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Original Article

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Does Wilms Tumour-1 Gene Mutation Affect Treatment Options and Response in Acute Myeloid Leukaemia?

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ABSTRACT

Aim: The prognostic impact of Wilms tumour-1 (WT-1) mutations is controversial for patients with acute myeloid leukaemia (AML). In this study, we aimed to determine the clinical effects of WT-1 mutations.

Methods: We retrospectively analysed the data of a total of 139 patients with AML, 50 negative and 89 positive, in whom WT-1 analysis was performed at the time of diagnosis.

Results: Among the patients, 47% were female and 53% were male; median age was 62 (18-88) years in the WT-1 negative group and 47 (18-90) years in the WT-1 positive group; median follow-up period was 5 (1-144) months in the WT-1 negative group and 28 (1-110) months in the WT-1 positive group. When the induction treatments were analysed, the regimen containing idarubicin and cytarabine was the most commonly used regimen in both groups (73% in the WT-1 positive group and 36% in the WT-1 negative group). When the response to treatment was evaluated in WT-1-negative and positive groups, complete response was 58% to 80% for WT-1-negative and positive groups respectively; partial response was 14% to 2%; refractoriness was 26% to 16%, respectively. Recurrence was 16% in the WT-1 negative group and 5.6% in the positive group. The survival rate was found to be 64% in the WT-1 negative group and 67.4% in the positive group.

Conclusion: It is uncertain whether the WT-1 test will be interpreted in diagnosis, treatment, and follow-up, or if its prognostic significance and future studies are much needed.

Keywords: Acute myeloid leukemia, prognosis, WT-1 mutations

Introduction

Acute myeloid leukaemia (AML) has a heterogeneous course due to many patient- and tumour-related factors [1-3]. Genetic characteristics are important prognostic factors [4]. *Wilms tumour-1* (WT-1) gene shows both tumor suppressor effects and oncogenic effects by controlling transcription, translation, and RNA metabolism at cellular levels [5,6]. WT-1 positivity is observed in 6-15% of newly diagnosed AML cases [7]. The European Leukaemia Network (ELN) 2022 update does not include WT-1 positivity in the genetic risk classification [4]. In the presence of WT-1, it has been reported that some mutations, including ten-eleven translocation methylcytosine dioxygenase 2, isocitrate dehydrogenase-1, isocitrate dehydrogenase-2 (IDH-2), and CCAAT/enhancer binding protein alpha (CEBPA), were not observed [8,9]. Detection of WT-1 levels is a marker of both residual disease and future relapse [10,11]. In addition, it is considered that WT-1 triggers malignant events through its interaction with Bcl-2, which is a protooncogene, and the *p53* gene, which is a tumor suppressor gene [12]. In one study, it was found that WT-1 positivity was more common under the age of 65 years, and affected relapse-free survival. Again in this study, it was reported that the frequency of WT-1 decreased in the presence of nucleophosmin (NPM1) and CEBPA [13]. In a phase-2 study evaluating the efficacy of azacitidine in myelodysplastic syndrome, no correlation was found between WT-1 level and treatment response. In other words, in this

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study, WT-1 was not a predictor of treatment response [14]. In another study, WT-1 was found to be associated with DEK oncogene and was reported to cause cytarabine, doxorubicin or azacitidine resistance [15]. Despite the partial understanding of this complex association and advances in the field of genetic mutation analyses, treatment remains elusive.

Our aim in this study was to retrospectively review the data of WT-1 positive AML patients, to determine the presence of concomitant mutations, to analyse the treatment response according to the type of treatment, to determine the prognostic effect, and, if possible, to make a treatment recommendation.

Methods

In our study, 139 patients diagnosed with AML who were followed up in the adult hematology clinic between 2011 and 2023 and who underwent *WT-1* gene mutation test analysis were included. Along with the demographic characteristics of the patients, complete blood count, genetic results, and treatment content at the time of AML diagnosis, treatment response and whether recurrence developed during follow-up were analysed, and overall survival rates were calculated. ELN 2022 categorises summarised: t(8;21)(q22;q22.1); RUNX1::RUNX1T1, inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); CBFB::MYH11, mutated *NPM1*, in-frame bZIP mutated are favorable; t(6;9)(p23;q34.1)/DEK::NUP214, (v;11q23.3)/KMT2A rearranged, t(9;22)(q34.1;q11.2)/BCR::ABL1, t(8;16)(p11;p13)/KAT6A::CREBBP, inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM (EVI1), t(3q26.2;v)/MECOM (EVI1)-rearranged, -5 or del(5q); -7; 17/abn(17p), monosomal karyotype or complex karyotype are adverse, t(9;11)(p21.3;q23.3)/MLLT3::KMT2A and cytogenetic and/or molecular abnormalities not classified as favorable or adverse are intermediate risk groups [4]. The genetic risks of the patients were determined.

The study was carried out with the permission of the University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee (decision no: 2024-07/107, date: 05.09.2024).

