HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Overview of Acute Myeloid Leukemia with TP53 Mutation: Single Center, Real-Life Data

TP53 Mutasyonlu Akut Myeloid Lösemiye Genel Bakış: Tek Merkez, Gerçek Yaşam Verisi

Selin Küçükyurt Kaya[1] | Hacer Berna Afacan Öztürk[1] | Lale Aydın Kaynar[1] | Jale Yıldız[1] Haktan Bağış Erdem[2] | Birgül Ay Karakuş[1] | Murat Albayrak[1] | Merih Kızıl Çakar[1] Şahika Zeynep Akı[1] | Ahmet Kürşad Güneş[1]

[1]Ankara Etlik City Hospital, Department of Hematology, Ankara, Türkiye
[2]Ankara Etlik City Hospital, Department of Medical Genetics, Ankara, Türkiye

Sorumlu Yazar | Correspondence Author
Selin Küçükyurt Kaya
dr.skucukyurt@hotmail.com
Address for Correspondence: Ankara Etlik City Hospital, Clinic of Hematology, Ankara, Türkiye.

Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1628279
Geliş Tarihi | Received: 29.01.2025
Kabul Tarihi | Accepted: 05.04.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Küçükyurt Kaya S, Afacan Öztürk HB, Aydın Kaynar L, et al. Overview of Acute Myeloid Leukemia with TP53 Mutation: Single Center, Real-Life Data. Hitit Medical Journal 2025;7(2):205-213. https://doi.org/10.52827/hititmedj.1628279

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 31/07/2024 tarihinde Ankara Etlik Şehir Hastanesi Bilimsel Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: AEŞH-BADEK-2024-592.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: SKK, AKG Tasarım: SKK, HBAÖ, LA, HBE, AKG Veri Toplama/Veri İşleme: JY, BAK, MA, MKÇ, ŞZA Veri Analizi: SKK, HBAÖ, LAK, HBE, AKG Makalenin Hazırlanması: SKK, AKG.
Hasta Onamı: Tüm hastalardan yazılı bilgilendirilmiş onam ve yayın için izin alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Ankara Etlik City Hospital Scientific Research Ethics Committee on 31/07/2024. Decision no: AEŞH-BADEK-2024-592.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: SKK, AKG Design: SKK, HBAÖ, LA, HBE, AKG Data Collection/Data Processing: JY, BAK, MA, MKÇ, ŞZA Data Analysis: SKK, HBAÖ, LAK, HBE, AKG Manuscript Preparation: SKK, AKG.
Informed Consent: Written informed consent and consent for publication were obtained from all patients.
Financial Disclosure: There are no financial funds for this article.

Overview of Acute Myeloid Leukemia with TP53 Mutation: Single Center, Real-Life Data

ABSTRACT

Objective: Acute myeloid leukemia (AML) with TP53 mutations represents a distinct and high-risk molecular subgroup characterized by aggressive disease progression, chemoresistance, and poor survival outcomes. This study provides a single-center analysis of clinical characteristics, treatment responses, and survival outcomes in a real-world cohort of patients with TP53-mutated AML.

Material and Method: A retrospective observational study was conducted at Ankara Etlik City Hospital, analyzing nine patients diagnosed with TP53-mutated AML between January 2023 and January 2024. Patients were treated with intensive or less intensive induction regimens based on patient-related factors. Cytogenetic and molecular abnormalities were recorded, alongside treatment responses were assessed per the European Leukemia Net 2022 guidelines. The primary endpoint was overall survival.

Results: The median age at diagnosis was 65 years, with 55.5% female patients. Complex karyotypes were observed in 66.7% of cases, and multi-hit TP53 mutations were identified in two patients. A complete response was achieved in 75% of patients treated with intensive induction therapy (7+3), while a complete or partial response was achieved in 60% of patients receiving the azacitidine-venetoclax regimen. Six patients died within 12 months, predominantly due to infection, while the three surviving patients underwent for allogeneic hematopoietic stem cell transplantation (allo-HSCT). The median overall survival (OS) of the entire cohort was 9 months. Patients with TP53-mutated AML who underwent allo-HSCT exhibited significantly prolonged OS (*p=0.01*).

Conclusion: The prognosisof TP53-mutated AML remains particularly poor, highlighting an urgent need for the development of novel therapeutic approaches to improve patient outcomes. While allo-HSCT offers a potential survival benefit, effective bridging therapies and post-transplant management are critical for improving outcomes in this high-risk population

Keywords: Acute myeloid leukemia, stem cell transplantation, survival, TP53 mutation, treatment.

