Original Article
Improved outcome in early induction deaths in patients with acute promyelocytic leukemia after therapeutic and supportive interventions: a follow up study of seven-years' experience at a tertiary care center

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Abstract: Introduction and objectives: Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia with characteristic morphology and clinical features. Early mortality rate of 30% has been reported in developed countries despite prompt initiation of treatment. We have previously reported an early induction mortality of approximately 62% in our cohort. Based on this mortality rate, we made changes in our treatment protocol. The objective of this follow-up study was to report the early induction mortality and overall survival of patients with APL after incorporating changes in chemotherapy and supportive care regimen. Subjects and methods: This was a prospective descriptive study conducted at Aga Khan University Karachi, Pakistan from October 2012 till October 2019. Data of patients included clinical features, morphological findings, cytogenetic and PCR studies, cytotoxic protocols, overall outcome and causes of early induction mortality. The changes in treatment protocol included prophylactic infusion of fresh frozen plasma, dexamethasone therapy and other changes in supportive care regimen. Results were recorded as frequencies and percentages. Statistical Package for the Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA) was used to analyze patient's data. Survival curves were calculated using the Kaplan-Meier method. Results: During the study period, total of 447 patients presented with acute myeloid leukemia at our institution out of which 40 patients were diagnosed with acute promyelocytic leukemia (9%). Out of these 40 patients 24 were males and 16 were females. The median age was 37 years. Twenty-five patients were in low risk group whereas 15 were high-risk. Differentiation syndrome was seen in 14 patients. As a part of induction chemotherapy, 13 patients received only ATRA because they were not eligible for chemotherapy and 17 patients received a combination of ATRA and anthracycline. Among the remaining patients, four received ATRA, arsenic and anthracycline while two received ATRA and arsenic only. Four patients did not receive any treatment because of rapid deterioration of clinical condition and death. The overall survival was 65% and early induction mortality was 30%. Conclusion: The early induction mortality decreased to 30% from 62% in this study and the overall survival was 65%. With the introduction of prophylactic infusion of fresh frozen plasma, dexamethasone and appropriate supportive treatment during the induction chemotherapy, we were able to improve the induction mortality and overall survival of patients.

Keywords: Early induction, deaths, improved outcome, APL

Introduction

Acute promyelocytic leukemia (APL) is an aggressive and unique subtype of acute myeloid leukemia with characteristic morphology and clinical features. It may be associated with high mortality especially in the early phase of the disease secondary to hemostatic abnormalities leading to disseminated intravascular coagulation (DIC) [1]. It is a relatively an uncommon myeloid malignancy representing approximately 10% of all acute myeloid leukemias (AML) [2]. Median age of APL is approximately 44 years [3]. Apart from clinical features, the diagnosis of APL is based on cytogenetic abnormality showing translocation t(15;17) which results from PML gene on chromosome 15 to the RARA gene on chromosome 17 producing a

PML-RARA fusion gene measurable by using polymerase chain reaction (PCR) [4]. This tool is also used to monitor the burden of the disease and remission status. Morphologically, hypergranular and microgranular variants are well established. Similarly other cytogenetic abnormalities like t(11;17) and t(5;17) are uncommon but the management plan and monitoring remains the same [5].

Before the introduction of all trans-retinoic acid (ATRA), APL carried a very high mortality due to bleeding diathesis and most of the deaths occurred in the first month of treatment. However, in 1980s, when ATRA was introduced, it changed the overall outcome. ATRA is a differentiating agent, which reverses the coagulopathy associated with APL [6]. The combination of ATRA and anthracyclines showed an excellent remission rate and prolonged overall survival [7].

Despite the introduction of differentiating agents like ATRA and arsenic trioxide (ATO), early death rate remains very high and up to 30% mortality is reported in advanced countries despite prompt and targeted therapy [8]. Reasons for early deaths are many and include intracranial and alveolar hemorrhage. The other contributing factor is differentiation syndrome that occurs in approximately 25% of APL patients. It is characterized by fever, rising white cell count and pulmonary infiltrates [9]. Because of the administration of anthracyclines drugs, which are integral part of induction protocols, profound and prolonged neutropenia is expected in all patients, which exposes them to febrile neutropenia and sepsis [10]. APL is a medical emergency and late presentation further contributes to early mortality. Other risk factors to predict early death are high risk patients categorized according to Programa Espinol de Tratamientosen Hematologica (PETHEMA) risk stratification, renal insufficiency, peripheral promyelocytic blast count of more than 30%, male gender and age more than 60 years [11].

