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Retrospective Analysis of Acute Promyelocytic Leukemia; A Single-center Experience

Akut Promiyelositik Löseminin Retrospektif Analizi; Tek Merkez Deneyimi

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Abstract

Objective: Acute myeloid leukemia (AML) is an uncommon illness in and of itself. Approximately 10% of AML cases have acute promyelocytic leukemia (APL), a particularly severe form of the disease. There is a dearth of information on Turkish patients with APL. Thus, our goal was to determine the clinical, laboratory, and survival characteristics of patients with APL diagnosed within the previous 5 years at our facility.

Methods: A retrospective analysis was performed on 15 individuals who received an APL diagnosis between 2017 and 2022. IBM SPSS Statistics 25.0 was used to conduct the statistical analysis. Kaplan-Meier analysis was used for survival analysis.

Results: With a median age of 61 years, the mean age was 56.5±15.7 years. The ratio of men to women was 1.5:1. Hypergranular variation was seen in 73.3% of our cases. Based on the risk classification, 93.3% of cases were low-risk diseases. In 40% of patients, bleeding occurred, and in 13.3%, thrombosis occurred. In total, 5 patients (33.3%) passed away and 10 patients (66.6%) survived. There was a 20% early death rate. There was a 100% rate of total remission. The medians for overall survival (OS) and event-free survival were not met; instead, they were 34.1 and 37 months, respectively. The OS rate after 1 year was 66.7%.

Conclusion: The majority of patients in our group were elderly females with low-risk illnesses. According to our research, the biggest cause of treatment failure for this normally treatable type of leukemia is early mortality.

Keywords: Acute promyelocytic leukemia, early mortality, highly curable

Öz

Amaç: Akut miyeloid lösemi (AML) kendi başına nadir görülen bir hastalıktır. Akut promyelositik lösemi (APL), AML'nin özellikle agresif bir alt tipidir ve AML olgularının yaklaşık %10'unu oluşturur. Türkiye'den APL hastalarına ilişkin veriler sınırlıdır. Bu nedenle, merkezimizde son 5 yılda tanı konulan APL hastalarının klinik, laboratuvar özelliklerini ve sağkalım sonuçlarını belirlemeyi amaçladık.

Yöntem: 2017-2022 yılları arasında APL tanısı alan 15 hasta retrospektif olarak incelendi. İstatistiksel analiz, IBM SPSS Statistics 25.0 kullanılarak yapıldı. Sağkalım analizi, Kaplan-Meier analizi kullanılarak yapıldı.

Bulgular: Yaş ortalaması 56,5±15,7 olup, medyan 61'dir. Kadın-erkek oranı 1,5:1 idi. Hastalarımızın çoğunda (%73,3) hipergranüler varyant mevcuttu. Risk sınıflandırması, düşük riskli hastalığın baskın olduğunu (%93,3) ortaya koydu. Hastaların sırasıyla %40 ve %13,3'ünde kanama ve tromboz meydana geldi. Toplamda 10 (%66,6) hasta hayatta kaldı ve 5 hasta (%33,3) öldü. Erken ölüm oranı %20 idi. Tam remisyon oranı %100 idi. Ortanca olaysız sağkalım ve genel sağkalıma (OS) ulaşılamazken, ortanca değerleri sırasıyla 34,1 ve 37 aydı. Bir yıllık OS oranı %66,7 idi.

Sonuç: Kohortumuzun çoğu ileri yaş ve düşük riskli hastalığı olan kadın hastalardan oluşuyordu. Çalışmamız, kür sağlanabilen bu lösemi formu için tedavi başarısızlığındaki en büyük faktörün erken mortalite olduğunu gösterdi.

