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ORIGINAL ARTICLE

Anemia in the patients with acute myeloid leukemia revisited: Prognostic importance of anemia on treatment-naïve patients

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ABSTRACT

Objective: To determine the independent prognostic influence of pre-treatment anemia severity in patients with acute myeloid leukemia.

Patients and Methods: This was a retrospective evaluation of AML patients between January 2002 and May 2018 at a university hospital hematology clinic. The patients were divided into four groups: intensive treatment achieving complete remission (CR), intensive treatment without CR, non-intensive treatment, and supportive treatment. Baseline clinicodemographic features, laboratory data including serum hemoglobin levels, were collected. Baseline and post-treatment hemoglobin levels were compared according to treatment and across groups. A logistic regression analysis was also made to evaluate the influence of anemia on achieving a complete remission.

Results: The mean hemoglobin level at the time of diagnosis was 8.5 g/dL (6.4 – 14.4). Although hemoglobin value was lower in the secondary AML subgroup, there was no significant difference between the groups at the time of diagnosis ($p = 0.082$). Hemoglobin values after induction chemotherapy were significantly different between treatment groups ($p < 0.001$). When the variables predicting complete remission are examined by logistic regression, per 1 gr/dL increase in hemoglobin level at the time of diagnosis increased the probability of remission significantly ($p = 0.047$, OR = 1.13, 95% CI 1.07 - 1.24).

Conclusion: A patient's baseline pre-treatment serum hemoglobin level can predict the achievement of complete remission in AML patients. Anemia improves with induction chemotherapy, even without complete remission.

Keywords: acute myeloid leukemia, anemia, prognosis, induction chemotherapy

INTRODUCTION

Acute myeloid leukemia (AML), which results from maturation block, abnormal proliferation, and differentiation of hematopoietic stem cells and myeloid progenitor cells, accounts for 80% of acute leukemias in adults [1]. Despite tremendous advances in the understanding of the molecular basis of the disease and a corresponding increase in the therapeutic armamentarium, mortality rates are still far more than acceptable. A national registry from England reported median survival as 0,6 years. 1-year and 5-year overall survival rates were 39.8% and 18.8%, respectively [2].

Not all AML patients fare similar. Variation of the prognostic markers in individual patients determines the fate of the disease. Modern prognostic classification systems such as ELN 2022 mostly rely on the presence or absence of molecular genetic abnormalities [3]. On the other

hand, several easily attainable clinical markers including blood counts, might inform additional prognostic data [4].

Anemia is a near-universal finding in AML patients at the time of the diagnosis [5,6]. The pathophysiologic mechanism is generally assumed as the damaging of erythroid progenitors by myeloblast cells in the bone marrow [7]. Normal erythropoiesis is significantly reduced or absent on bone marrow examination in treatment-naive patients [8].

Few studies examined the independent effect of anemia on the prognosis of AML patients. Tsimberidou et al. evaluated the prognostic significance of beta-2 microglobulin in addition to several clinical and laboratory parameters in AML patients [9]. They found that having a serum hemoglobin (Hgb) level lower than 8 g/dL was associated with a worse prognosis in AML patients who were <60 years old. Data regarding the influence of anemia on different AML subtypes are scarce.

Thus, we intended to evaluate the prognostic importance on anemia in treatment-naive AML patients with a emphasis on AML subtypes.

PATIENTS AND METHODS

Patients and setting

All adult (>17 years old) patients diagnosed with acute myeloid leukemia (AML) treated at the Department of Hematology of Hacettepe University hospitals from January 2002 to May 2018 were retrospectively screened for eligibility for the study. Missing data regarding induction treatment type and remission status, failure to complete the scheduled treatment regimen due to any problem, and history of erythrocyte transfusion within 1 month before diagnosis were determined as exclusion criteria. Hacettepe University Ethics Committee approved the study protocol with the document number 18/428-12.