An important aspect in the management of APL is to introduce the differentiating agents as soon as the clinical diagnosis is suspected i.e. the need to wait for the confirmatory diagnosis of cytogenetic and molecular studies is not mandatory.

We have previously reported a five-year experience of outcome and early deaths in 26 consecutive patients who presented with APL. The overall early induction mortality rate was 61% which was very high with major causes being hemorrhage and differentiating syndrome noted in 86% of patients [12].

Based on these findings, we changed our management protocol of APL patients to prevent early induction deaths. This is a follow-up study where we report the outcome after incorporating changes in chemotherapy and supportive care regimen.

Subjects and methods

Data collection

This was a prospective descriptive study conducted at Aga Khan University Karachi, Pakistan from October 2012 till October 2019. Data of patients with APL was collected, based on morphological findings, cytogenetic and PCR studies. The data tool also documented clinical features, laboratory findings, cytotoxic protocols, overall outcome and causes of early induction mortality. Laboratory data of the patients, included complete blood count, peripheral blood and bone marrow findings, karyotyping for t(15;17) (q24.1; q21.1) and PCR studies for PML-RARA. Other laboratory data included investigations for coagulopathy i.e. prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen and D-Dimer.

Treatment regimen

Risk stratification of patients was performed according to the PETHEMA [11] and Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) [13] studies. Patients were subgrouped into two categories (i.e. low risk and high risk). Low-risk patients had leucocyte counts $\leq 10 \times 10^9$/L and platelets $\geq 40 \times 10^9$/L and high-risk patients had leucocytes $\geq 10 \times 10^9$/L.

Patients were treated according to the NCCN guidelines. Induction therapy was administered with all-trans retinoic acid (ATRA) and idarubicin (AIDA) along with injection cytosar in high-risk patients. In few patients, idarubicin was replaced by daunorubicin, depending on the phy-

Table 1. Laboratory parameters in 40 patients with APL

Hematological Parameters	Descriptive Statistics Mean (range)
Age (years)	34 (17-60)
Hb (gm/dl)	8.6 (3.3-13.6)
Fibrinogen (mg/dl)	186.58 (20-601)
PT (secs)	12.7 (11.9-14.8)
APTT (secs)	25.3 (23-27)
D-Dimer	14.35 (5.07-37.8)
Bone Marrow Blast (%)	81 (79-90)
WBC (× 10^9/L)	5.85 (3-19.9)
Platelets (× 10^9/L)	27 (13-56)
Peripheral blast (%)	69 (40-84)

sician's preference. Due non-availability of gemtuzumab ozogamicin (GO), it was not considered an option. In the low risk group, both differentiating agents ATRA and arsenic trioxide (ATO) was administered. Consolidation therapy consisted of three cycles of anthracycline-based drugs (idarubicin 5-7 mg/m^2 × 4 days; mitoxantrone 10 mg/m^2 × 5 days; and idarubicin 12 mg/m^2 × 1-2 days), with a 15-day period of ATRA during consolidation cycles. In high-risk patients, the induction and consolidation were followed by maintenance therapy with daily oral 6-mercaptopurine (6-MP), weekly oral methotrexate and intermittent ATRA (45 mg/m^2 × 15 days every three months) for a total period of two years. The diagnosis of DS was based on any of the two following clinical or radiological features: 1-unexplained fever; 2-unexplained hypotension; 3-acute renal failure and 4-pulmonary infiltrate or pleural effusion on chest radiograph. Early induction death was defined as death from any cause during first thirty days of hospitalization. Transfusion thresholds were <30 × 10^9/L for platelet infusion and <9 g/dL for packed red cell transfusion. Cryoprecipitates were transfused if fibrinogen was <150 mg/dL. The other intervention included:

i: To achieve D-Dimer level of <5 mg/L FEU by transfusing three units of fresh frozen plasma twice daily during length of stay.

ii: Once the targeted D-Dimer was achieved, we transfused three units of fresh frozen plasma once daily for first 15 days of induction irrespective of normal prothrombin time and activated partial thromboplastin time.

iii: Administration of injection dexamethasone 10mg daily for 15 days as prophylaxis against DS.

All neutropenic patients were treated with empiric antimicrobial agents according to the hospital protocol.