ÖZET

Amaç: TP53 mutasyonlu akut myeloid lösemi (AML), agresif hastalık seyri, kemoterapi direnci ve kötü sağkalım sonuçlarıyla karakterize, yüksek riskli ve farklı bir moleküler alt grup olarak tanımlanır. Bu çalışma, TP53 mutasyonlu AML hastalarının klinik özelliklerini, tedavi yanıtlarını ve sağkalım sonuçlarını tek merkezden bir gerçek yaşam kohortunun analiziyle sunmaktadır.

Gereç ve Yöntem: Ocak 2023 ile Ocak 2024 tarihleri arasında Ankara Etlik Şehir Hastanesi'nde TP53 mutasyonlu AML tanısı alan dokuz hastanın verileri retrospektif gözlemsel bir çalışmayla incelendi. Hastalar, hasta ile ilgili faktörlere bağlı olarak yoğun veya yoğun olmayan indüksiyon rejimleriyle tedavi edildi. Sitogenetik ve moleküler anomaliler kaydedildi ve tedavi yanıtları Avrupa Lösemi Ağı (ELN) 2022 kılavuzuna göre değerlendirildi. Birincil sonlanım noktası genel sağkalım idi.

Bulgular: Tanı anındaki medyan yaş 65 olup, hastaların %55,5'i kadındı. Olguların %66,7'sinde kompleks karyotip gözlendi ve iki hastada çoklu-vuruş TP53 mutasyonları tespit edildi. Yoğun indüksiyon tedavisi (7+3) ile tedavi edilen hastaların %75'inde tam yanıta ulaşılırken, azasitidin-venetoklaks rejimi alan hastaların %60'ında tam veya kısmi yanıt elde edildi. Tanıdan sonraki 12 ay içinde altı hasta, çoğunlukla enfeksiyon nedeniyle hayatını kaybederken, hayatta kalan üç hasta allojeneik hematopoetik kök hücre nakli (AHKHN) yapılan hastalardı. Tüm kohortun ortanca genel sağkalımı 9 ay idi. AHKHN yapılan hastalarda genel sağkalım anlamlı şekilde daha uzundu (*p=0,01*).

Sonuç: TP53 mutasyonlu AML'nin prognozu halen son derece kötü olmaya devam etmektedir ve bu durum hasta sonuçlarını iyileştirmek için yeni tedavi yaklaşımlarının geliştirilmesine acil ihtiyaç duyulduğunu göstermektedir. AHKHN potansiyel bir sağkalım faydası sunsa da, etkili köprüleme tedavileri ve nakil sonrası yönetim, bu yüksek riskli popülasyonda sonuçların iyileştirilmesinde kritiktir.

Anahtar Sözcükler: Akut myeloid lösemi, kök hücre nakli, sağkalım, tedavi, TP53 mutasyonu.

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, defined by the heterogeneous and uncontrolled clonal expansion of myeloid blasts, which suppresses normal hematopoiesis. Despite significant advancements in our understanding of AML pathophysiology and the development of targeted therapies, the prognosis for patients with specific molecular abnormalities remains poor. TP53 mutations have emerged as a critical biomarker associated with high-risk disease, chemoresistance, and inferior survival outcomes (1).

The TP53 gene, often as called the "guardian of the genome," plays a central role in maintaining genomic stability by regulating cell cycle arrest, apoptosis, and DNA repair. Mutations in TP53 are detected in approximately 5–10% of newly diagnosed AML cases and are more prevalent in therapy-related AML, secondary AML, and AML with complex karyotypes. These mutations confer aggressive disease behavior and resistance to conventional cytotoxic chemotherapy and hypomethylating agents, highlighting the need for novel therapeutic strategies tailored to this patient population (1-3).

Managing TP53-mutated AML remains challenging, with limited data guiding clinical decision-making. Existing evidence is primarily derived from small, retrospective cohorts or clinical trials that often exclude patients with this mutation due to their poor prognosis. There is a growing recognition that TP53 mutations represent a distinct biological and clinical entity within AML, necessitating specialized management approaches that integrate molecular, cytogenetic, and clinical risk factors (4).

This study aims to provide a comprehensive overview of TP53-mutated AML through a single-center analysis of real-world data. By exploring the clinical characteristics, treatment paradigms, and preliminary outcomes of patients with this high-risk molecular subtype, our findings aim to enhance understanding and inform future therapeutic approaches.

