), respectively. Although the RFS in men was shorter (27.73±10.44 months vs. 44.82±14.21 months), the difference in terms of CR was not significant between the sexes (p<0.05). Sex was not of importance regarding RR (male sex 63.63% vs. female sex 54.54%) (p<0.05), however women had statistically lower OS comparing to men (9.71±4.54 months vs. 38.03 ±9.17 months) (p<0.01). The WBC count <50x10^9/l statistically correlated with CRI rate, while the WBC count >50x10^9/l was statistically correlated with CRII rate (p<0.05). Patients with WBC count <50x10^9/l and >50x10^9/l had equal distribution of favorable treatment response (CRI + CRII) and adverse treatment response (PR +RB) as well as PR and RB separately (p>0.05). The WBC count ≥50x10/^{9}/l statistically correlated with shorter RFS comparing to the WBC count <50x10/^{9}/l (17.86±10.21 months vs. 44.87±11.54 months), with higher RR (85.7% vs. 46.7%) and shorter OS (12.18±5.35 months vs. 25.55±6.84 months) (p<0.05 for all measures). The smaller the WBC count was, the longer RFS was (Spearman's correlation coefficient in total was: -0.3422; 95% CI: -0.6749 to 0.1061; p<0.05) (Figure 2).

The concentration of Hb <100 g/l and ≥100 g/l were not significant regarding the treatment response (p>0.05) and RFS (Spearman's correlation coefficient in total was: 0.26; 95% CI: -0.1945 to 0.6225; p>0.05). Hb concentration <100 g/l statistically correlated with higher RR (68.75% vs. 33.3%) (p<0.05) and shorter OS, comparing to Hb concentration ≥100 g/l (16.97±4.51 months 38.12±16.78 months) (p<0.05). The PLT count <100x10^9/l and ≥100x10^9/l did not statistically correlated with the treatment response rate (CRI 35.3% vs. 30%, CRII 14.7% vs. 20%, PR 5.9% vs. 10%, RD 44.1% vs. 40%) (p>0.05), RFS (37.06±10.57 months vs. 33.6±16.42 months) (Spearman's correlation coefficient in total was: -0.09420; 95% CI: -0.5061 to 0.3527; p>0.05), RR (64.71% vs. 40%) (p>0.05), and OS (21.64±5.98 months vs. 19.07±9.25 months) (p>0.05). Karnofsky score >60% compared to Karnofsky score <60% statistically correlated with lower rates of CRI (39.39% vs. 18.18%) and CRII (21.21% vs. 0%) i PR (9.01% vs. 0%) (p<0.05 for all measures), with lower rates of RD (30.3% vs. 81.82%) (p<0.05), longer RFS (39.15±9.46 months vs. 7.5±2.5 months) (p<0.001), lower RR (55% vs. 100%) (p<0.05) and longer OS (27.25±6.76 months vs. 7.08±3.1 months) (p<0.05) (Figure 3).

Reduced induction therapy compared to the standard induction chemotherapy, statistically correlated with lower rates of CRI (16.67% vs. 40.62%) (p<0.05), lower CR rates (CRI + CRII) (18.18% vs. 56.25%) (p<0.01), higher rates of RD (58.33% vs. 37.5%) (p<0.05), shorter RFS (10.25±2.63 months vs. 42.06±10.29 months) (p<0.01), higher RR (100% vs. 50%) (p<0.05) and shorter OS (7.33±2.14 months vs. 26.2±6.68 months) (p<0.01).

HDT/SCT (ASCT + HLA matched, related, Allo) (10/22) compared to standard postremission chemotherapy (12/22) statistically correlated with longer RFS (57.2±13.34 months vs. 18.83±9.45 months) (p<0.05), lower RR (30% vs. 83.3%) (p<0.01) and longer OS (59.2±12.7 months vs. 21.58±9.36 months) (p<0.05) (Figure 4). HDT/AlloSCT (6/22) compared to standard postremission chemotherapy (12/22) statistically correlated with longer RFS (63.33±20.27 months vs. 18.83±9.45 months) (p<0.01), lower RR (33.3% vs. 83.3%) (p<0.05) and longer OS (65.67±19.11 months vs. 21.58±9.36 months) (p<0.01).

HDT/ASCT (4/22) compared to standard postremission chemotherapy (12/22) statistically correlated with longer RFS (48±16.11 months vs. 18.83±9.45 months) (p<0.05), lower RR (25% vs. 83.3%) (p<0.05) and longer OS (49.5±15.64 months vs. 21.58±9.36 months) (p<0.05). HDT/ALLO SCT (6/10) and HDT/ASCT (4/10) did not have statistically different RFS (63.33±20.27 months vs. 48±16.11 months) (p>0.05), RR (33.3% vs. 25%) (p>0.05) and OS (65.67±19.11 months vs. 49.5±15.64 months) (p>0.05). Cytogenetic analysis was available in 86.4% (38/44) of patients, since in 9.1% (4/44) of patients, mitoses were not achievable, while in 4.54% (2/44) of pa-

