Real-life outcomes of unselected acute promyelocytic leukemia patients: a single-center 14-year experience

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Background. After the inclusion of all-trans retinoic acid (ATRA) into the treatment of Acute Promyelocytic leukemia (APL), a notable improvement concerning the survival rates of patients with APL has been observed. However, the population-based studies demonstrated that there was no marked improvement in the survival of patients after the 2000s. We aim to describe the clinical response and prognosis of adult patients diagnosed with APL and examine the change in these outcomes by the time period of diagnosis.

Methods. We retrospectively reviewed thirty-six unselected APL patients who were diagnosed between September 2003 and February 2016.

Results. The probability of survival at two years was 58%, while disease-free survival (DFS) was 87%. The overall early death (ED) rate was 33% and remain stable over time [42% in 2003–2009 vs. 24% in 2010–2016 ($p=.20$)]. In addition, the 2-year overall survival (OS) rates were 47% in 2003–2009 and 70% in 2010–2016 ($p=.29$), and no differences were noted. Univariate analyses showed possible predictors of poor OS were defined as leukocytosis ($\geq 10 \times 10^9/L$), high Sanz score, hemorrhage, infection, disseminated intravascular coagulopathy (DIC) at presentation and microgranular morphologic subtype.

Conclusions. This study shows that long-term survival remains low in APL patients, particularly related to a high ED rate. Initiatives to reduce ED are exceedingly substantial for improving the survival in APL.

Key words: acute promyelocytic leukemia, early death, overall survival, real-life outcomes, predictors.

INTRODUCTION

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia, which is characterized by distinct morphologic and cytogenetic aberrations and a potentially life-threatening coagulopathy. APL is defined as balanced reciprocal translocation $t(15; 17)$ which is present in more than 98% of cases, resulting in the fusion of PML (promyelocytic leukemia) and RAR α (retinoic acid receptor- α) genes that lead to the production of the oncoprotein PML-RAR α [1]. Patients mostly present with peripheral cytopenias, including low or normal total white blood cell count (WBC).

APL is a rare disease (600–800 cases/year in the USA) that accounts for approximately 5% of all AML patients [2]. The frequency of APL seems to be higher in some countries of Latin America and some European populations [3, 4]. For many years, APL had a poor prognosis with a rate of early death (ED) due to hemorrhages from disseminated intravascular coagulation (DIC), hypercoagulability, fibrinolysis, proteolysis and thrombocytopenia,

infections and multi-organ failure. In the 1970s, anthracycline-based therapies produced complete remission in 65–80% and long-term survival in 15–30% of patients with APL [5, 6]. After the addition of all-trans retinoic acid (ATRA) to induction therapy, notable improvement has been seen in the survival of APL [7].

Large, multicenter clinical trials have reported the rate of ED between 5 and 10% [8, 9]. 5-year disease-free survival (DFS) and overall survival (OS) rates above 80%. However, many patients (up to 30%) excluded from these trials because of high age, poor performance status (PS), abnormal hepatic or kidney function, or other comorbidities; therefore, trials may underestimate the actual mortality rates associated with APL [10, 11]. Also, some trials have excluded patients from analyses if they die before receiving treatment [6]. On the other hand, in population-based analyses and single-center experiences from different countries, the rate of induction mortality rate is up to 61.5%, which is higher than expected [11–14]. Especially population-based reports from the developed countries emphasize

neither ED nor OS improved in the past two decades despite modern therapy methods [15–17]. Nevertheless, APL remains associated with a high incidence of ED.

This study intended to investigate the clinical response and prognosis of newly diagnosed APL patients in our real-life experience. We also sought to examine the change in these data with the time of diagnosis.

MATERIALS AND METHODS

Study population

This retrospective study conducted at Hacettepe University Hospital. The Ethics Committee approved the design and procedures of the study (Protocol ID: 567) in agreement with the principles of the Declaration of Helsinki and ethical standards for human experimentation. Written informed consent was taken from all participants. Thirty-six cases of newly diagnosed APL treated at Hacettepe University Hospital from September 2003 to February 2016 were included in this study.