Anahtar Kelimeler: Akut promiyelositik lösemi, erken ölüm, yüksek oranda tedavi edilebilir

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Introduction

A malignant condition of the bone marrow known as acute myeloid leukemia (AML) is characterized by a maturational arrest in blood cell progenitors, which prevents normal hematopoiesis. Approximately 10% of AML cases are acute promyelocytic leukemia (APL), a subtype of AML with an aggressive clinical course that is different from other forms of AML. APL was once categorized as AML-M3 in the French-American-British classification system. Presently, it is classified as t(15;17) (q24.1;q21.2); PML-RARA by the World Health Organization (WHO)[1,2]. Two morphological variations of APL have been found; the hypergranular variety is the most prevalent. APL's more aggressive microgranular type of APL, which accounts for 25% of cases, is linked to an increased risk of hemorrhagic mortality at an early stage[3]. Upon diagnosis, individuals with APL were separated into two groups solely on the basis of their white blood cell (WBC) count (≤10,000 or >10,000/μL)[4]. APL cells typically exhibit some immunophenotypic characteristics in common with their typical promyelocytic counterparts. The hypergranular variations express bright cytoplasmic myeloperoxidase, CD13, and CD33; they have a significant side scatter; they are partially, weakly, or negatively expressed for CD34; and they either do not express CD11b or express it very poorly. Compared with typical promyelocyte, APL cells display low CD15 levels and unusually moderate CD117 levels. Similar in phenotype, the microgranular variety of APL frequently co-expresses CD2 and occasionally expresses CD34, in addition to having comparatively bright myeloperoxidase expression. In addition, some cases may have CD56, which has been linked to a worse prognosis[4]. HLA-DR negative, CD33 positive, CD13 positive, CD117 moderate, occasionally CD2 positive, CD56 positive, CD11b negative, CD15 weak or negative, and CD34 negative/partially or weakly positive are the phenotypes associated with APL, with the aforementioned caveats[5]. Patients with APL present with non-specific symptoms such as weakness, infections, and hemorrhagic signs, similar to any other acute leukemia subtype. Because of its potentially lethal coagulopathy, APL has a unique shape and clinical presentation that may be linked to a high early fatality rate. The intricate process of coagulopathy involves both primary hyperfibrinolysis and disseminated intravascular coagulation (DIC), which can occur either before or immediately after cytotoxic treatment is starte[6].

Data on APL patients from Turkey are limited. The medical records of individuals diagnosed within the last 5 years at our center were examined. Demographic information, anatomical characteristics, risk assessment, clinical characteristics like bleeding and thrombosis, results from laboratory and flow cytometry testing, mutations in FLT3 (fms-like tyrosine kinase 3), treatment, response rate, overall survival (OS), event-free survival (EFS), and causes of death in patients with APL are all presented here.

Materials and Methods

The study was approved by the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (date: 15/04/2022, no: 2022/04-22). This study was conducted in the Hematology Department of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital. The study included 15 patients with APL who were over the age of 18, screened between 2017 and 2022, and had sufficient laboratory data, flow cytometry, bone marrow aspirates, and the presence of t(15;17)/PML-RARA by fluorescence *in situ* hybridization (FISH) studies and/or conventional cytogenetics. Excluded from consideration were cases that tested negative for t(15;17)/PML-RARA or for which cytogenetics/FISH results were not available. Demographic data, morphologic features, risk stratification, clinical features such as bleeding and thrombosis, laboratory and flow cytometry findings, FLT3 mutation, treatment, response rate, OS, EFS, and causes of death were recorded. Early mortality was defined as death from any cause within the first month after diagnosis. OS was computed from the diagnostic date to the day of any cause of death. The amount of time a patient remains free of illness or complications associated with the disease (EFS) following the conclusion of primary treatment for APL.

Response criteria: Morphologic complete remission (CR) was defined as the presence of normal bone marrow cellularity without leukemic promyelocyte, with an absolute neutrophil count (ANC) and platelet count >$1x10^9$/L and >$100x10^9$/L that became independent of red blood cell transfusions. Molecular CR was defined as negativity in RT-PCR analysis for the *PML-RARA* hybrid gene.

Statistical Analysis

Statistical analysis was performed using the program IBM SPSS (Statistical Package for the Social Sciences) Statistics 25.0. Data are expressed as mean ± standard deviation or median (min-max) for continuous variables and as number n (%) for categorical variables. Survival analysis was performed using Kaplan-Meier analysis.

Results

Demographics: The average age was 61 years, and the mean age was 56.5±15.7 years (range 29-83 years). The female-to-male ratio was 1.5:1. Nine (60%) of them were female and six (40%) were male.

Risk stratification: According to risk stratification, 14 (93.3%) patients belonged to the low-risk group and 1 (6.7%) to the high-risk group.

Morphological characteristics: Judging by morphology, 11 (73.3%) patients had hypergranular variants, whereas 4 (26.7%) patients had microgranular variants.