tients it was not possible to found cytogenetic results. The most common cytogenetic risk was intermediate 81.57% (31/38), then unfavorable 13.1% (5/38), and favorable 5.26% (2/38). Statistical analysis of the ratio between the cytogenetic risk and morphological types of AML, with the degree and duration of the treatment response, RR and OS was not possible to carry out due to a small number of patients in stratified groups. The positive expression of the CD56 antigen was statistically higher in adverse and favorable cytogenetic risk groups, while the negative CD56 expression was statistically higher in the intermediate cytogenetic risk group ($p<0.05$). Regardless of the fact that the CD56 positive expression did not correlated to the treatment response rate ($p<0.05$), CD56+ statistically correlated with shorter RFS (37.67±29.28 months vs. 44.14±12.11 months) ($p<0.05$), higher RR (25% vs. 11.1%) ($p<0.05$) and shorter OS in comparison to CD56- expression (18.19±13.09 months vs. 23.01±6.71 months) ($p<0.05$). The CD56+ expression statistically correlated with lower PLT count comparing to CD56- expression (47±13.88x10^9/l vs. 81.68±14.02x10^9/l) ($p<0.05$). CD56+ expression and CD56- expression had equal distribution of WBC count (34.10±14.16x10^9//l vs. 51.84±14.62 x10^9/l) ($p>0.05$) and concentration of Hb (88.67±5.3 g/l vs. 84.92±3.52 g/l) ($p>0.05$). Morphological types of AML MO, M1, and M7 had the same occurrence of CD56+ ($p>0.05$), however, it was statistically higher comparing to its frequency in types M2, M4 and M5 ($p<0.01$). Morphological types M3, M4, and M5 had the same occurrence of the positive expression of the CD56 antigen ($p>0.05$).

4. DISCUSSION

The mean age of 53.02±2.55 years in total sample, does not reflect the mean age of AML patients in our surrounding, considering the fact that the study did not include all patients diagnosed with AML. The incidence of the secondary AML in our sample (13.6%) was within the rate found in literature, that is 10-30% (4,5). Our results confirmed the older age as a adverse prognostic parameter in AML due to lower treatment response, frequent relapse, shorter remission duration, and shorter overall survival, as a consequence of lower possibility to use intensive induction therapy, either because of low performance status or presence of comorbidity, which is consistent with the results of Stone RM et al., 2002 (6) and Appelbaumm FR et al. 2006 (7). Sex did not statistically correlated with CR, RR, and RFS rates, however, women had shorter OS comparing to the men (9.71±4.54 months vs. 38.03±9.17 months) ($p<0.01$). Poor performance status measured with Karnofsky score less than 60% was a strong negative prognostic parameter at presentation, and statistically correlated to lower CR rates, and shorter RFS, higher RD rates, frequent relapse, and shorter OS ($p<0.05$ for all measures). Gunnar Juliusson et al. in 1999, in the Swedish population register, showed that poorer performance status of patients statistically correlated with higher mortality rate in comparison to the older patients with good performance status ($p<0.001$) (5). Estey et al. in 2001 published that the performance status and the age was the basic predictors of early death of patients with AML (8), which is consistent with our results. Reduced induction chemotherapy resulted in lower CR rates and higher RD rates. The WBC count >50x10^9/l statistically correlated with shorter RFS, higher RR, and shorter OS ($p<0.0$ for all measures). The lower the WBC count was, the longer RFS resulted ($p<0.05$). Adverse prognostic value of the WBC count >50x10^9/l in patients with AML was also confirmed by other investigators (9,10,11). The concentration of Hb ≤ 100 g/l statistically correlated with higher relapse rates (68.75% vs. 33.3%) and shorter OS in comparison to the concentration of Hb >100 g/l (16.97±4.51 months vs.38.12±16.78 months) ($p<0.05$ for all measures). The PLT count <100x10^9/l and >100x10^9/l was not statistically significant regarding of achieving and duration of CR, frequency of relapse and OS ($p<0.05$ for all measures). Both types of HDT/SCT (autologous and HLA matched, related allogeneic SCT, total and separately) comparing to standard postremission chemotherapy, resulted in longer RFS, lower RR, and higher OS. Patients treated with HDT/ASCT (4/10) and with HDT/AlloSCT (6/10) did not yield different RFS, RR, and OS. The positive expression of the CD56 antigen statistically correlated with lower PLT count, higher RR, shorter RFS, and shorter OS.

5. CONCLUSIONS

We should consider the possibilities of standard induction therapy in patients who are ≥ 55 years old with good performance status. The results after achieving CR, regarding the relapse free survival, relapse and overall survival are significantly better with performing high dose chemotherapy/stem cell transplantation, comparing with standard postremission chemotherapy. Female sex, the WBC count >50x10^9/l, the concentration of Hb <100 g/l, and CD56 + expression, at presentation of AML should be considered as parameters of adverse risk, especially in latter decisions considering post-remission treatment with HDT/SCT. The research on a larger sample is necessary in order to analyze prognostic impact of cytogenetic risk and morphological types of AML. Introducing molecular analysis is important for better stratification of cytogenetic risk in terms of appropriate selection of patients for allogeneic stem cell transplantation.

• Conflict of interest: none declared.

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