Material and Method

This is a retrospective, single-center, observational study carried out at Ankara Etlik City Hospital. Our study enrolled 86 patients aged 18 years or older who were diagnosed with AML according to the WHO/ICC 2022 classification (5,6). Of these, 9 patients with pathogenic TP53 mutations who received first-line treatment at our center were analyzed between January 2023 and January 2024. Patients diagnosed with acute promyelocytic leukemia were not included in the study. The primary endpoint of our study was overall survival (OS). Per the principles outlined in the Declaration of Helsinki, the Institutional Review Board of the Ankara Etlik City Hospital reviewed and approved the study protocol (Date: 31-07-2024, Number: AEŞK-BADEK-2024-592). Informed consent for publication was obtained from the patients.

Patients' demographic characteristics, clinical features, comorbidities, and laboratory data were gathered from both manual and electronic medical records. These data included age, sex, date of diagnosis, disease subtype, values of complete blood count (CBC) at diagnosis, accompanying cytogenetic and molecular abnormalities, treatments received and treatment responses, and treatment-related toxicities (if any).

TP53 mutation analysis was conducted via Sanger sequencing for 8 patients and next-generation sequencing (NGS) for 1 patient. Any variants detected within the limitations of the Sanger method were reported (Table I). The presence of a pathogenic TP53 mutation was defined as AML with TP53 mutations that are mutated at variant allele frequency (VAF) of at least 10% (Table I). All cases underwent a comprehensive diagnostic workup that included conventional G-banding analyses, FISH testing (to detect 5q, 7q, 8, 20q deletions, t(8,21), t(15,17), inversion 16, t(9,22), KMT2A, DEK/NUP 214, inversion 3), as well as molecular studies (to detect inversion 16, t(8,21), t(9,22), t(15,17), NPM1, WT1, FLT3, C-KIT, CEBPA).

The induction regimens were classified into two categories: intensive and less intensive. Intensive induction treatments consisted of infusional cytarabine with idarubicin (7+3) and fludarabine with cytarabine, G-CSF, and idarubicin (FLAG-IDA), sometimes in combination with venetoclax (VEN). Less intensive induction regimens consisted of hypomethylating agents (HMA, azacitidine) with or without VEN (VEN-HMA or HMA).

The risk classification of AML and assessment of

treatment response were performed by the 2022 European Leukemia Net (ELN) guideline (7). Complete remission (CR) is defined as bone marrow blasts less than 5%, absence of circulating blasts, absence of extramedullary disease, absolute neutrophil count (ANC) less than 1.0 x 109/L (1000/mL), and platelet count less than 100 x 109/L (100.000/mL). CR with incomplete hematologic recovery (CRi) is defined as meeting all criteria for CR, except for residual neutropenia with an ANC of 1.0 x 109/L (1000/mL) or less, or residual thrombocytopenia with a platelet count of 100 x 109/L (100.000/mL) or less. Partial response is defined as meeting all hematologic criteria for CR, and achieving a reduction in bone marrow blast percentage to between 5% and 25%, with a decrease of at least 50% from pre-treatment levels. Refractory disease is defined as failure to achieve CR, CR with partial hematologic recovery (CRh), or CRi after two courses of intensive induction treatment, or within 180 days of starting less intensive therapy (7).

All data were analyzed by using IBM SPSS Statistics 25.0. Nominal variables were presented as frequency and percentages. Categorical variables were compared using the Pearson's chi-square test or Fisher's exact test, as appropriate. For variables not normally distributed, median with variables range (minimum to maximum) were used. Mann–Whitney U test was used for continuous variables that did show non-normal distribution to test whether there were any differences between the two groups. All tests were two-sided, and $p<0.05$ was considered statistically significant. Survival probabilities were calculated and plotted using the Kaplan-Meier method. Overall survival (OS) was determined by calculating the time between the date of AML diagnosis and the date of death from any cause or the date of the last follow-up (for patients who were still alive). Duration of follow-up were also documented.

Results

Nine patients with TP53-mutated AML followed in our center were included in the study. Table I provides a comprehensive overview of the patients' demographic and clinical profiles, including treatment regimens, therapeutic responses, comorbidities, and detailed follow-up and survival data. Also, demographic and clinical characteristics of the patients were grouped and summarized in Table II.

The median age at diagnosis was 65 years (range 34–78), and 55.5% of cases were female (n=5) (Table II). At least one comorbidity was present in 66.7% of patients (n=6), most commonly hypertension (n=4, 44.4%). Myelodysplastic syndrome-related cytogenetic or bone marrow dysplasia findings were observed in 88.9% of cases (n=8) (except Patient #6). Secondary AML developed in two patients with myeloproliferative neoplasm (Patient #8 and #9), and one patient had therapy-related AML (Patient #5) (Table I). No neoplasia was reported in other members of the families of all patients.

