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Frequency of NPM1 Mutation and Its Impact on Prognosis in Cytogenetically Normal AML Patients: Hyperleukocytosis Remains an Unfavorable Prognostic Marker Among NPM1 Positive Patients

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ABSTRACT

Aim: Nucleophosmin 1 (NPM1) mutation is the most frequent genetic abnormality that points to a favorable prognosis in patients with cytogenetically normal acute myeloid leukemia (CN-AML). NPM1 mutation rate has not been documented yet in Turkish patients. We aimed to investigate NPM1 frequency and its prognostic impact.

Methods: A total of 160 patients diagnosed with CN-AML were enrolled in this study retrospectively. Clinical and laboratory data, as well as results from polymerase chain reaction tests for NPM1 and FMS-like tyrosine kinase 3 (FLT3) mutations, were analyzed.

Results: The NPM1 mutation was found in 35 (21.9%) patients. Patients were followed for a median of 16.5 (0.5-132.0) months. Patients with NPM1 mutation were characterized by a higher leukocyte count (p=0.03). Primary refractory disease (p=0.02) and early mortality (p=0.02) were lower in patients with NPM1 mutation positivity. Relapse-free survival (70.9% vs. 41.8%, p=0.03) and overall survival (OS) (65.5%vs. 47.0%, p=0.04) were higher in NMP1 mutation positive patients. In NPM1 positive group, relapse free survival (21.4%vs. 81.5%, p=0.01) and OS (22.9%vs. 70.0%, p=0.03) were lower in patients with hyperleukocytosis (p<0.05).

Conclusion: NPM1 mutation frequency was lower in Turkish CN-AML patients than western populations. NPM1 mutation status is related to good prognosis. However, we showed that hyperleukocytosis is a poor prognostic marker for NMP1-positive, FLT3-negative CN-AML patients.

Keywords: NMP1, FLT3-ITD, hyperleukocytosis, prognosis, acute myeloid leukemia

Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults. The disease prognosis is heterogeneous due to various mutations at cytogenetic and molecular levels. Genetic properties are known as one of the most important prognostic markers that determines consolidation therapy modality in AML. Almost half of the patients with AML have a normal karyotype [cytogenetically normal (CN)-AML], which is considered an intermediate risk disease. This subgroup shows quite heterogeneous prognoses [1,2]. Several studies reported that a positive nucleophosmin 1 (NPM1) mutation and a negative FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) status are usually associated with more favorable outcomes in CN-AML [3-6].

The NPM1 mutation is the most commonly identified genetic abnormality in AML. NPM1 frequency has been reported as 41-66% in Europe and the USA [7-9]. However, the frequency

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of NPM1 mutation and the impact of these mutations on prognosis have not been documented yet in the Turkish population with CN-AML. We aimed to investigate the NPM1 frequency and factors contributing to survival in Turkish patients with NPM1-mutated AML.

Methods

This is a single-center database retrospective cohort study. A total of 160 patients diagnosed with CN-AML from January 2007 to December 2018 [median age: 51.5 (18-91) years; male/female: 94/66] were enrolled in this study consecutively. Demographic information, complete blood count, percentage of blast at bone marrow aspiration, flow cytometry, conventional cytogenetic, and polymerase chain reaction (PCR) test results were obtained retrospectively. All of the patients had NPM1 data, but only 95 patients had FLT3-ITD test results.

We recorded follow-up data, including chemotherapy/transplantation information and response assessment. The induction regimen was cytarabine and idarubicin (3+7). Hypomethylating agents were used for elderly patients. Response assessment was performed at day 28 of intensive induction chemotherapy, at the end of 4th course of hypomethylating agents treatment. Fludarabine, cytarabine, granulocyte colony-stimulating factor (FLAG-Ida), regimen was used for primary refractory patients. High-dose cytarabine (HDAC), FLAG-Ida, hypomethylating agents, autologous stem cell transplantation (ASCT), or allogeneic stem cell transplantation (allo-SCT) were used as consolidation treatment in patients who obtained a complete response. The study was approved by the Clinical Research Ethics Committee of Keçiören Training and Research Hospital (decision no: 958, date: 14.10.2015). All patients signed informed consent forms and agreed to the use of their clinical data in medical research.