Data analysis

Results were recorded as frequencies and percentages. Statistical Package for the Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA) was used to analyze patient's data. Haematological parameters were expressed in mean with ranges. Survival curves were calculated using the Kaplan-Meier method. Patient disease characteristics were compared using chi-square analysis. Mann-Whitney U test and independent sample t-test was used to compare low-risk and high-risk groups. *P*-value was calculated as <0.05 at 95% confidence interval.

Results

General characteristics

During the study period a total of 447 patients presented with acute myeloid leukemia at our institution out of which 40 patients were diagnosed with APL on the basis of clinical features, peripheral and bone marrow morphology and the presence of t(15;17) (q24.1;q21.1) and PML-RARA mutation. The t(15;17) (q24.1; q21.1) translocation was detected using conventional cytogenetic techniques, fluorescence *in situ* hybridization and PCR. Morphologically on peripheral smear and bone marrow, all patients had hypergranular variant of APL. There was no secondary APL. Out of total 40 patients, 24 were males and 16 were females. Male to female ratio was 1:1.5. The median age of patients was 37 years (range 17-60 years). Other important laboratory findings are summarized in **Table 1**.

Risk stratification

According to risk stratification, 25 patients were in low risk group whereas 15 were in high-risk category (laboratory findings according to risk category is given in **Table 2**). Differentiation syndrome was seen in 14 patients and it was fatal in seven cases.

Table 2. Laboratory parameters in 40 patients according to risk category

Characteristics	Risk Stratification		p-value
	High Risk	Low Risk	
N	14	26	-
Age	33 ± 11	35 ± 12	0.608
Hb	8.8 ± 1.9	8.5 ± 2.4	0.689
PT	15.19 ± 3.29	19.35 ± 32.9	0.642
APTT	29.68 ± 15.08	31.42 ± 31.15	0.846
D Dimer	37.51 ± 28.01	20.67 ± 23.16	0.048*
Fibrinogen	163.36 ± 96.26	199.08 ± 105.58	0.300
Bone Marrow Blast	89 ± 5	77 ± 14	0.004*
WBC	53.34 ± 64.41	4.03 ± 2.44	<0.001*
Platelets	40 ± 24	48 ± 76	0.705
Peripheral Blast	80 ± 14	48 ± 25	<0.001*

*p value <0.05 at 95% confidence interval.

Chemotherapy regimen

As a part of induction chemotherapy, 13 patients received only ATRA because they were not eligible for chemotherapy and another 17 patients received a combination of ATRA and anthracycline. Among the remaining patients, four received ATRA, arsenic and anthracycline while two received ATRA and arsenic only. Four patients did not receive any treatment because of rapid deterioration of clinical condition and death.

Outcome

Out of the 40 patients in the study, 14 (35%) expired, while 26 (65%) are alive and in remission on follow-up at 42 months (**Figure 1**). Overall survival rate, stratified according to risk group, showed that low-risk patients had a survival rate of 72% at 42 months. The outcome was inferior for patients in the high-risk group, with an overall survival of 53.3% (**Figure 2**).

Early induction death was seen in 12 (30%) patients with APL. The causes were, DS in 6 patients (50%), hemorrhage in 3 patients (two with intracranial and one patient with pulmonary bleeding), acute renal failure in 2 patients and sepsis in one patient.

Eight patients in the high-risk category received maintenance therapy. However, two out of eight patients expired after achieving complete remission (causes of death were *mycobacterium tuberculosis* infection and *klebsiella* sepsis).

The survival rate among patients who remained alive in the early period was 95% at 42 months.

Discussion

With the introduction of ATRA in 1985, the outcome of APL has changed dramatically which was once considered the most lethal leukemia because of bleeding diathesis [14]. Several trials have shown an excellent outcome of APL especially in low risk category of patients [15]. However, the mortality in the induction phase of the treatment is still significantly high reaching 29% in few developed countries and more than 50% in developing countries [16]. Major causes of death are hemorrhage, differentiation syndrome and sepsis.

In our earlier article we reported an early induction mortality rate of 61.5% and the major causes were hemorrhage and differentiating syndrome noted in 86% of APL patients [12]. Based on this high mortality rate we reviewed our management plan of APL patients to prevent the early induction deaths.

We report a 50% reduction in early deaths as compared to our previous study (61.5% in 2014 [12] and 30% in current study) that showed a significant improvement due to the intervention made in the treatment protocol. Major causes of death were DS and hemorrhage. The early death rate profile in clinical trials for APL shows a marked difference when compared to population-based studies. Most of the clinical trials showed death rate in single digits [17] whereas population based studies revealed early death rates in the range of 15-60% [18].