Data collection

The data had been retrospectively recorded from electronical and/or hard-copy medical records of the patients. We collected patient characteristics, such as age, sex, subtypes of AML, bone marrow findings before and after the treatment, blast percentages in the peripheral blood, type of AML treatment, number of blood transfusions, and blood counts, including serum Hgb levels before and after induction chemotherapy from electronic hospital database system and patient charts. Hgb levels were recorded within one month of completion of treatment and at the end of short-term myelosuppressive episodes following chemotherapy. The maximum Hgb level achieved by patients within one month after completion of treatment, within an increasing trend and not attributable to a recent erythrocyte suspension transfusion, is recorded as the zenith Hgb value. This is used to refer to the post-induction Hgb status.

Chemotherapy regimens

AML was categorized into three groups: acute promyelocytic leukemia (APL), AML other than APL (non-APL AML), and secondary AML.

Complete remission (CR) was defined as per ELN International Working Group criteria [10].

Various intensive chemotherapy regimens with the aim of achieving CR were used, such as idarubicin + cytarabine, mitoxantrone + cytarabine, daunorubicin + cytarabine, etoposide + mitoxantrone + high-dose cytarabine, high-dose cytarabine + mitoxantrone, idarubicin + all-transretinoic acid, and regimens containing high-dose cytarabine. Non-intensive regimens without the aim of CR included hydroxycarbamide, azacitidine, and subcutaneously administered cytosine-arabinoside.

For complete remission evaluation, blast percentages and morphologic features of the bone marrow, cytogenetic analysis, if available, flow cytometry results, and complete blood count findings after the scheduled treatment regimen were used. According to CR evaluation, patients were divided into four groups as those who achieved CR with intensive chemotherapy, those who did not achieve CR with intensive chemotherapy, those who received a non-intensive regimen without a CR intent, and those who received only supportive therapy.

Statistical analysis

The conformity of the variables to normal distribution was evaluated using histograms,

probability graphs, and the Kolmogorov-Smirnov and the Shapiro-Wilk tests. Descriptive statistics were presented as "mean" and "standard deviation (SD)" for normally distributed variables; "median", "minimum-maximum," and "interquartile range (IQR)" for variables not conforming to the normal distribution, and "frequency tables" for nominal and ordinal variables. In case of more than 2 subgroups in categorical variables, the comparison of continuous variables was made by the One way ANOVA test if the normality assumption was met, and with the Kruskal-Wallis test if it was not. The relationship between continuous variables was investigated by the Pearson correlation analysis if the normality conditions were met and by the Spearman correlation analysis, if they were not. We also performed multivariable logistic regression after univariate analyses to determine independent predictors of complete remission. The IBM SPSS Statistics v25 was used for statistical analyses. Statistical significance level was accepted as "$p < 0.05$".

RESULTS

Patients, treatment regimens, and remission

Overall, 276 AML patients (163 males, 59.1%) were retrospectively examined and included in this study. Median age was 53 years (range 40 – 87 years) in the whole group. Table 1 displays the clinical features and demographic characteristics of the study participants.

The most common AML subtype was non-APL AML (194 patients, 70.3%). Number of patients who had APL and secondary AML were 37 (23.4%) and 45 (16.3%), respectively. Regardless of AML type, 229 (83%) patients were treated with an intensive induction chemotherapy regimen with the goal of CR, 28 (10.1%) with the non-intensive regimen, and 19 (6.9%) with supportive care, taking into account their age, comorbidities, and performance status. Patients in the secondary leukemia subgroup received non-intensive chemotherapy regimens more commonly than APL and non-APL AML patients (35.6%, 0%, and 6.2%, respectively. $p<0.0001$). According to the bone marrow and peripheral blood findings performed for response evaluation after the completion of the induction chemotherapy, complete remission (CR) was not achieved in 149 patients (54%), and complete remission criteria were met in 127 patients (46%). As expected, the majority of patients who achieved CR were in the patient group receiving intensive chemotherapy (Table 2). Twenty-eight patients who received chemotherapy did not seek CR, and 19 patients merely received supportive care.