Detection of NPM1 Mutation

Detection of NPM1 mutation: Total ribonucleic acid (RNA) was isolated from bone marrow samples using the QIAamp RNA Blood Mini Kit (QIAGEN, Hilden, Germany). RNA integrity was assessed using a NanoDrop Lite spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA), and samples with adequate quality, (260/280 ratio >1.8), were processed for complementary deoxyribonucleic acid (cDNA) synthesis. Total RNA from each sample was reverse-transcribed into cDNA using Ipsogen® RT kit (QIAGEN) according to the manufacturer's protocol. Real-time quantitative PCR (RQ-PCR) assay for detection and quantification of NPM1 type A mutation (the most common variant, representing ~75-80% of all NPM1 mutations) was performed using NPM1 mut A MutaQuant Kit (IPSOGEN, Marseille, France) on QIAGEN's Rotor-Gene Q real-time PCR cycler. The assay targets the 4-base pair insertion Timine, Sitozin, Timine, Guanin in exon 12 of the *NPM1* gene, which creates a frameshift mutation leading to aberrant cytoplasmic localization of the NPM1 protein. Each reaction was performed in duplicate with appropriate positive and negative controls. A sample was considered NPM1-mutated if the mutation was detected in both replicates with adequate amplification curves.

Quality control measures included: Use of abelson murine leukemia viral oncogene homologous 1 as a housekeeping gene for RNA quality assessment. Negative controls (water blanks) in each run. "Positive controls with known NPM1 mutations." Assessment of PCR efficiency and linearity.

Detection of FLT3 Mutations

Genomic DNA was extracted from bone marrow samples by the EZ1 Advanced XL System, QIAGEN. ITD mutation and tyrosine kinase domain (TKD) mutation (D835) of *FLT3* gene were identified using the LeukoStrat® CDx FLT3 mutation Assay Kit, INVIVOSCRIBE. DNA was amplified via PCR according to the manufacturer's instructions, and the size of the ITD PCR product was determined by the FlashGel™ System, Lonza. However, the FLT3 TKD PCR product was digested with EcoRV, and the presence of the mutation was also assessed using the FlashGel™ System, Lonza. A product measured at 327±1 bp was identified as wild-type for FLT3-ITD mutations, while alleles that contain ITD mutations produced a product that exceeds 327±1 bp. For FLT3-TKD mutations, wild-type alleles of the *FLT3* gene yield digestion products of 79±1 bp whereas mutant alleles yield products of 125±1 bp or 127±1 bp from the original undigested amplicon product of 145±1 bp or 147±1 bp [10].

Statistical Analysis

Continuous and categorical variables were compared with the Mann-Whitney U test and chi-squared test, respectively. Kaplan-Meier analysis was used for survival analysis SPSS 16.0 program was used for statistical analysis (SPSS Inc, Chicago, IL, USA). $P<0.05$ was considered to be statistically significant.

Results

NPM1 mutation was found in 35 (21.9%) patients. Patients' characteristics were similar between NPM1 positive and negative groups with respect to age, gender, French–American–British classification, hemoglobin levels, platelet counts, and percentage of bone marrow blast (p>0.05) (Table 1). Median white blood cell (WBC) count was found to be significantly higher in patients with NMP1 mutation-positive than in mutation-negative patients [62.8 (12.6-182.3) vs. 31.4 (1.2-69.7)] (p=0.03) (Table 1). The percentage of patients with hyperleukocytosis at the time of diagnosis was more frequent in the NPM1 mutation positive group (34.2% vs. 6.6%, p=0.02). Among patients who had an FLT3-ITD test result (n=95), FLT3-ITD was positive in 4 (14.8%) patients in the NPM1 positive group (n=27) and in 18 patients (26.6%) in the NPM1 negative group (n=68). FLT3-ITD positivity was not significantly different between NPM1 positive, and negative, patients (p>0.05).