Diagnosis

APL diagnosis established based on WHO criteria and was carried out by evaluation of hemogram, peripheral blood smear, marrow aspirate with immune phenotyping, cytogenetics, and reverse-transcriptase polymerase chain reaction (RT-PCR) for promyelocytic leukemia/retinoic acid receptor alpha (PML/RAR α) [1]. Leukemic cells were analyzed by flow cytometry, and the diagnosis was validated by the presence of t (15; 17) with fluorescence in situ hybridization (FISH) analysis.

Treatment

Induction therapy consisted of oral ATRA (45 mg/m²/day) divided into two daily doses plus idarubicin (12 mg/m²/day) given as an intravenous bolus on days 2, 4, 6 and 8 (AIDA regimen). Treatment with ATRA was started as soon as a diagnosis of APL was made by morphologic criteria and maintained until complete hematologic remission or for a maximum of 90 days. Consolidation and maintenance treatment was also given according to the AIDA regimen [18].

Supportive therapy was applied to patients during the diagnosis and treatment period. Treatment with platelets, fresh frozen plasma, or cryoprecipitate

transfusion was administered when bleeding occurred. Patients received fresh frozen plasma in case of any PT/aPTT/TT derangement and to keep fibrinogen >100 mg/dL. Prophylactic platelet transfusion strategy was available when the platelet count was less than 50×10^9 /L. Packed red cell transfusions were recommended to maintain blood hemoglobin greater than 8 g/dL. Prophylaxis for differentiation syndrome (DS) was not given. At the first signs of suspected DS, patients were given 10 mg dexamethasone every 12 hours. ATRA was interrupted only in case of progression to severe DS.

Study outcomes

All clinical and follow-up data were collected retrospectively by reviewing the charts of patients. Risk stratification at presentation based on the Sanz score was performed [19]. Performance status was measured according to the Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO) scale and grouped as (0–1, ≥ 2).

Complete remission (CR) was defined as less than 5% of abnormal promyelocytes in bone marrow aspirate, along with neutrophil count $> 1 \times 10^9$ /L, platelet count $> 100 \times 10^9$ /L in peripheral blood. ED was defined as death occurring during induction therapy. OS was defined as the time from the day of registration until death, last follow-up or censoring of the data on the patients. DFS was defined as the time from CR to relapse, death from any cause, last follow-up, or censoring of the data on the patients. We examined the data on patients treated at our institution during approximately the same time period that were predetermined according to the year of diagnosis: 2003–2009 and 2010–2016.

Statistical analysis

Data obtained in the study were analyzed statistically using Statistical Package for the Social Science software version 25 (IBM Corp., SPSS for Windows, Armonk, NY, USA). Data distribution was determined using the Kolmogorov-Smirnov test. The homogeneity of variables was determined using the One-way ANOVA homogeneity of variance test. Symmetrically distributed variables in the text and tables were shown as mean $\pm$ standard deviation values. If the distribution was heterogeneous, variables were shown as median (min-max) values. Categorical variables were stated as number (n) and percentage (%). The Student's t-test or the Mann-Whitney U test were used to compare continuous variables,

and the Chi-square test or Fisher's exact test was used to compare categorical variables according to the data distribution. Cox regression analysis was used to identify possible predictors of overall survival in patients with APL. Overall and disease free survival was assessed by Kaplan-Meier analysis, and the difference was evaluated by log-rank tests. P value ≤ 0.05 was considered to indicate statistical significance.

RESULTS

Patients

We identified 36 patients who underwent initial treatment at our center from September 2003

to February 2016. The median age was 39 years (18–78), with a female predominance (56%). The median presenting leukocyte count of the patients was $2 \times 10^9/L$ (0.5–200). Using the Sanz risk criteria, there were 11 (31%), 14 (38%), and 11 (31%) patients with high, intermediate, and low-risk disease, respectively. Nine (25%) patients applied to our clinic with any bleeding, 24 (66%) patients had an infection, and 16 (44%) patients had DIC during the disease presentation. When we separated the patients into two groups according to the time of diagnosis (2003–2009 vs. 2010–2016), we found a significant difference only in gender distribution [14 (74%) vs. 6 (35%) for female, $p = .02$]. Other features of the patients were similar between both time periods. The clinical characteristics of the total cohort are summarized in Table 1.