Only one patient (Patient #4) presented with leukocytosis, and while the hemoglobin (Hb) level exceeded 10 g/dL in this case, all patients exhibited anemia. At the time of admission, thrombocytopenia with a platelet (PLT) count below 50,000/µL was observed in five patients (Table I). Median Hb, white blood cell (WBC), PLT counts at diagnosis for both the entire cohort and transplanted and non-transplanted patients were shown in Table II.

All patients were classified as high-risk according to the 2022 ELN risk stratification. TP53 mutations were accompanied by WT1 mutation in five patients, while six patients (66.7%) presented with a complex karyotype (Table I, II). Additionally, multi-hit TP53 mutations were identified in two patients (Patients #3 and #7).

Of the patients included, 55.5% (n=5) were aged 65 years or younger. Four patients received standard 7+3 induction chemotherapy as their first-line treatment, achieving a CR in three cases (Table II). Five patients were treated with an azacitidine-venetoclax (Aza-Ven) regimen; of these, two of them achieved CR (Patient #8 and #9), one of them had a partial response (Patient #1), and the remaining two patients were refractory to this treatment (Patient #4 and #7) (Table II). Progression was observed during follow-up in both patients who initially responded to Aza-Ven (Patients #1 and #8). Among the nine patients, six patients died within the first 12 months following diagnosis, with infection being the leading cause of mortality. Of the three surviving patients, two of them underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) at our center

(Patients #2 and #6), while the remaining patient was referred to another facility for transplantation (Patient #3).

Patient 2 underwent a haploidentical transplant from her nephew while in CR for AML. Also, patient 6 received an allotransplant from a fully compatible donor through the TURKOK (Turkey's National Stem Cell Coordination Center) registry on May 31th, 2024. Patient #3 initially planned a haploidentical transplant from his brother but ultimately chose to proceed with transplantation at another center (Table I).

Table I. Patients Demographics, Comorbidities, Genetic Features, Treatment Responses, and Clinical Outcomes

Pts	Sex	Date of diagnosis	Age at diagnosis	Hematologic parameters at diagnosis	*TP53* pathogenic variants	Accompanying cytogenetic abnormalities	Accompanying molecular abnormalities	Treatments And Treatment Responses	Comorbidities	OS
1	M	May 2023	66	Hb 3.7 g/dl WBC 1320 /µl PLT 11000 /µl	c.406delC (exon5) c.742C>T (exon 7)	complex karyotype 5q,7q, 20q deletion Trisomy 8, DEK/ NUP214 CBFB (16q22) deletion	*WT1 +*	Aza-Ven → PR at the end of the 3rd cycle, disease progression at the end of the 6th cycle	CHD COPD Pulmonary HT BPH	8 mo
2	F	Jan 2024	59	Hb 8.1 g/dl WBC 1380 /µl PLT 121000 /µl	c.821T>A (exon 8)	5q deletion CBFB (16q22) monosomy	*WT1 +*	7+3 → CR Then, 2 cycles of IDAC →CR Then, 5/10 haploidentical transplant from nephew (4th June 2024)	None	NR
3	F	Jan 2024	34	Hb 7.5 g/dl WBC 3900 /µl PLT 24000 /µl	c.814G>A (exon 8)	complex karyotype Trisomy 8 7q, 20q deletion CBFB (16q22) and MYH11 (16p13.1) monosomy ETO (8q21.3) trisomy		7+3 → CR (long-term ICU follow up) Then, one course Aza → CR Then, haploidentical transplant from a 36-year-old brother in an external center	None	NR
4	M	Apr 2023	68	Hb 12.3 g/dl WBC 24540 /µl PLT 95000 /µl	c.797G>T (exon 8)	complex karyotype 5q, 7q deletion inversion 3	*WT1 +*	4 courses of Aza-Ven → refractory disease 1 cycle of Etoposide - ARA-C → refractory 1 course of FLAG-Ven → refractory disease	DM HT HL Arrhythmia	9 mo
5	F	Sept 2023	61	Hb 5.7 g/dl WBC 3570 /µl PLT 42000 /µl	c.427G>A (exon 5)	complex karyotype 5q, 7q deletion inversion 3	*WT1 +*	7+3 --> refractory disease Transplant ineligible patient Then, received 1 cycle of Aza-Ven	Metastatic breast cancer (chemotherapy history)	3 mo
6	F	Dec 2023	60	Hb 7.1 g/dl WBC 2070 /µl PLT 26000 /µl	c.524G>A (exon 5) c.375G>A (exon 4) VAF %40-41	complex karyotype		7+3 → CR Then, 3 cycles of IDAC →CR Then, allotransplantation from a fully compatible TURKOK donor on 31st May 2024	None	NR
7	M	Jan 2023	65	Hb 8.2 g/dl WBC 4180 /µl PLT 33000 /µl	c.797G>A (exon 8)	46, XY [10]		2 courses of Aza-Ven → refractory disease 7+3 → refractory disease FLAG-Ida refractory disease	HT HL CHD (CABG +)	8 mo
8	F	May 2023	78	Hb 8.7 g/dl WBC 890 /µl PLT 76000 /µl	c.517G>A (exon 5)	5q, 7q deletion Trisomy 8 ETO (8q21.3) trisomy CBFB (16q22) deletion	*WT1 +*	Aza-Ven → iCR at first, obvious relapse at the end of the 7th cycle	ET (hydroxyurea +) HT Osteoporosis Asthma Hypothyroidism	12 mo
9	M	Sept 2023	78	Hb 8.3 g/dl WBC 2770 /µl PLT 242000 /µl	c.716A>G (exon 7)	complex karyotype 5q, 20q deletion Monosomy 7	*JAK2 V617F +*	Aza-Ven → CR at the end of the 4th cycle, febrile neutropenia and septic shock developed in the 5th cycle	PV (hydroxyurea +) HT HL DM	6 mo