Patients were followed median 16.5 (0.5-132.0) months. Primary refractory disease was found more frequently in NPM1 mutation negative patients compared to NPM1 mutation positive patients (22.4% vs. 5.7%, p=0.02). Early mortality

Table 1. Patient's characteristics respect to NPM1 positive and negative patients

	NPM1 positive n=35 (21.9%)	NPM1 negative n=125 (78.1)	p
Gender (male/female) n (%)	20/15 (57.1/42.8)	77/48 (61.6/38.4)	NS>0.05
Age (years)	50.0 (20-90)	44.0 (19-91)	NS
Hemoglobin (g/dL)	8.9 (5.7-14.0)	8.1 (4.1-13.2)	NS>0.05
WBC (/mm^3)	62.8 (12.6-182.3)	31.4 (1.2-119.7)	0.03
Hyperleukocytosis (WBC≥100000/mm^3) n (%)	12 (34.2)	10 (6.6)	0.02
Platelet (/mm^3)	71000 (3900-284000)	51650 (3000-85000)	NS>0.05
Blast in bone marrow (%)	90 (22-100)	90 (22-100)	NS>0.05
FAB classification (n/%) M0 M1 M2 M4 M5 M6	 3 (8.6) 5 (14.2) 6 (17.1) 14 (40.0) 6 (17.1) 1 (2.8)	 24 (19.2) 35 (28.0) 19 (15.2) 39 (31.2) 6 (4.8) 2 (1.6)	NS
FLT3 positivity (n/%)	4 (14.8)	18 (26.6)	NS>0.05
Early mortality (within first month)	1 (2.8%)	15 (12.0%)	0.03
Refractory to first line chemotherapy	2 (5.7%)	28(22.4%)	0.02
Consolidation chemotherapy/ASCT	n=34 28 (82.4)	n=95 46 (55.8)	0.02
Consolidation allo-SCT	6 (17.6)	42 (44.2)	0.003

NPM1: Nucleophosmin 1, FLT3: FMS-like tyrosine kinase 3, ASCT: Autologous stem cell transplantation, Allo-SCT: Allogeneic stem cell transplantation, WBC: White blood cell, FAB: French–American–British

within the first month was higher in the NPM1 negative group compared to the NPM1 positive group (12.0% vs. 2.8%) (p=0.02). Consolidation procedures included chemotherapy, including high-dose cytarabine, FLAG-Ida, or hypomethylating agents, in 65 patients, and ASCT in 16 patients and allogeneic stem cell transplantation in 48 patients at first complete remission. Allo-SCT was a more frequent consolidation approach in the NPM1 mutation negative group. ASCT or chemotherapy was preferred in the NPM1 mutation positive group (p=0.02) (Table 1).

When the FLT3-ITD positive patients are excluded from survival analysis, relapse free survival (RFS) [70.9% vs. 41.8%, p=0.03, confidence interval (CI): 52.0-75.5, standard error (SE): 5.9] and overall survival (OS) (65.5% vs. 47.0%, p=0.04, CI: 52.6-76.2, SE: 6.0) were lower in the NPM1 mutation positive group compared to the negative group (Figures 1, 2). Among NPM1 positive patients, RFS (21.4% vs. 81.5%, p=0.01, CI:35.6-54.3 SE:4.7) and OS (22.9% vs. 70.0%, p=0.03, CI:37.7-54.9, SE: 4.3) probabilities were significantly lower in patients WBC >100,000/mm^3 compared to <100,000/mm^3, respectively (Figures 3, 4).

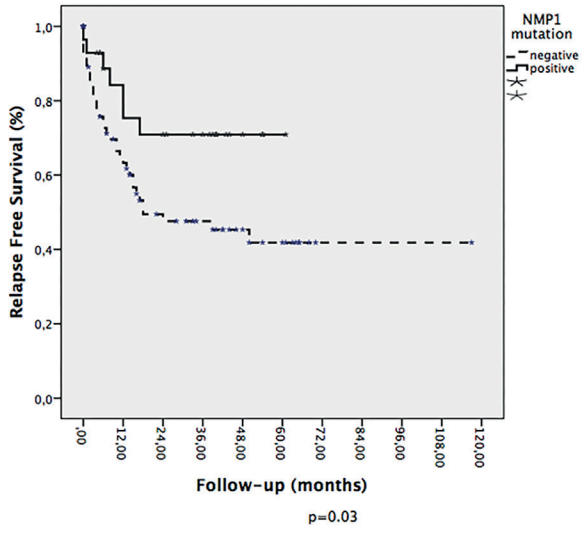

Figure 1. Relapse-free survival in NPM1 positive and negative patients
NPM1: Nucleophosmin 1