Table 1

Demographic characteristics of patients

		Time period of diagnosis		
Variable	Total patients n = 36	2003–2009 n = 19	2010–2016 n = 17	P value
Gender				
Male (n,%)	16 (44)	5 (26)	11 (65)	0.02
Female (n,%)	20 (56)	14 (74)	6 (35)	
Age (years)				0.21 ^a
Median (range)	62 (18–97)	37 (17–79)	41 (19–63)	
Peripheral blood counts, median (range)				
Hemoglobin (g/dl)	9.15 (4.0–15.6)	9.1 (6.1–14.0)	9.3 (4.0–15.6)	0.76 ^a
White blood cells (× 10 ⁹ /L)	2 (0.5–200)	2.6 (0.6–200)	1.8 (0.5–150)	0.50 ^a
Platelets (× 10 ⁹ /L)	20 (5–231)	19 (10–231)	28 (5–153)	0.68 ^a
Symptom at presentation (n,%)				
Hemorrhage	9 (25)	4 (21)	5 (29)	0.70
DIC	16 (44)	9 (47)	7 (41)	0.97
Infection	24 (66)	12 (63)	12 (70)	0.63
ECOG PS (n,%)				
0–1	26 (72)	12 (63)	14 (82)	0.27
≥2	10 (28)	7 (37)	3 (18)	
Sanz risk group (n,%)				
Low	11 (31)	5 (26)	6 (35)	0.67
Intermediate	14 (38)	7 (37)	7 (41)	
High	11 (31)	7 (37)	4 (24)	
Morphologic classification (n, %)				
Classic	28 (78)	13 (68)	15 (88)	0.23
Microgranular variant	8 (22)	6 (32)	2 (12)	

^a Mann-Whitney U test

Early death and treatment response

The overall ED rate was 33% (12/36) during the study period, with a median time to death was 12 days (1–26). Bleeding was the main cause of death at this period [intracranial (7/12) and abdominal

hemorrhages (1/12)]. Infection (3/11) was the second common reason for death in this period. DS was diagnosed in 11 patients (31%), one of whom died due to DS during the induction therapy. Comparison of ED rates in 2003–2009 and in 2010–2016 were similar (42% vs. 24%, $p = .20$) (Table 2).

Table 2

Treatment results of APL patients by the time period of diagnosis

Variable	Total	2003–2009	2010–2016	P value
Number of patients (n)	36	19	17	
Induction results (n, %)				
Early death	12 (33)	8 (42)	4 (24)	0.20
Complete hematological remission	24 (67)	11 (58)	13 (76)	
Differentiation syndrome in induction	11 (31)	8 (42)	3 (18)	0.11
Outcome at 2 years (%[95% CI])				
Overall survival	58 ± 8	47 ± 11	70 ± 11	0.29 ^a
Disease free survival	87 ± 7	82 ± 11	92 ± 7	0.94 ^a

^a Log-rank test.

Twenty-four patients (67%) achieved complete hematologic remission after induction (median 32 days, range 18–90 days) and proceeded to consolidation therapy. There were three deaths (8%) occurred in the consolidation phase. Two patients died because of sepsis and the other by central nervous system bleeding. At the end of the consolidation therapy, 21 patients achieved molecular remission.

Long-term outcome

The median follow-up of the entire cohort was 11.4 (0.07–126.8) months. The 2-year OS and DFS of all 36 patients were 58% and 87%, respectively (Figure 1A–B). Survival decreased markedly in the first three months after the diagnosis. The 2-year OS rates were 47% ± 11% in patients diagnosed between 2003–2009 and 70% ± 11% in patients diagnosed between 2010–2016 ($p = .29$; Table 2).