Apr; april, ARA-C; cytarabine, Aza-Ven; Azacitidine-Venetoclax, BPH; benign prostatic hyperplasia, CR; complete response, CABG; coronary artery bypass graft, CHD; coronary heart disease, COPD; chronic obstructive pulmonary disease, Dec; december, DM; diabetes mellitus, ET; essential thrombocythemia, F; female, FLAG-Ven; fludarabine with cytarabine, G-CSF-Venetoclax, ICU; intensive care unit, Hb; hemoglobin, HL; hyperlipidemia HT; hypertension, IDAC; intermediate-dose cytarabine, iCR; Complete Remission with Incomplete Count Recovery, Jan; january; M; male, mo; months, NR; not reached, OS; overall survival, PLT; platelet, PR; partial response, Pts; patients, PV; polycythemia vera, Sept; september, TURKOK; Turkey's National Stem Cell Coordination Center, VAF; variant allele frequency, WBC; white blood cell, WT-1; wilms tumor gene-1, 7+3; cytarabine with idarubicin

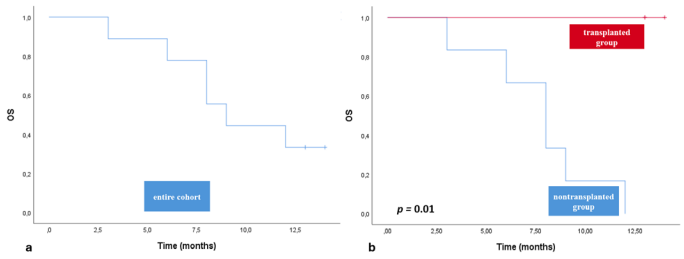
Table II. Demographic Features and Characteristics of the Patients

Characteristics	**Entire Cohort (n=9)**	**Transplanted Group (n=3)**	**Nontransplanted Group (n=6)**	*p*
Age at diagnosis, years Median (Range)	65 (34 – 78)	59 (34 – 60)	67 (61 – 78)	*0.024*
Sex, n (%) Female Male	5 (55.5) 4 (44.4)	3 (100) 0 (0)	2 (33.3) 4 (66.7)	*0.119*
Median Hb count at diagnosis (g/L) (range)	8.1 (3.7 – 12.3)	7.5 (7.1 – 8.1)	8.25 (3.7 – 12.3)	*0.548*
Median WBC count at diagnosis (k/mm³) (range)	2.77 (0.89 – 24.54)	2.07 (1.388 – 3.9)	3.17 (0.89 – 24.54)	*0.905*
Median PLT count at diagnosis (k/mm³) (range)	42 (11 – 242)	26 (24 – 121)	59 (11 – 242)	*0.714*
Co-mutation, n (%) WT1 mut JAK2 V617F	5 (55.5) 1 (11.1)	1 (33.3) 0 (0)	4 (66.7) 1 (16.7)	*0.548*
Complex karyotype, n (%)	6 (66.7)	2 (66.7)	4 (66.7)	*0.762*
First line therapy, n (%) Intensive Less intensive	4 (44.4) 5 (55.6)	3 (100) 0 (0)	1 (16.7) 5 (83.3)	*0.048*
Initial response following intensive therapy, n (%)(n: 4) CR + CRi PR Refractory	3 (75) 0 (0) 1 (25)	3 (100) 0 (0) 0 (0)	0 (0) 0 (0) 1 (16.7)	
Initial response following less intensive therapy, n (%) (n: 5) CR + CRi PR Refractory	2 (40) 1 (20) 2 (40)	0 (0) 0 (0) 0 (0)	2 (33.3) 1 (16.7) 2 (33.3)	
Median follow-up (months) (range)	9 (3 – 14)	13 (13 – 14)	8 (3 – 12)	*0.024*