Discussion

NPM1 mutation is found in AML frequently, but some studies lack information regarding the NPM1 frequency in CN-AML due to a heterogeneous patient population, including mixed karyotype features or translocations. Almost all of the studies from the USA and Europe reported NPM1 frequency of 41-68%, and FLT3-ITD frequency has been reported: 20-38% of patients with CN-AML [11-14]. These data were obtained generally from phase I/II studies about AML genetic features and prognosis. On the other hand, lower NPM1 mutation

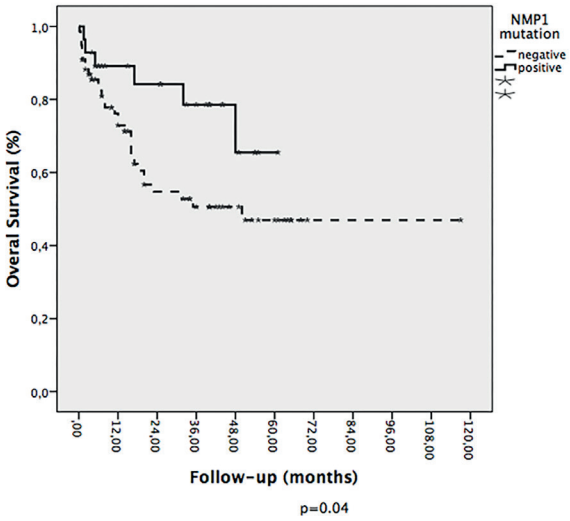

Figure 2. Overall survival in NPM1 positive and negative patients
NPM1: Nucleophosmin 1

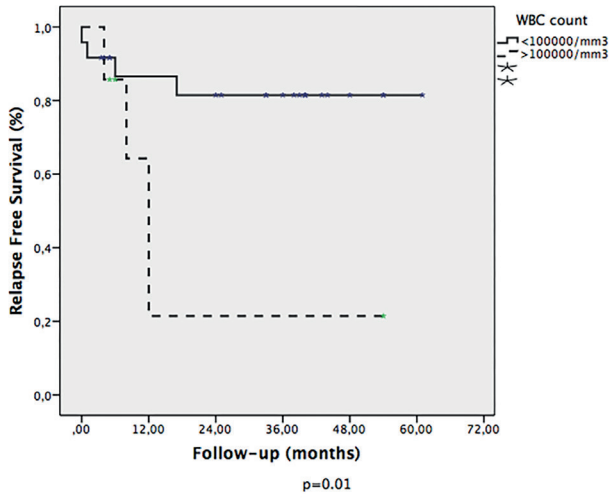

Figure 3. Relapse-free survivals according to WBC count in patients with NPM1 mutation
WBC: White blood cell, NPM1: Nucleophosmin 1

frequency was reported as 28.3% in the Egyptian [15], 27.7% in the Bulgarian [16], 24.7% in the Brazilian [17], 20.8% in the Iranian [18], and 17.1% in the Indian [19] CN-AML population. We found that 21.9% of CN-AML patients aged over 18 had mutated NPM1. This situation could indicate that the mutation in question may be influenced by ethnicity and geographic origin. However, it could be argued that limitations in the evaluation and laboratory testing (such as isolation issues or not performing the test on the same kit) may also play a role in this situation.

In some studies, NPM1 mutation has been reported more frequently in females and correlated with older age [20]. We did not confirm these findings. among NPM1 positive and negative patients, gender and median age were similar. As

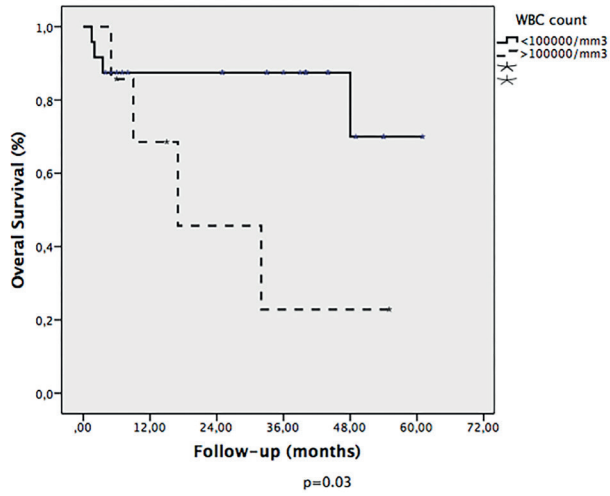

Figure 4. Overall survival according to WBC counts in patients with NPM1 mutation
WBC: White blood cell, NPM1: Nucleophosmin 1

seen in the literature, leucocyte count was higher in NPM1 positive patients; thrombocyte count and hemoglobin levels were not different in this study.