Early death rates among patients with APL reported in the literature vary widely. While early induction death in our previous study was 61.5% [12], another study from the region reported a mortality rate of 28.6% in patients with APL who were administered anthracycline and ATRA therapy [19]. Park has reported an ED rate of 17.3% [20] while Altman [21] has published a rate of 11% with 44% of deaths occurring in the first week of treatment. These population-based studies suggest that the early death rates depicted in clinical trials are

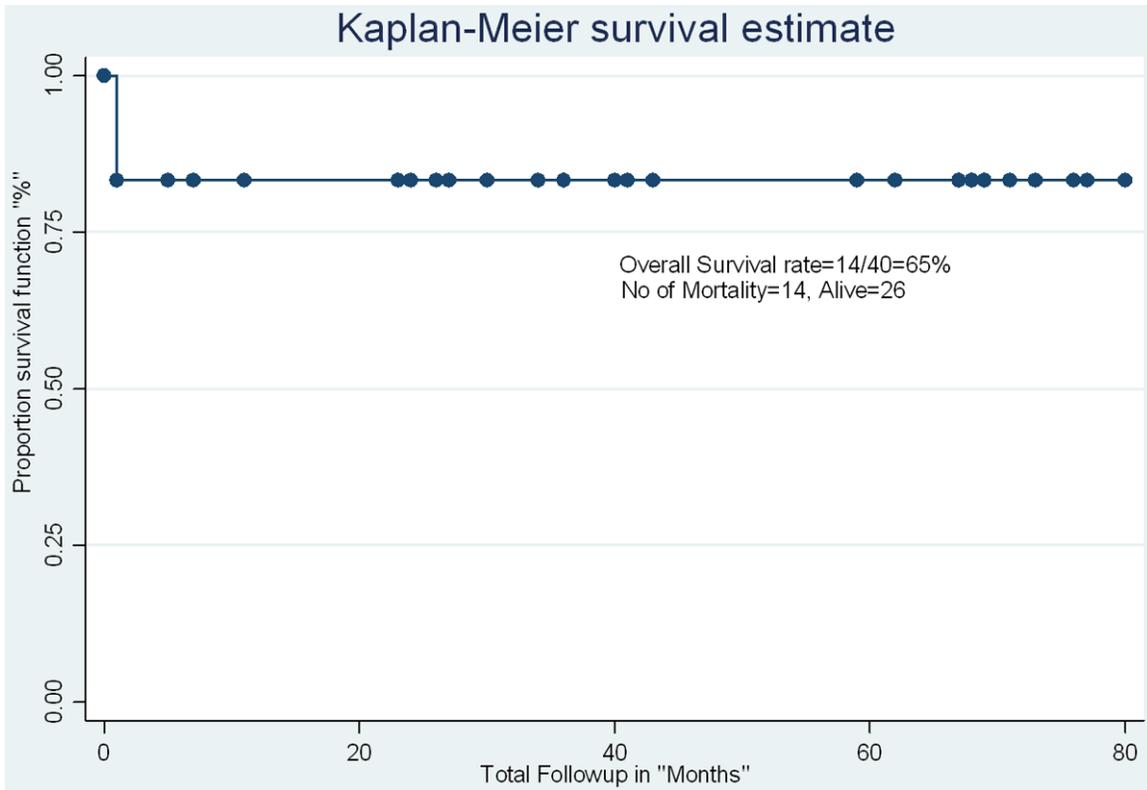**Figure 1.** Overall survival in 40 patients with APL.