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) statistics (SPSS V26.0, Armonk, NY) was used for statistical analysis. Descriptive statistics were used to present the data. Categorical data were presented as numbers and ratios, and numerical data were presented as median, minimum, and maximum. Comparison of numerical data in two groups was performed using the Mann-Whitney U test. Comparison of categorical variables was performed using chi-square or Fisher's exact tests. Overall survival (OS) was defined as the duration from the first day of the treatment to the date of death or to the last follow-up date for survivors. Kaplan-Meier survival analysis was applied for OS. P values of ≤0.05 were considered statistically significant.

Results

A total of 139 patients, 50 WT-1 negatives and 89 positives, were included in our study. The female to male ratio was 0.78 in the WT-1 negative group and 0.49 in the WT-1 positive group. The median follow-up period was 5 (1-144) months in the WT-1 negative group and 28 (1-110) months in the positive group. When evaluated according to blood group, A, B, O and AB blood groups were found to be 40.8%, 28.5%, 26.5%, 4%, respectively, in the WT-1 positive group and 39%, 9%, 26.5%, 9%, respectively, in the WT-1 negative group (p=0.01). When analysed according to performance status, Eastern Cooperative Oncology Group (ECOG) 0-1 was found more frequently in the WT-1 positive group than in the WT-1 negative group, with proportions of 70% and 30%, respectively. ECOG ≥2 was found to be 11% more frequent in the WT-1 negative group compared to 34% in the WT-1 positive group, but this difference was not statistically significant (p=0.07). Extramedullary involvement rates were not significant between the groups (p>0.05). Patient characteristics were summarized according to the groups in Table 1.

The frequency of leukaemia with genetic abnormalities was 78% in the WT-1 negative group and 25.8% in the WT-1 positive group. In the WT-1 positive group, 21% were in the poor; 42% in the medium; 37% in the good risk group. In the WT-1 negative group, 20% were in the poor; 46% in the medium; 34% in the good risk group. No statistically significant difference was found between the two groups in terms of genetic risk class distribution (p=0.87). When the correlation between WT-1 and other molecular genetic mutations was analysed, WT-1 was positive in 12 of 14 patients with the positive NPM1 mutation, 2 of 3 patients with the positive CEBPA mutation, 4 of 6 patients with the positive FLT-3 mutation, and 4 of 4 patients with the positive PML-RAR-A mutation (p=0.15). The FISH negative detection rate was 75% higher in the WT-1 positive group (p=0.00). The most common translocations were t(15;17) and t(8;21), which were found more frequently in the WT-1 negative group (88% and 80%, respectively). There was no difference between the groups, in terms of the detection of anomalies in karyotyping (p>0.05).

When the induction treatments were analysed, the regimen containing idarabucine and cytarabine was the most commonly used regimen in both groups (73% in the WT-1 positive group and 36% in the WT-1 negative group). The second most frequently used regimen were hypomethylating agents, which were preferred by 20% and 24% in the WT-1 positive and negative groups, respectively (p=0.00). When the response after induction therapy was grouped as complete, partial response, and refractoriness, it was 58%, 14%, 26% in the WT-1-negative group and 80%, 2%, 16% in the WT-1-positive group, respectively (p=0.01). The rate of receiving reinduction therapy was 14% in the WT-1 negative group and 15% in the WT-1 positive group (p=0.87). Recurrence was 16% in the WT-1 negative group and 5.6% in the positive group (p=0.04). Allogeneic bone marrow transplantation (ABMT) was performed in a total of 36 patients; the rate of ABMT was 22% in the WT-1 negative group and 28% in the positive group (p=0.43).

The survival rate was found to be 64% in the WT-1-negative group and 67.4% in the positive group (p=0.18) (Figure 1).

Table 1. Characteristics of patients with or without WT-1 mutations

	WT-1 genetic status	No (n)	Median (min-max)	p
Gender (female/male)	Negative Positive	22/28 44/45		0.597
Age (years)	Negative		62 (18-88)	0.175
	Positive		47 (18-90)	
Follow-up period (month)	Negative		5 (1-144)	0.000
	Positive		28 (1-110)	
Performance status (ECOG ≥2)	Negative Positive	17 10		0.07
Blood type	Negative A/B/O/AB Positive A/B/O/AB	20/14/13/2 34/8/37/8		0.014
Leukocyte count (/µL)	Positive		2670 (90-160000)	0.001
	Positive		9755 (430-361000)	
Hemoglobin (g/dL)	Negative		8.6 (4.4-10.9)	0.060
	Positive		8.9 (5.5-15.2)	
Platelet (/µL)	Negative		42500 (6000-327000)	0.416
	Positive		64000 (8000-300000)	
Genetic risk	Negative Good Medium Poor Positive Good Medium Poor	 17 23 10 33 37 19		0.87

ECOG: Eastern Cooperative Oncology Group, min-max: Minimum-maximum, *WT-1: Wilms tumour-1*