Clinical features: Bleeding occurred in 6/15 (40%) patients. Two/15 (13.3%) patients died because of early hemorrhagic complications with DIC. Thrombosis was seen in 2/15 (13.3%) patients (1 patient had pulmonary embolism and the other had multiple thromboses in coronary and cerebral vessels).

Laboratory findings: Mean hemoglobin was 8.4±1.7 (range 6.2-11.9) g/dL with a mean hematocrit of 23.3±4.9% (range 17.6-33.5). WBC count was 3.07±3.66 x10^9/L (range 0.3-13.9); ANC was 1.12±3.05x10^9/L (range 0.05-11.7), lymphocytes 0.69±0.54x10^9/L (range 0.1-2), monocytes 1.26±1.92 x10^9/L (range 0-6.7), and platelets 52±42.79x10^9/L (range 9-162). The mean value of activated partial thromboplastin time was 25.4±4.6 seconds (range 20.1-37.9); prothrombin time was 14.7±1.9 seconds (range 11.5-17.6); international normalized ratio was 1.2±0.2 (range 0.93-1.56); D-dimer was 14096.7±8110.1 µg/L (range 5000-35000); and fibrinogen was 183.4±99.4 (range 66-369) mg/dL.

Flow cytometry: CD13, CD33, CD45, and CD117 expressions were found to be positive in all patients. CD64, CD34, and CD2 were positive in 12, 4, and 3 patients, respectively. HLA-DR, CD14, CD16, and CD19 were not detected in any sample. CD34-positive samples were microgranular variants.

FLT3 mutation: The FLT3 mutation status was known in eight patients. FLT3-ITD (internal tandem duplication) mutation was found in two patients and FLT3-TKD (tyrosine kinase domain) mutation was found in three patients. No FLT 3 mutation was observed in 3 of 8 patients. One of two (50%) patients who had FLT3-ITD and 1 of 3 (33.3%) patients who had FLT3-TKD mutations died.

Treatment: Three patients (20%) died within 2 days after diagnosis. Five (33.3%), one (6.6%), and six (40%) patients were treated with all-trans retinoic acid + arsenic trioxide (ATRA+ATO), ATRA + idarubicin, and 7+3 regimens + ATRA, respectively.

Response rate: All 12 patients achieved morphologic and molecular CR after the induction regimen. The CR rate was 100%.

Survival: Median EFS and OS were not reached. The mean EFS was 34.1 months (21.2-47.1). The mean OS was 37 months (24.2-49.9). In post-remission follow-up, non-APL AML was observed in 1 patient. The 1-year survival rate was 66.7%. OS and EFS are shown in Figure 1 and 2, respectively. The clinical and laboratory features of all patients are shown in Table 1.

Death: A total of 10 (66.6%) patients survived and 5 patients (33.3%) died. Four of the five patients who died were female. The mean age was 65 years (range, 49-83 years). The hypergranular variant occurred in two (40%) patients, whereas three (60%) patients had the microgranular variant. One patient had FLT3-ITD and one patient had FLT3-TKD mutations. Three patients died within 2 days of diagnosis, and the early mortality rate was 20%. Two of them died of early hemorrhagic complications with DIC and one of them died of to thrombotic complications. One of two patients who achieved CR died on day 36 because of sudden cardiac arrest attributable to ATO cardiotoxicity, and the other died on day 40 because of cytokine release syndrome. The characteristics of the deceased patients are shown in Table 2.

Table 1. Clinical and laboratory features of all patients

	All patients (n=15)
Age, year	56.5±15.7
Gender	
-Male, n (%)	6 (40)
-Female, n (%)	9 (60)
Risk rating	
-High, n (%)	1 (6.7)
-Low, n (%)	14 (93.3)
Morphological variants	
Hypergranular, n (%)	11 (73.3)
Microgranular, n (%)	4 (26.7)
Clinical features	
Bleeding, n (%)	6 (40)
Thrombosis, n (%)	2 (13.3)

