

Analysis of pre-chemotherapy WBC, PLT, monocyte, hemoglobin, and MPV levels in acute myeloid leukemia patients with WT1, FLT3, or NPM gene mutations

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Abstract

Effects of mutations on AML (acute myeloid leukemia) patients have been an area of clinical interest. The aim of this study was to analyze pre-chemotherapy WBC (white blood cell), platelet, monocyte, hemoglobin, and mean platelet volume (MPV) levels in acute myeloid leukemia patients with Wilms tumor 1 (WT1), FMS-like tyrosine kinase 3 (FLT3), or nucleophosmin (NPM) gene mutations, attempting to detect and compare possible differences in these values.

The study included 71 patients with acute myeloid leukemia known to have WT1, FLT3, or NPM gene mutations. The patients were divided into 3 groups: FLT3-mutated AML patients without any accompanying known mutations other than WT1 at the time of diagnosis (Group 1), NPM-mutated AML patients without any accompanying known mutations other than WT1 at the time of diagnosis (Group 2), WT1-mutated AML patients with no other accompanying known mutations at the time of diagnosis (Group 3). We carried out intergroup comparisons of WBC, platelet (PLT), monocyte, hemoglobin, and MPV levels before chemotherapy.

There was a statistically significant difference between the groups in terms of WBC parameters ($P=.001$). There were no statistically significant differences between the groups with respect to hemoglobin, platelet, and monocyte levels.

Higher white blood cell counts could be observed in patients with FLT3-mutated AML.

Abbreviations: AML = acute myeloid leukemia, ASXL1 = Additional Sex Combs Like-1, CBC = complete blood count, FLT3 = FMS-like tyrosine kinase 3, FLT3-ITD = FMS-like tyrosine kinase 3-internal tandem duplication, G-CSFRs = granulocyte-colony stimulating factor receptors, HSPCs = hematopoietic stem and progenitor cells, LOF = loss-of-function, MPV = mean platelet volume, MRD = minimal residual disease, NPM = nucleophosmin, PLT = platelet, Ribi = ribosome biogenesis, RUNX1 = Runt-related transcription factor 1 gene, WBC = white blood cell, WT1 = Wilms tumor 1.

Keywords: FLT3, hemogram, mutation, NPM, WT1

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1. Introduction

Wilms tumor 1 (WT1), FMS-like tyrosine kinase 3 (FLT3), or nucleophosmin (NPM) gene mutations could be seen in acute myeloid leukemia patients. While NPM gene mutations, along with FLT3-ITD (FMS-like tyrosine kinase 3-internal tandem duplication) mutations, are known to exert a prognostic impact, they also play a role in determining the treatment approach to acute myeloid leukemia. Patients with FLT3-ITD mutations are considered to have a poor prognosis, so they are advised to receive allogeneic stem cell transplant following the induction therapy. WT1 mutations have yet to influence the clinical approach in patients with acute myeloid leukemia; they can only be used in the follow-up of minimal residual disease (MRD).

Braoudaki et al reported that there was no significant association between NPM1 mutation and high white blood cell (WBC) count in pediatric acute myeloid leukemia (AML) patients.^[1] Besides, NPM1 (Nucleophosmin 1) gene is also named as NPM gene, Nucleophosmin (Nucleolar Phosphoprotein B23, Numatrin) gene, nucleophosmin gene and/or Nucleolar Protein NO38 gene.^[2] On the other hand, Colovic et al showed that AML patients with FLT3/ITD mutations had higher WBC counts than patients without FLT3/ITD mutations.^[3] Hereby, the

Table 1
Comparison of the levels of WBC, PLT, monocyte, MPV, and hemoglobin according to the groups (patients with FLT3 mutation: Group 1, patients with NPM mutation: Group 2, patients with only WT1 mutation: Group 3).

Variable (N=71)	FLT3 (n=16) ^[1]		NPM (n=23) ^[2]		WT1 (n=32) ^[3]		P*
	Mean	Median	Mean	Median	Mean	Median	
Hemoglobin	9.10	8.97	8.8439	8.9	9.0391	8.9	F=0.107 P=.899
WBC	47.5213	25.32	25.0213	16.88	16.1953	3.135	$\chi^2=13.685$ P=.001 [1.2–3]
PLT	71.0625	62.5	117.7826	111.0	102.125	71.5	$\chi^2=5.478$ P=.065
Monocyte	8.4369	2.685	4.9413	1.61	5.9388	0.8	$\chi^2=4.520$ P=.104
MPV	8.525	8.35	9.3739	8.9	8.3906	8.4	$\chi^2=3.324$ P=.190

* ANOVA test (F-table value) was used for comparison of 3 or more independent groups with normal distribution, and Kruskal–Wallis H test (χ^2 -table value) statistics was used to compare the data with no normal distribution.

aim of this study was to analyze pre-chemotherapy WBC, platelet, monocyte, hemoglobin, and mean platelet volume (MPV) levels in acute myeloid leukemia patients with WT1, FLT3, or NPM gene mutations, attempting to detect and compare possible differences in these values.