After induction treatment median follow-up of the surviving patients was 29.3 months. The 2-year DFS rates were 82% ± 11% in 2003–2009 and 92% ± 7% in 2010–2016 ($p = .94$; Table 2). Kaplan-Meier curves of OS and DFS by both time periods are shown in Figure 2A–B.

Possible predictors of poor OS were defined as leukocytosis [hazard ratio (HR) : 6.33 (95% confidence interval (CI) (2.19–18.31), $p = .001$], high Sanz score [HR : 6.37 95% CI (1.66–24.32), $p = .007$], DIC [HR : 4.32 95% CI (1.46–12.76), $p = .008$], hemorrhage [HR : 3.29 95% CI (1.16–9.35), $p = .02$], infection at diagnosis [HR : 5.05 95% CI (1.11–22.31), $p = .03$], ECOG PS ≥ 2 [HR : 3.71 95% CI (2.12–6.50), $p < .001$] and microgranular morphologic subtype [HR : 4.81 95% CI (1.74–13.27), $p = .002$] on cox proportional hazard regression analysis. No differences were observed by gender, age, thrombocytopenia and the time period of diagnosis (Table 3).

A

B

Figure 1A–B. Two-year overall and disease free survival of all patients.

Figure 2A–B. Two-year overall and disease free survival by the time of diagnosis.

Table 3

Cox proportional hazards regression analysis for risk factors to predict overall survival in patients with APL

Variable	Hazard ratio (95%CI)	P value
Gender		
Female	Ref.	
Male	0.79 (0.28–2.18)	0.65
Age (years)	1.00 (0.96–1.04)	0.73
Hemoglobin (g/dl)	0.89 (0.73–1.10)	0.30
White blood cells ($\times 10^9/L$)		
<10	Ref.	
≥ 10	6.33 (2.19–18.31)	0.001
Platelets ($\times 10^9/L$)		
≥ 40	Ref.	
<40	2.27 (0.73–7.10)	0.15
Symptom at presentation		
Hemorrhage	3.29 (1.16–9.35)	0.02
DIC	4.32 (1.46–12.76)	0.008
Infection	5.05 (1.11–22.31)	0.03
Time period of diagnosis		
2003–2009	Ref.	
2010–2016	0.58 (0.21–1.60)	0.29
Differentiation syndrome in induction	0.91 (0.31–2.64)	0.87
Sanz score		
Low	Ref.	
Intermediate	1.01 (0.22–4.58)	0.99
High	6.37 (1.66–24.32)	0.007
ECOG PS		
0–1	Ref.	
≥ 2	3.71 (2.12–6.50)	<0.001
Morphologic classification		
Classic	Ref.	
Microgranular variant	4.81 (1.74–13.27)	0.002

During the follow-up period, no relapse was observed. Only one patient died due to secondary malignancy. The patient died because of MDS/AML in the 48th month of follow-up.

DISCUSSION

In this single-center retrospective study, we present our results of ED, survival rates and

change of these parameters over time in patients with APL. We demonstrated that ED remains a major problem and causes shortening of overall survival in these patients. However, we demonstrated that there were no favorable changes regarding ED, OS, and DFS during the 14 years. Also, we found that the presentation form of the disease, high Sanz and ECOG scores, and microgranular morphologic subtype were associated with poor prognosis.

Significant improvements have been achieved since the addition of ATRA to APL therapy from the early 1990s. Multicenter clinical trials with newly diagnosed APL patients reported high response rates and ATRA approved by the FDA for the treatment of APL [20]. Subsequently, ATRA plus chemotherapy with idarubicin (or daunorubicin) and/or cytarabine became the standard induction regimen for APL [21, 22]. In many randomized clinical trials, the ED rate was reported as 5% to 10% [9, 22, 23]. Nevertheless, many population-based studies demonstrated higher ED rates of 20–32% [11, 24, 25]. We found that the overall ED rate in our study was 33%, and it was similar to population-based studies. The most frequent cause of ED in our study was hemorrhage and infection. In this study, the distribution of the causes of death during the induction therapy was similar to previous reports [26, 27]. The main reason for the higher ED rates contrasted with trials is probably the inclusion of patients with very early deaths, and also patients with poor performance status, higher Sanz risk score, and life-threatening coagulopathy/hemorrhage at diagnosis [28]. Compared to 7-year time periods (2002–2009 and 2010–2016) to examine change over time, there was no significant improvement in ED, which was still represented the most important reason for treatment failure [24, 29].