Table 1. Continued

	All patients (n=15)
Blood tests on admission	
WBC, (/μL)×10^9	3.07±3.66 (0.3-13.9)
Neutrophils, (/μL)×10^9	1.12±3.05 (0.05-11.7)
Lymphocytes, (/μL)×10^9	0.69±0.54 (0.1-2)
Monocytes, (/μL)×10^9	1.26±1.92 (0-6.7)
Hemoglobin, g/dL	8.4±1.7 (6.2-11.9)
Hematocrit (%)	23.3±4.9 (17.6-33.5)
Platelets (/μL)×10^9	52±42.79 (9-162)
aPTT (sec)	25.4±4.6 (20.1-37.9)
PT (sec)	14.7±1.9 (11.5-17.6)
INR	1.2±0.2 (0.93-1.56)
D-dimer (μg/L)	14096.7±8110.1 (5000-35000)
Fibrinogen (mg/dL)	183.4±99.4 (66-369)
Flow cytometry	
CD2, n (%)	3 (20)
CD13, n (%)	15 (100)
CD14, n (%)	0 (0)
CD16, n (%)	0 (0)
CD19, n (%)	0 (0)
CD33, n (%)	15 (100)
CD34, n (%)	4 (26.7)
CD45, n (%)	15 (100)
CD64, n (%)	12 (80)
CD117, n (%)	15 (100)
HLA-DR, n (%)	0 (0)
FLT 3 mutation	
-FLT3 ITD n (%)	2 (13.3)
-FLT3 TKD n (%)	3 (20)
-None n (%)	3 (20)
-N/A n (%)	7 (46.7)
Treatment (remission-induction)	
-ATRA + ATO n (%)	5 (33.3)
-ATRA + idarubicin n (%)	1 (6.6)
-7+3 regimen + ATRA n (%)	6 (40)
-Any treatment n (%)	3 (20)
(Death within 2 days of diagnosis)	

Data are shown as number of means ± SD (minimum-maximum). WBC: White blood cells, aPTT: Activated partial thromboplastin time, PT: Prothrombin time, INR: International normalized ratio, ATRA: All-trans retinoic acid, ATO: Arsenic trioxide, FLT3: Fms-like tyrosine kinase 3, TKD: Tyrosine kinase domain, ITD: Internal tandem duplication, N/A: Not assessed, SD: Standard deviation

Discussion

AML is a rare disease in and of itself. Approximately 10% of adult AML cases are APL instances. According to the WHO classification system, PML-RARA is categorized as APL with t(15;17) (q24.1;q21.1); PML-RARA. With a poor median OS of 1 month, APL is the most aggressive subtype of AML in the absence of therapy. It is anticipated that a large number of patients with APL will pass away before seeing a hematologist[7-9]. Data on APL patients from Turkey are limited. We have examined the information from 15 APL patients who were previously diagnosed at our hospital. The age distribution of individuals with APL differs from that of those with other types of AML. The illness is usually diagnosed in patients between the ages of 20 and 50, and after 60, it becomes less common[10]. The median age is between 33 and 40 years, according to large research[11,12]. However, in this study, the median age was 61 years, which is high compared with previous results for APL.

The incidence did not vary by gender[13]. A predominance of female gender was observed in this study, which was also found in a large cohort of 1400 patients from the United States[14]. Similarly, in Malaysian and Pakistani patients with APL, the disease was prominent in the female gender[15,16].

Patients with APL were classified into two groups according to their WBC count at diagnosis (low risk ≤10,000 or high risk >10,000/μL)[4]. Risk stratification revealed that low-risk disease was prevalent in our center. In this study, most patients had the hypergranular variant (n=11, 73.3%), whereas 26.6% (n=4) patients had the microgranular variant. Our study showed similar results to previous studies from Spain and Italy, which revealed 28%, 29%, and 20% microgranular variants, respectively[17-19].

The mechanism underlying the coagulopathy is complex and includes both primary hyperfibrinolysis and DIC, which can occur in the absence of chemotherapy or soon after the initiation of cytotoxic chemotherapy. This complication is a medical emergency because, if left untreated, it can lead to pulmonary or cerebral hemorrhage in up to 40% of patients and early hemorrhagic death in 10 to 20%[6,20]. Bleeding was observed in 40% of our patients. 13.3% of patients died of of early hemorrhagic complications with DIC. Our results were similar to previous findings. In previous studies, thrombotic complications of APL were reported with a frequency of 2-10%[21,22]. In this study, thrombotic complications were observed in 13.5% of patients, which was slightly higher than that reported in the literature.