CR, complete remission; CRi, CR with incomplete hematologic recovery; Hb, hemoglobin; PLT, platelet; PR, partial response; WBC, white blood cell

In May 2024, Patient #6 underwent an allo-HSCT using a fully HLA-matched donor identified through the TURKOK registry. The procedure utilized a myeloablative conditioning regimen consisting of fludarabine and busulfan (Flu-Bu). Graft-versus-host disease (GvHD) prophylaxis was managed with post-transplant cyclophosphamide (post-Cy), tacrolimus, and mycophenolate mofetil, ensuring a balanced approach to minimize GvHD while supporting successful engraftment. Also, Patient 2 underwent a haploidentical transplant from his nephew using myeloablative conditioning regimen with fludarabine-busulfan (Flu-Bu) using post-Cy, tacrolimus and mycophenolate mofetil as graft-versus-host disease (GvHD) prophylaxis o June 4, 2024.

Figure I. Overall survival of the entire cohort in patients with TP53-mutated acute myeloid leukemia (a) Overall survival of the transplanted and non-transplanted arms (b) (OS, overall survival)



Upon comparing TP53-mutated AML patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) with those who did not, it was observed that the median age at diagnosis was significantly younger in the transplanted group (p=0.024). Additionally, a higher proportion of patients in the allotransplanted cohort received intensive induction therapy as their first-line treatment (p=0.048). The median follow-up duration was longer in the transplanted group compared to the non-transplanted group. Other demographic and clinical characteristics were comparable between the two groups (Table II).

The median OS of the entire cohort was 9 months with a total follow-up duration of 14 months. The OS of the entire cohort was presented in Figure 1a. Patients with TP53-mutated AML who underwent allo-HSCT exhibited significantly prolonged OS (p=0.01) (Figure 1b).

Discussion

In our clinic, supported by a robust genetic laboratory and high-quality care infrastructure in

Turkey, we analyzed TP53-mutated AML patients during our inaugural year. Patients were treated with either intensive or less intensive induction regimens based on their age, performance status, comorbidities and patients' preferences. Among the four patients with TP53-mutated AML who received intensive induction therapy, three of them achieved first remission and subsequently underwent allo-HSCT; currently, only those bridged with transplantation have survived (Table I). The remaining five patients received less intensive induction therapy. Although two patients initially responded, their responses were not durable, and the disease subsequently relapsed; the remaining three patients were refractory to initial treatment. Efforts to intensify treatment in patients who did not respond to less intensive regimens with more aggressive therapies were ultimately unsuccessful. These findings emphasize the critical importance of selecting appropriate first-line therapy and employing allo-HSCT in eligible patients who achieve remission.

Myelodysplastic syndromes (MDS) and MDS/AML originate from clonal hematopoiesis driven by somatic mutations, but the presence of a TP53 mutation alone is insufficient to trigger leukemogenesis. The 2022 ELN guideline classifies TP53 mutations as a marker of unfavorable prognosis, correlating with median OS rates of less than two years. Patients with TP53-mutated AML or MDS with excess blasts-2 (MDS-EB-2) demonstrate overlapping biological and clinical characteristics, including aggressive disease progression, high relapse rates, and complex karyotypic abnormalities. Complex or monosomal karyotypes, observed in 80–90% of cases, frequently involve deletions or structural abnormalities in chromosomes 5, 7, and 17. These mutations typically originate in DNA-damage-resistant progenitor cells, which expand in response to cytotoxic therapies. Such mutations confer resistance to standard treatments, further complicating disease management and underscoring the necessity for novel therapeutic approaches tailored to this high-risk population (1,8,9). In our cohort, all but one patient exhibited the genetic abnormalities commonly associated with TP53 mutations, consistent with findings reported in the literature (Table I).