Hemoglobin levels

The patients were divided into three treatment groups, as mentioned above, to better understand the interaction between chemotherapy and serum Hgb levels. Hgb levels at the time of diagnosis did not significantly differ across the four groups ($p=0.888$), although it was lower in the secondary leukemia group.

Table 1. Basic characteristics, treatment type, and remission status of the study participants

		Number (%)	Type of treatment		
			Non-intensive	Intensive	Supportive
Sex	Male	163 (59.1%)	--		
	Female	113 (40.9%)	--		
Type of AML	APL	37 (13.4%)	0	33 (89.2%)	4 (10.8%)
	Non-APL	194 (70.3%)	12 (6.2%)	175 (90.2%)	7 (3.6%)
	Secondary	45 (16.3%)	16 (35.6%)	21 (46.7%)	8 (17.8%)
Type of treatment	Intensive	229 (83.0%)	--		
	Non-intensive	28 (10.1%)	--		
	Supportive	19 (6.9%)	--		
Status of complete remission	Yes	127 (46.0%)	--		
	No	149 (54.0%)	--		

AML: Acute Myeloid Leukemia, APL: Acute Promyelocytic Leukemia

Table 2. Pre- and post-treatment serum Hgb levels in groups according to AML subtype, treatment type, and CR attainment status

Patient group	Subgroup	Pre-Treatment serum hemoglobin (g/dL)	Post-Treatment serum hemoglobin* (g/dL)	p-value
AML type	APL	8.7 ± 2.0	10.4 ± 1.6	p=0.063**
	NonAPL	8.5 ± 1.7	10.3 ± 1.5	
	Secondary	8.0 ± 1.0	8.4 ± 1.6	
Treatment type	Intensive	8.5 ± 1.8	10.3 ± 1.5	**p=0.006*** **
	Non-intensive	8.2 ± 1.4	9.2 ± 1.9	
	Supportive	8.2 ± 0.7	8.3 ± 1.1	
Remission status	Complete remission	8.8 ± 1.9	10.8 ± 1.4	**p=0.048[α]**
	No Complete remission	8.2 ± 1.4	9.5 ± 1.6	p=0.062[β]

*Zenith Hgb level achieved after chemotherapy, **comparison of pre-treatment serum hemoglobin level in three leukemia subtypes, ***Comparison of post-treatment serum hemoglobin levels between non-intensive chemotherapy and supportive therapy groups. [β] Comparison of pre-treatment serum hemoglobin levels. βComparison of post-treatment serum hemoglobin levels between patients with and without CR. APL: acute promyelocytic leukemia.

However, following treatments, these three groups' Hgb levels varied statistically significantly from one another (Table 2, p<0.001). The CR group that received intensive chemotherapy had the greatest Hgb level (10.3 g/dL) following the treatments. Patients who achieved CR and those who were not following intensive treatment showed a statistically significant difference in post-chemotherapy Hgb levels (p=0.001). The intensively treated group that did not achieve CR had the second-highest post-treatment Hgb levels. Between the non-CR intensive treatment group and the non-intensive treatment group, there was no statistically significant difference as per post-treatment serum Hgb levels (p=0.696). Hgb levels were greater in the non-intensive treatment group than in the supportive therapy group, and this difference was statistically significant (p=0.006).

Effect of pre-treatment Hgb value on complete remission

The variables affecting complete remission were analyzed in multivariable logistic regression. Higher Hgb value at the time of diagnosis increased the likelihood of achieving remission [p = 0.047, OR = 1.13 (95% CI 1.07 - 1.24)].

DISCUSSION

The results of the current study showed that (i) chemotherapy improves anemia significantly in one month in AML patients compared to pre-treatment levels. (ii) Predictably, post-treatment serum zenith Hgb levels within one month were significantly higher in patients who achieved complete remission compared to those who did not. (iii) Multivariable logistic regression analysis showed that pre-treatment serum Hgb level was an independent predictor of achieving complete remission. Per 1 gr/dL increase in serum Hgb level at the time of diagnosis increased the probability of remission significantly.