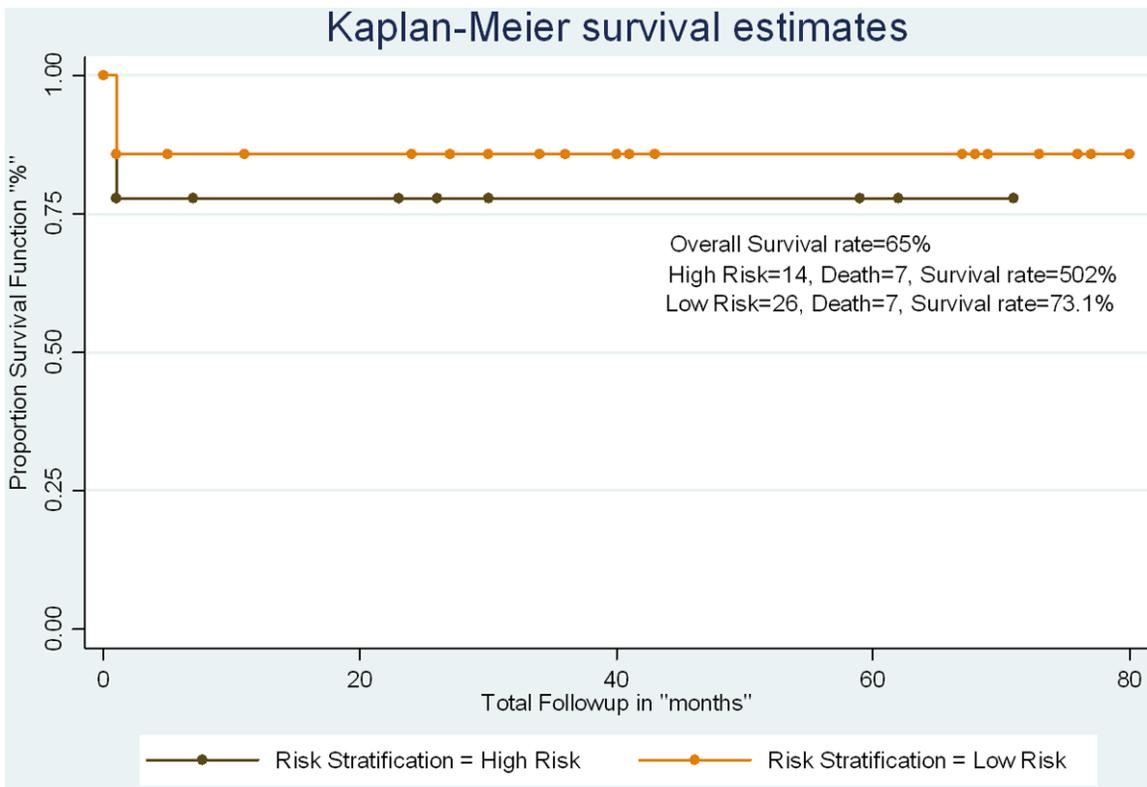**Figure 2.** Overall survival according to risk category in 40 patients with APL.

not homogenous to early death rates at tertiary care centers which treat patients with APL.

The common causes of early death in our study were differentiation syndrome and hemorrhage. Early deaths due to hemorrhage are characteristic of APL. This is because even after the correction of DIC, the bleeding risk remains and aggressive triggers of transfusion criteria needed to be followed in order to prevent massive bleeding diathesis as shown by the results published by Di Bona E [22].

Patients in this study once achieved remission after induction chemotherapy did very well with an overall survival rate of 65% at 42 months. DS was noted in 14/40 (35%) despite prophylactic steroids. Out of these 14 patients, 6 (42.8%) expired because of DS. This is in stark contrast to our previous study where the frequency was 26.9% with 100% mortality [12]. The decrease in mortality was probably secondary to prophylactic steroids which was not considered previously. The PETHEMA LPA 96 and 99 trials have shown 15% deaths due to DS. All patients received prophylactic steroids subsequently leading to decreased incidence as shown in our study [11, 23].

A relapse rate of 30% was observed in our previous study, however, in the current study only one (2.5%) patient relapsed, and the same patient achieved and remained in remission till the end of the study period. There were only two deaths after the completion of induction therapy, and both were secondary to infection. One patient died because of *klebsiella* sepsis while the other had *mycobacterium tuberculosis* infection of brain. Relapse rates ranging from less than 10% [24] to 20% [25] have been reported in literature. Our study has shown extremely low relapse rate in APL patients in all risk groups.

Overall survival was much better in our current study, which was 65%. The survival rate of high-risk patients has improved from 15.4% to 53.3% in comparison with previous study [12]. Similarly, in the low risk group, the survival rate was 72%, which is comparable to international literature.

FMS-like tyrosine kinase 3 (FLT-3)/internal tandem duplication (ITD) mutations are a bad prognostic indicator in acute myeloid leukemia as it is associated with induction mortality. Its role in the management of APL is still controversial [26]. However, it is not associated with long-term outcome and relapse [27]. The status of FLT-3 was available in 18 patients out of which 15 were negative for the mutation while remaining three were positive. All three of them are in molecular remission till last follow up.

Conclusion

We infer that after the introduction of prophylactic infusion of fresh frozen plasma, dexamethasone and appropriate supportive treatment during the induction chemotherapy, we were able to improve the induction mortality and overall survival of patients with APL admitted at our center.

Disclosure of conflict of interest

None.

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