A retrospective study compared post-allo-HSCT outcomes between AML patients with WT1 and TP53 mutations, two groups with distinct genetic profiles. None had concurrent WT1 mutation and TP53 mutation. WT-1 mutated AML patients were significantly younger and less likely to have therapy-related disease and complex, or monosomal karyotypes compared to TP53-mutated AML. Despite these more favorable features, WT-1 mutated AML patients had similar 2-year OS (38.7% vs. 39.4%), relapse incidence, and non-relapse mortality compared to TP53-mutated AML patients. The findings suggest that WT1 mutations confer high-risk characteristics akin to TP53 mutations (10). In our cohort of nine patients with TP53-mutated AML, five also harbored concurrent WT1 mutations. Investigating the potential impact of this co-occurrence on treatment responses and survival outcomes is essential. Among these five patients with WT1 mutations, all exhibited a coexisting 5q deletion. Treatment outcomes varied, with two patients responding to Aza-Ven, one of them achieving a response with the 7+3 regimen, and the remaining two patients showing refractory disease despite therapy. Only one patient underwent allo-HSCT. By day +100 post-transplantation, her disease was in remission (Patient #2).

TP53 mutations are highly heterogeneous, the complex landscape in terms of co-mutation and gene expression profiles makes it difficult to develop effective treatment strategies targeting all TP53 mutated cancer clones, and the optimal treatment strategy in this subgroup of the disease is unknown (1, 4). Therefore, enrolling these patients in clinical trials should be strongly encouraged if available. This approach would allow access to innovative treatments or new drug combinations with the potential to improve outcomes, as the current median OS remains limited to about 10 months despite available therapies (1,3,11). There is no ongoing clinical trial on the treatment of TP53-mutated AML in Turkey. Also, unfortunately, in our cohort, the median OS was 9 months.

In elderly patients with AML, poor-risk cytogenetic abnormalities, including abnormalities of chromosomes 5 or 7 and the presence of complex or monosomal karyotypes, are more prevalent and are strongly associated with inadequate therapeutic responses, increased relapse rates, and dismal OS. The TP53

gene plays a critical role in maintaining genomic stability by activating DNA repair and inducing cell-cycle arrest. TP53 mutations, often linked to poor-risk cytogenetics, represent a major resistance mechanism to DNA-damaging chemotherapy, further contributing to poor outcomes (1,8,12).

The molecular subgroup analysis of the VIALE-A trial revealed that azacitidine combined with venetoclax achieved a significantly higher composite complete remission (CRc) rate compared to azacitidine alone in older patients with TP53-mutated AML. Specifically, the CRc rate was 55.3% (95% CI, 38.3–71.4) with the combination therapy, compared to 0% with azacitidine monotherapy (P<0.001) (12). While the combination therapy demonstrated an improvement in remission rates compared to AZA monotherapy, it did not significantly enhance the duration of response or OS, particularly in patients with low-risk cytogenetics and TP53 mutations. These findings highlight the ongoing challenges in improving outcomes for this high-risk patient population, despite advancements in combination therapies (13). If we look from another perspective, in our study, the response rates to the azacitidine and venetoclax combination in TP53-mutated AML patients were lower compared to those reported in the VIALE-A trial. This discrepancy may be attributed to our limited sample size and the stringent inclusion criteria of clinical trials, which often do not fully account for factors such as patients' comorbid conditions, concomitant medications, and potential drug interactions, thereby not always reflecting real-world scenarios. Additionally, ethnic and genetic factors can influence treatment responses. Therefore, our findings highlight the challenges faced in treating TP53-mutated AML patients in real-life settings and emphasize the need for larger, multicenter studies to better understand and address these issues.

On the other hand, a retrospective, single-center study analyzed 88 patients with TP53-mutated AML focusing on clinical and treatment outcomes. The median age was 67 years, with a male predominance, and most patients exhibited a high VAF with ASXL1 as the most frequent co-mutation, followed by KRAS and NRAS. Among the cohort, 17.1% had therapy-related AML, and 45.5% presented with secondary AML. Intensive therapies demonstrated superior outcomes, with higher CR rates (51.6% vs. 25.7%) and improved 2-year OS (13% vs. 3%) compared to ess intensive regimens. Among intensive regimens, 7+3 showed better OS than CPX-351. Patients who underwent allogeneic transplantation had significantly better survival (2-year OS: 21% vs. 4%). The findings suggest intensive treatment and transplantation confer a survival benefit in TP53-mutated AML, though patient fitness may influence outcomes (14). A multicenter real-world study evaluated treatment outcomes of patients with TP53-mutated AML. The median OS was 8.5 months, and no significant differences observed among patients receiving intensive, less-intensive, or venetoclax-based induction therapies. Notably, only 16% of patients proceeded to allo-HSCT, which was the sole factor independently associated with improved survival in multivariate analysis. These findings highlight the critical role of allo-HSCT in enhancing survival outcomes for patients with TP53-mutated AML, despite the challenges in making this treatment accessible to all eligible patients (15). Despite the persistently poor survival rates in this highly adverse AML subgroup, all patients in our cohort who survived approximately one year of follow-up had undergone allo-HSCT, highlighting its potential as a critical therapeutic intervention for these patients.