2. Materials and methods

The study included 71 patients with acute myeloid leukemia known to have WT1, FLT3, or NPM gene mutations from the patient files in the archives of the Hematology Polyclinic at the University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Education and Research Hospital. Patients under 18 years of age and foreign nationals (those who were not citizens of Turkish Republic) were excluded from the study. The study retrospectively analyzed pre-chemotherapy WBC, PLT (platelet), monocyte, hemoglobin, and MPV levels in acute myeloid leukemia patients with WT1, FLT3, or NPM gene mutations. The patients who had complete blood count (CBC) results before chemotherapy were divided into 3 groups: FLT3-mutated AML patients without any accompanying known mutations other than WT1 at the time of diagnosis (Group 1), NPM-mutated AML patients without any accompanying known mutations other than WT1 at the time of diagnosis (Group 2), WT1-mutated AML patients with no other accompanying known mutations at the time of diagnosis (Group 3).

We also carried out intergroup comparisons of WBC, PLT, monocyte, hemoglobin, and MPV levels before chemotherapy. The study was a retrospective review of medical records. The patients diagnosed with mixed phenotype acute leukemia and/or biphenotypic acute leukemia were also excluded from the study. ANOVA test (F-table value) was used for comparison of 3 or more independent groups with normal distribution, and Kruskal–Wallis H test (χ^2 -table value) statistics was used to compare the data with no normal distribution. Statistical analyses were performed with IBM SPSS Statistics 24.0 software package. $P < .05$ was considered statistically significant. Known mutation statuses in the patient files were retrospectively evaluated for the study. This study was approved by the local ethics committee in the hospital.

3. Results

There was a statistically significant difference between the groups in terms of WBC parameters ($\chi^2=13.685$; $P=.001$). Bonferroni-

corrected values for paired comparisons conducted to determine from which group the significant difference stemmed revealed a statistically significant difference between the WBC value of the FLT3 and NPM group and that of WT1 group. WT1 group had significantly lower levels of WBC than those of FLT3 and NPM groups (Table 1). No difference was found between the groups in terms of hemoglobin, platelet, and monocyte levels (Table 1).

In the WT1 group, the MPV levels of 2 patients (6.25%) were higher than the normal range, and the MPV of 1 patient (3.125%) was lower than the normal range. In the FLT3 group, the MPV values of 2 patients (12.5%) were lower than the normal values, whereas the MPV of 1 patient (6.25%) was higher than the normal values. In the NPM group, MPV values of 4 patients ($\approx 17.4\%$) were higher than the reference values, and the MPV values of 2 patients ($\approx 8.7\%$) were lower than the normal values. On the other hand, no statistically significant difference was found between the groups in terms of MPV levels (Table 1).

4. Discussion

In their study, Santos et al reported a median WBC level of $37 \times 10^9/L$ in AML patients with FLT3 mutation and a median WBC level of $14 \times 10^9/L$ in those with no FLT3 mutation, showing that the median WBC level of patients with FLT3 mutation was significantly higher than that of patients with no FLT3 mutation.^[4] They also found that there were no statistically significant differences between these groups in terms of platelet counts and hemoglobin levels.^[4] Fröhling et al also reported that FLT3–ITD positivity was related to high white blood cell counts.^[5] In addition, Hou et al demonstrated that there was no difference in the levels of WBC, hemoglobin, and PLT between AML patients with WT1 mutation and those with no WT1 mutation.^[6] Chauhan et al also reported that patients with NPM1 mutation had higher platelet counts than those with no NPM1 and FLT3 mutations.^[7] In our study, we found that AML patients with WT1 mutation only had lower WBC levels than those with FLT3 or NPM mutations. However, the platelet, monocyte, MPV, and hemoglobin levels showed no significant differences dependent on the existence of mutations. Furthermore, amino acid phosphorylation is an important process in signaling cascades. In their studies, Dwivedi et al performed phosphoproteomics analyses of granulocyte-colony stimulating factor receptors (G-CSFRs).^[8,9] Phosphoproteomics analyses of the protein products of the aforementioned genes may give new

information about the clinical findings of acute myeloid leukemia.

We found that higher WBC levels could be seen in patients with FLT3-mutated AML. This might be a potential reason for the worse prognosis of FLT3-mutations in AML. Rezaei et al showed that there were no significant differences in mean white blood cell counts between cytogenetically normal AML patients with wild-type and mutant FLT3-ITD and NPM1 genes.^[10] But, we did not determine cytogenetics as an exclusion or inclusion criteria in our study. Furthermore, our study was a retrospective study. The patients were grouped according to their known mutation status, and the data in the patient files were used to gather the mutation status of the patients. Furthermore, only the known mutation statuses in the patient files could be used for analyses. On the other hand, mutations such as ASXL1 (Additional Sex Combs Like-1), CEBPA, RUNX1 (Runt-related transcription factor 1 gene) had not been routinely tested for the patients. Hilgendorf et al showed that ASXL1 could have a role in erythroid development and differentiation.^[11] Walker et al reported an autosomal dominant inherited point mutation of the RUNX1 gene that might cause thrombocytopenia.^[12] One of the family members evaluated in the work of Walker et al developed AML.^[12] Cai et al showed that early LOF (loss-of-function) RUNX1 mutations could reduce Ribi (ribosome biogenesis) in mice HSPCs (hematopoietic stem and progenitor cells).^[13] In addition, we included all the patients whose records/files could be found during the period of study. Leukemia is an infrequent disease. Therefore, multiple center prospective studies may also help to include larger number of patients.

Further prospective studies which specify the mutations more detailly and more homogenous will give accurate results about the effect of mutations on hemogram parameters. Future studies in this area may also reveal new genetic mutations predicting worse prognosis in non-FLT3-mutated AML patients with high WBC levels.

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