The 2-year OS was 58%, and it was lower than the expected range for adult APL. Disappointingly, this rate was very similar to historical data [30], OS was lower than the randomized clinical trials [31, 32]. Noteworthy, patients with high risk according to the Sanz score, ECOG PS ≥ 2 (31%), and infection at presentation (66%) were constituted an essential part of our study, which is higher than in the majority of other APL studies [10, 32]. This may have

caused a lower OS rate in our study. We defined leukocytosis, higher Sanz score, DIC, hemorrhage, infection at diagnosis, poor performance status, and microgranular morphologic subtype as risk factors for reduced OS. In many studies, the relationship between these factors and OS has been demonstrated [24, 33]. However, age was not a risk factor for OS in our study. Similar to our result, the Danish Registry was reported that while the age is not an independent risk factor for OS, the performance status of the patients is the main determinant of OS [34]. This may reflect the importance of performance status rather than the age during the treatment process.

In the present study, we observed no improvement in 2-year OS rates from 2003–2009 to 2010–2016. Similarly, epidemiologic data demonstrated that there was no significant change in survival and remained relatively stable in recent years [16, 34]. However, The International Consortium on Acute Promyelocytic Leukemia (IC-APL) demonstrated that the effort to recognize and treat APL early had been associated with significantly improved 2-year OS up to 80% in developing countries [35]. Another remarkable finding of our study was 2-year DFS of patients was 87%. It pointed at the expected survival rate of patients who achieved complete remission is high. Considering these findings, that was critical to evaluate patients with clinical suspicion of APL immediately to reduce early death and increase long-term survival.

The study has several limitations. The first and major important limitation is that this study was single center. Within the limits of single-center and rare nature of the disease, the study population was localized and included a small number of patients. These were limiting the analytic possibilities. Second, the design of the study is not sufficient to establish a cause and effect relationship.

In conclusion, our study showed that long-term survival remains low in APL patients, particularly related to a high ED rate. Improvement of the prognosis in APL patients seems dependent on increased clinical awareness, rapid confirmation of the diagnosis, and prompt initiation of ATRA treatment. Improving early death rates should be the main objective for the future treatment of APL.

Introducere. Odată cu introducerea tratamentului cu acid transretinoic (ATRA) pentru tratamentul leucemiei acute promielocitare (APL) s-a observat o creștere a supraviețuirii acestor pacienți. Totuși studiile populaționale nu au putut observa o îmbunătățire majoră a supraviețuirii pacienților după anii 2000. Scopul studiului a fost de a descrie răspunsul clinic și prognosticul pacienților adulți care s-au prezentat cu diagnosticul APL.

Metode. Au fost analizate retrospectiv 36 de cazuri cu APL diagnosticate între septembrie 2013 și februarie 2016.

Rezultate. Supraviețuirea la 2 ani de la diagnostic a fost de 58%. Iar supraviețuirea disease free (DFS) a fost de 87%. Rata mortalității a fost de 33% și a rămas stabilă pe parcursul celor 14 ani (42% în 2003–2009 vs. 24% în 2010–2016 ($p = 0,20$). În plus supraviețuirea la 2 ani a fost 47% în 2003–2009 și 70% în 2010–2016 ($p = 0,29$). Analiza univariată a arătat că leucocitoza (mai mare de $10 \times 10^9/L$), scorul mare Sanz, hemoragia, infecția, sindromul de coagulare intravasculară diseminată și subtipul morfologic microgranular au avut prognostic mai prost.

Concluzii. Studiul a arătat ca supraviețuirea a rămas redusă la pacienții cu APL.

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