Among CN-AML patients, NPM1 mutation positive, patients reached complete response more frequently at the end of the first induction regimen compared to mutation negative, patients. In addition, the early mortality rate within the first month was lower in NPM1 mutation-positive patients. When the FLT3 positive patients were excluded from the survival analysis, both RFS and OS were higher in NPM1 positive patients than negative ones. These data confirmed those previously reported [4-6,21]. In our study, NPM1-positive patients were divided into two groups according to whether their leukocyte count was higher than or lower than 100,000/mm^3. Patients with higher leukocyte counts had significantly lower RFS and OS probabilities. Higher leukocyte count was known as a classical negative prognostic factor, but novel European LeukemiaNet (ELN) pretreatment risk stratification is now only based on cytogenetic and mutational status [22]. According to ELN, CN-AML with NPM1 mutation without FLT3-ITD has a good prognosis and is referred to allo-SCT at relapse. However, Bazarbachi et al. [23], reported that survival outcomes are better when patients with NPM1 mutation are transplanted in first complete remission (CR1) versus second CR2. Tien et al. [24] reported that hyperleukocytosis, defined as >50,000/mm^3, was an independent prognostic factor for poor outcomes in distinct genetic alterations and CN-AML patients. The authors pointed out allo-SCT in first CR, ameliorated the negative impact of hyperleukocytosis on survival. A higher leucocyte count may already be an important poor prognostic marker besides the cytogenetic markers.

The molecular processes underlying hyperleukocytosis remain unclear. However, we do know that there are interactions between leukaemic blasts and endothelial cells that lead to leukostasis. Leukemic blasts interact with endothelial

cells via cell adhesion molecules, such as various members of the selectin family. These molecules are upregulated by inflammatory cytokines released by the leukemic blasts themselves [25]. To understand the molecular processes contributing to hyperleukocytosis in AML, a METASCAPE analysis, and Gene Set Enrichment Analysis were conducted. The analyses revealed several gene sets that exhibited a negative association with hyperleukocytosis, including cytokine-cytokine receptor interaction, extracellular matrix-receptor interaction, cell cycle regulation, DNA replication, cell adhesion molecules, cytokine signaling pathway, adhesion signaling pathway, and epithelial mesenchymal transition. The correlation between hyperleucostasis and gene mutations, particularly those of FLT3 and DNA (Cytosine-5)-methyltransferase 3 alpha, suggests the importance of these mutations in hyperleucostasis development and progression in AML. Further research is needed to elucidate the underlying mechanisms and explore targeted therapies for patients with these specific genetic markers [26].

Study Limitations

The limitations of the study include the small number of NMP1 mutation positive cases and the short follow-up period.

Conclusion

In conclusion, this is the first report on the frequency and clinical characteristics of NPM1 mutation in the CN-AML Turkish population. We found that the NPM1 mutation frequency is 21.9% in the Turkish CN-AML population. NPM1 mutation status related with good prognosis. However, we showed that the hyperleukocytosis is a poor prognostic marker for NMP1 positive, FLT3 negative CN-AML patients. We may refer to allo SCT as first CR for NMP1 positive, FLT3 negative CN-AML patients if they have hyperleukocytosis at the time of diagnosis. These results should be confirmed by prospective randomized clinical trials.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Keçiören Training and Research Hospital (decision no: 958, date: 14.10.2015). **Informed Consent:** All patients signed informed consent forms and agreed to the use of their clinical data in medical research.

Footnotes

Authorship Contributions

Concept: M.S.P., Z.N.Ö., S.G., H.K., Design: A.S., M.Y., Data Collection or Processing: M.S.P., Z.N.Ö., A.K., S.G., H.K., Z.A.Y., M.Y., Analysis or Interpretation: H.K., Z.N.Ö., A.S., H.K., M.Y., Literature Search: M.S.P., A.K., H.K., Z.N.Ö., Writing: M.S.P., Z.N.Ö., A.K., A.S., M.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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