Table 2. Characteristic features of the deceased patients

	Age	Gender	Morphologically variants	FLT3 mutation	Bleeding or thrombosis	Early death	Death after treatment	Causes of death
Patient 1	65	Female	Hypergranular	FLT3 TKD	Bleeding	Yes	No	Early hemorrhagic complications (DIC)
Patient 2	83	Female	Microgranular	N/A	Bleeding	Yes	No	Early hemorrhagic complications (DIC)
Patient 3	49	Male	Microgranular	None	Thrombosis	Yes	No	Multiple thromboses in coronary and cerebral vessels
Patient 4	67	Female	Microgranular	FLT3 ITD	Bleeding	No	Yes (on day 40)	Cytokine release syndrome
Patient 5	61	Female	Hypergranular	N/A	None	No	Yes (on day 36)	Sudden cardiac arrest (ATO induced cardiotoxicity?)

FLT3: Fms-like tyrosine kinase 3, TKD: Tyrosine kinase domain, ITD: Internal tandem duplication, DIC: Disseminated intravascular coagulation, ATO: Arsenic trioxide, N/A: Not assessed

Although FLT3-ITD is associated with higher WBC count and lower fibrinogen levels, there are limited data showing an association between the FLT3-ITD mutation and decreased OS. On the other hand, a higher FLT3-TKD mutation burden was associated with lower OS and EFS. In conclusion, the clinical significance of FLT3 mutations in patients with APL remains controversial, suggesting that further studies are needed to clarify the clinical significance of this mutation. Conversely, FLT3-TKD mutation has not been associated with the hematologic features of APL, and studies have shown no correlation between FLT3-TKD mutation and disease outcome[23-26]. FLT3 inhibitors are not recommended for FLT3-positive APL[27]. In this study, FLT3 mutation status was known in eight patients. FLT3- ITD and FLT3-TKD mutations were found in two and three patients, respectively. FLT3 inhibitors were not administered for FLT3-positivity. CR was observed in all patients who received standard therapy for APL. Relapse was not observed in this group. One of two (50%) patients who had FLT3-ITD and 1 of 3 (33.3%) patients who had FLT3-TKD mutations died. Further studies with a larger number of patients are needed to confirm the abovementioned findings.

APL represents a medical emergency with a high early mortality rate. This is evidenced by the fact that the early mortality rate in patients participating in clinical trials is less than 10%[28-30], whereas the early mortality rate in the general population is still more than 15%[31-33]. On the other hand, data from the surveillance, epidemiology, and end results registry revealed an average 30-day mortality rate of 20% between 1977 and 2007[31]. The addition of ATRA to the treatment of this subtype improved survival outcomes for patients with APL. The ability of ATRA to induce terminal differentiation of leukemic promyelocyte can improve coagulopathy, which is the major cause of mortality. Treatment should be initiated immediately when the diagnosis is suspected based on morphology and before confirmation of definitive diagnosis by cytogenetic or immunological criteria.

Similarly, we found an early mortality rate of 20%, and the main cause of mortality was considered to be coagulopathy due to late consultation with an experienced hematologist. APL is the most curable subtype of AML[9]. In this study, the high molecular CR rate was found to be independent of remission induction therapy for APL. In real-world data, OS reached approximately 92% when ATRA plus ATO was used as the first-line treatment. However, in previous studies, OS was reported between 54.6% and 68%[17,31,34-36]. Likewise, we discovered that the OS rate at 1 year was 66.7%. The median EFS and OS did not meet expectations, although they were 34.1 and 37 months, respectively.

Study Limitations

The limitation of our study could be elaborated as a single-center retrospective study that was conducted with a small number of patients.

Conclusion

In conclusion, for this usually treatable form of leukemia, early mortality is now the main cause of treatment failure. The bulk of the patients in our group were elderly females with low-risk illnesses. It is crucial to keep in mind that even in situations where clinical studies indicate low odds of early death, early mortality may actually be greater.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (date: 15/04/2022, no: 2022/04-22). This study was conducted in the Hematology Department of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: H.B., Design: H.B., Data Collection or Processing: H.B., A.T., Analysis or Interpretation: H.B., Literature Search: H.B., A.T., Writing: H.B., A.T.

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

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