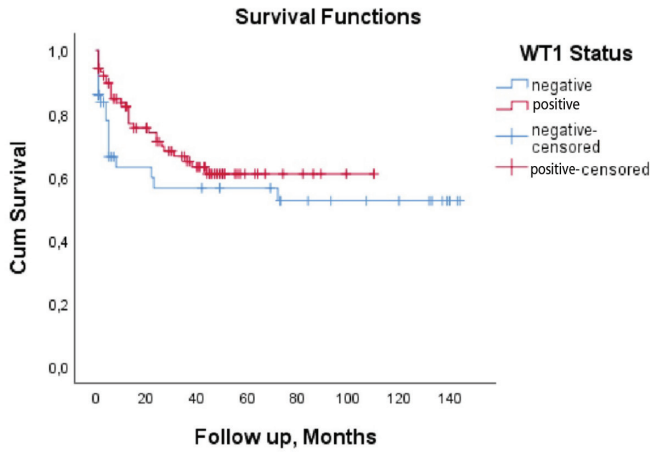

Figure 1. Survival data AML patients with and without WT-1 mutations
WT-1: Wilms tumour-1, AML: Acute myeloid leukaemia

Discussion

In our study, statistically significant differences were found between WT-1 negative and positive AML groups in terms of blood groups, frequency of defining genetic abnormalities, treatment regimens, treatment response, and relapse rates. Although AML-defining conditions such as t(8;21) and t(15;17), which are also associated with good genetic risk, are detected more frequently in the WT-1 negative group, the better performance status in the WT-1 positive group may contribute to better response and reduced relapse with the more frequent use of intensive induction therapy. Although WT-1 is not used in the genetic risk analysis of ELN, the correlation between genetic mutations and WT-1 mutation raises questions about its importance in the choice of treatment. Our study includes a long follow-up period in the WT-1 positive group, and different study kits were used for the detection of WT-1 mutation presence. Therefore, WT-1 expression levels at the time of diagnosis could not be evaluated. We believe that there is still a need to evaluate the prognostic role of WT-1 in AML.

The *WT-1* gene, located on chromosome 11p13, plays a role in the regulation of cell survival, proliferation, and differentiation and can function both as a tumor suppressor and oncogene [16,17]. According to the ELN 2022 risk stratification, the prognostic significance of WT-1 mutation in three risk groups is unclear. In one study, it was reported that WT-1 positivity was a negative factor in terms of both overall and disease-free survival and overall response rates in the absence of FLT-3 and NPM1. The expression level at the time of diagnosis was also important in terms of prognosis. However, in the presence of

FLT-3 and NPM1 mutations, WT-1 positivity was not a negative risk factor in terms of treatment efficacy and survival [18]. In another study, it was reported that WT-1 positivity has been managed with cytarabine and anthracycline-based treatment, and even increased expression was an independent positive factor for complete response [19]. In another study, in which 173 patients with normal cytogenetic analysis were evaluated, WT-1 status was found to be associated with event-free survival, while a high WT-1 expression level was found to be associated with a higher leukocyte count and a blunted FLT-3 ITD and NPM1 mutation [20]. It was found that high expression of WT-1 was associated with inv(16), NPM1, and 11q23 rearrangement, whereas low expression of WT-1 was associated with t(8; 21) [21,22]. In another study, no correlation was found between WT-1 positivity and age, gender, leukocyte, platelet, response, relapse, and transplantation rates at the time of diagnosis, while good genetic risk was higher in the WT-1 negative group and intermediate risk was higher in the WT-1 positive group. NPM1, FLT3, and IDH-2 mutations were correlated with expression levels. The most commonly used regimen is the treatment schedule containing cytarabine and idarubicin, and no difference was found between WT-1 negative and positive groups in terms of treatment response [23].

In our study, the frequency of fusion defined in AML was higher in the WT-1, negative group. There was no correlation between WT-1 positivity and other molecular genetic markers. However, we consider that this may be because the expression level could not be evaluated due to the difference in WT-1 study kit and the low number of positive results for other molecular mutations. The most commonly used treatment regimen was idarubicin and cytarabine. In terms of response, more complete responses were obtained and recurrence was less common in the WT-1 positive group. There was no difference between the two groups in terms of overall survival. This may be explained by the positive contribution of the idarubicin and cytarabine treatment regimen to complete response rates. However, WT-1 expression levels at the time of diagnosis and WT-1 mutation status after treatment could not be evaluated.

Study Limitations

There are some shortcomings in our study. Firstly, it is retrospective. Secondly, the expression levels could not be included in the study, due to variations in WT-1 study kits. Thirdly, WT-1 mutation evaluation could not be performed in each patient in response to treatment; therefore, a detailed evaluation could not be made regarding the type of treatment.

Conclusion

Our study includes long-term data from a good patient population and WT-1 may be associated with some genetic abnormalities. Although no association between WT-1 and prognosis was found in our study, there is a need to evaluate WT-1 mutation positivity or even burden in treatment response. We believe that large cohort studies with not only the presence of WT-1 mutation but also the WT-1 expression level are needed.

Ethics

Ethics Committee Approval: The study was carried out with the permission of the University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee (decision no: 2024-07/107, date: 05.09.2024).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Y., Concept: S.Y., T.Z., S.C., E.H., A.D., N.O., A.B., Design: S.Y., T.Z., A.D., N.O., A.B., Data Collection or Processing: S.Y., T.Z., S.C., E.H., Analysis or Interpretation: S.Y., N.O., Literature Search: S.Y., Writing: S.Y.

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