To our knowledge, this is the first study in the literature demonstrating the independent prognostic significance of baseline anemia in different subtypes of AML patients.

Anemia is a constant feature of newly diagnosed AML, regardless of subtype. There are several causes of anemia in AML, including but not limited to reduced red blood cell lifespan and reduced bone marrow production. The latter is the most prominent mechanism of anemia in these patients. As a result of bone marrow invasion by blastic cells, erythrocyte morphology shows slight abnormalities in addition to the presence of nucleated erythrocytes. Consistent with the peripheral blood picture, bone marrow examination reveals several abnormalities in erythroblastic progenitor cells. These include normoblasts of extreme size, with nuclear fragmentation or location.

Anemia has long been excluded from the prognostic classification schemes for AML because it is a near-universal finding at baseline and is considered a mere consequence of bone marrow invasion by blast cells. Moreover, the flood of genetic molecular discoveries left little room for blood counts and some clinical features in the prognosis estimation of AML patients.

The impact of untoward effects of anemia was shown in solid tumors [11]. The relative risk of death was increased between 19% and 75% in several cancers, including lung, head and neck, and prostate cancer. The same holds true for several hematologic malignancies including lymphoma, chronic myeloid leukemia and childhood acute lymphoblastic leukemia [11-13].

Anemia has not been rigorously studied as a prognostic marker in AML. This is especially true for subtypes of AML patients. Vucinic et al. evaluated prognostic value of red cell distribution width in newly diagnosed AML patients [14]. The authors found that the higher the RDW value, the worse the prognosis. Interestingly, the predictive ability of RDW was robust enough to remain in the multivariate analysis that included ELN2017 as a covariate. In our opinion, RDW here serves as a surrogate marker for the abnormalities in the erythroblastic precursors in the bone marrow. Yanada and colleagues [15] evaluated the prognostic value of blood counts (platelet, neutrophil counts and Hgb value) at the time of complete remission in AML patints. The authors revealed that platelet and neutrophil counts but not Hgb levels were independent predictors of relaps-free survival.

Some other studies did not find serum Hgb level as an independent predictor of outcomes in pre-treatment AML. For instance, Colovic et al. [16] reported patient age, comorbidities, performance status, leukocytosis, hepatomegaly, lactate dehydrogenase, and cytogenetics as independent predictors of prognosis. Serum Hgb was not among them.

The discordance among studies regarding anemia status or serum Hgb level as an independent prognostic variable may be due to the inclusion of different established prognostic markers in the logistic regression models and to differences in sample sizes of the studies.

Our results showed that those with secondary AML had the lowest mean Hgb level at baseline. In addition, these patients still had the lowest, but not significantly different from other groups, mean serum Hgb level after chemotherapy. Secondary AML includes patients whose pre-existing hematologic disease has progressed to AML. This heterogeneous group of patients traditionally has a worse prognosis compared to other AML subtypes [17]. Predictably, the resistance of this type of AML to treatment is responsible for the inadequate clearance of blasts from the bone marrow and the resulting anemia. Regardless of the underlying AML subtype, patients who received intensive chemotherapy had significantly higher serum Hgb levels at the end of chemotherapy in our study.

The present study has several limitations worth mentioning. The retrospective design of the study has inherent limitations thereof. Blood transfusions and some concomitant disease states that may affect serum Hgb levels might have been missed out. When considering subgroups, the sample size of the study was relatively small. We did not include molecular genetic abnormalities because we included patients who were treated decades ago, when modern genetic analyses were not widely available.

CONCLUSION

In conclusion, our results revealed worse anemia in secondary AML as well as better anemia improvement with intensive chemotherapy. More importantly, pre-treatment serum Hgb level was an independent predictor of prognosis in AML patients.

Author contribution

Study conception and design: ICH, OEC, and HG; data collection: OEC, UYM and EAK; analysis and interpretation of results: YB, HD and ICH; draft manuscript preparation: OEC and HG. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Ethics Committee (Protocol no. 18/428-12).

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Conflict of interest

The authors declare that there is no conflict of interest.

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