The limitations of our study include its retrospective nature, the small cohort size, and the fact that TP53 mutations were assessed using NGS method in only one patient, while Sanger sequencing was employed for the remaining cases. Therefore, we could not evaluate some important co-mutations like ASXL1, TET2, DNMT3a, etc. except for 1 patient, and could not measure VAF. In AML, TP53 mutations are considered pathogenic when the VAF is at least 10% (7). The TP53 VAF burden has prognostic significance and it is inversely correlated with OS. TP53 VAF clearance is a biomarker for the assessment of response to treatment and may provide valuable information for follow-up in patients undergoing allo-HSCT (1). We are currently using the NGS method in our center and will report more comprehensive data in future studies.

Conclusion

In conclusion, patients with TP53-mutated MDS/AML represent a distinct and highly aggressive

disease subgroup with dismal outcomes and limited therapeutic success to date. Extensive recent efforts to evaluate novel therapies for this challenging molecular subgroup have yet to yield success in pivotal trials. Clinicians often prefer less intensive strategies for this patient group due to the historically poor outcomes with intensive chemotherapy. To our knowledge, this is the first report from Turkey specifically addressing patients with TP53-mutated AML. Regardless of whether intensive or less intensive induction is used, facilitating allo-HSCT in eligible patients and optimizing post-transplant care could enhance treatment efficacy and improve survival outcomes. Future therapeutic strategies should focus on developing more effective agents, further investigating the role of transplantation, and determining whether specific patient subsets (e.g., those with a single TP53 mutation and low variant allele frequency) may benefit from existing treatments. Additionally, prioritizing prolonged maintenance therapy may be essential in improving outcomes in this high-risk population.

References

1. Santini V, Stahl M, Sallman DA. TP53 Mutations in Acute Leukemias and Myelodysplastic Syndromes: Insights and Treatment Updates. Am Soc Clin Oncol Educ Book 2024;44(3):e432650.

2. Brown CJ, Lain S, Verma CS, Fersht AR, Lane DP. Awakening guardian angels: drugging the p53 pathway. Nat Rev Cancer 2009;9(12):862-873.

3. Wong TN, Ramsingh G, Young AL et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature 2015;518(7540):552-555.

4. Rücker FG, Schlenk RF, Bullinger L et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood 2012;119(9):2114-2121.

5. Arber DA, Orazi A, Hasserjian RP et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood 2022;140(11):1200-1228.

6. Khoury JD, Solary E, Abla O et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms. Leukemia 2022;36(7):1703-1719.

7. Döhner H, Wei AH, Appelbaum FR et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood 2022;140(12):1345-1377.

8. Döhner H, Dolnik A, Tang L et al. Cytogenetics and gene mutations influence survival in older patients with acute myeloid leukemia treated with azacitidine or conventional care. Leukemia 2018;32(12):2546-2557.

9. Shin DY. TP53 Mutation in Acute Myeloid Leukemia: An Old Foe Revisited. Cancers (Basel) 2023;15(19):4816.

10. Gannamani V, Baranwal A, Langer KJ et al. Impact of Wilms Tumor (WT1) Mutation on Relapse and Overall Survival in Acute Myeloid Leukemia Patients Following Allogenic Stem Cell Transplantation. Transplantation and Cellular Therapy, Official Publication of the American Society for Transplantation and Cellular Therapy 2024;30(2):112 - 113.

11. Bowen D, Groves MJ, Burnett AK et al. TP53 gene mutation is frequent in patients with acute myeloid leukemia and complex karyotype, and is associated with very poor prognosis. Leukemia 2009;23(1):203-206.

12. DiNardo CD, Jonas BA, Pullarkat V et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med 2020;383(7):617-629.

13. Pollyea DA, Pratz KW, Wei AH et al. Outcomes in Patients with Poor-Risk Cytogenetics with or without TP53 Mutations Treated with Venetoclax and Azacitidine. Clin Cancer Res 2022;28(24):5272-5279.

14. Sumransub N, Steinwand GK, Lee Y et al. TP53-Mutated Acute Myeloid Leukemia Patients Treated with Intensive Therapies Have Superior Outcomes: A Single Institution, Retrospective Study. Blood 2023;142(Supplement 1):1526.

15. Badar T, Atallah E, Shallis RM et al. Outcomes of TP53-mutated AML with evolving frontline therapies: Impact of allogeneic stem cell transplantation on survival. Am J Hematol 2022;97(7):232-235.