Article published online: 2022-11-02

Hematological Malignancies

Complications during Induction Chemotherapy in Acute Promyelocytic Leukemia: An Institutional Experience

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South Asian J Cancer 2023;12(3):274–279.

Abstract

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Introduction Acute promyelocytic leukemia (APL) has transformed from a highly fatal disease to a highly curable one. Induction deaths continue to represent one of the major impediments in modern therapy of APL. Sepsis, hemorrhage, and differentiation syndrome are the major complications during induction therapy in APL. The present study reports the incidence and prognostic factors of major complications during induction chemotherapy in patients with newly diagnosed APL.

Materials and Methods The present study was a single institutional, observational, retrospective study. All cases of APL diagnosed by morphology and confirmed by RT PCR (PML RARα) were included in this study. Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25.

Results A total of 73 patients were analyzed. The median age at presentation was 30 years (range, 3–60 years) with a female to male ratio of 1.02:1. The most common symptom at presentation was fever (80%), followed by fatigue (56%) and gum bleeding (37%). The majority of the patients at presentation were high risk (42.4%), followed by intermediate risk (38.4%) and low risk (19.2%). Fifty-seven (78%) patients achieved complete hematological remission and 16 (22%) succumbed during induction chemotherapy. Infection was the most common cause of induction death (50%), followed by hemorrhage (37.5%) and differentiation syndrome (12.5%). On univariate analysis of prognostic factors, bcr3 variant, grade 3/4 bleeding during induction, and low levels of albumin at presentation were significant for induction mortality ($p = 0.034$, 0.041, and 0.008 respectively). On multivariate analysis, only serum albumin < 3.5 g/dL was an independent predictor for induction mortality ($p = 0.043$).

Conclusion The majority of patients were high risk at presentation. Sepsis was the most common complication during induction and also the leading cause of induction death. Identifying induction complications at the earliest and providing aggressive supportive measures can further improve outcomes in APL.

Keywords

- acute promyelocytic leukemia
- febrile neutropenia
- differentiation syndrome
- bleeding
- induction complications

DOI https://doi.org/10.1055/s-0042-1757303 ISSN 2278-330X

How to cite this article: Yedla RP, Bala SC, Pydi VR, et al. Complications during Induction Chemotherapy in Acute Promyelocytic Leukemia: An Institutional Experience South Asian J Cancer 2023;12(3):274–279.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Acute promyelocytic leukemia (APL) is a biologically and clinically distinct variant of AML. The use of *all*-trans retinoic acid (ATRA) and in combination with anthracycline-based chemotherapy have led to remission induction rates of more than 90% as reported by several large multicenter studies.[1–6] However, induction deaths continue to represent one of the major impediments in modern therapy of APL. The most common causes of induction mortality are bleeding, differentiation syndrome, and infection.[7] Uncertainty remains as to which prognostic factors are associated with various causes of induction mortality and complications in patients with APL.

The present study reports the incidence, time of occurrence, and prognostic factors of major complications during induction chemotherapy in patients with newly diagnosed APL.

Materials and Methods

The present study was a single institutional, observational, retrospective study done from 2012 to 2018.

Clinical characteristics, chemotherapy protocols used, outcome, and causes of early induction deaths were recorded from medical records and hospital death registry. All cases of APL diagnosed by morphology and confirmed by RT PCR (PML RARα) were included in this study. Patients who died within 72 hours of admission or declined treatment and patients who had taken prior chemotherapy or radiotherapy for the treatment of any malignancy were excluded from the analysis.

Definitions

Risk stratification: Patients were categorized into three groups. Low-risk patients had leucocyte counts $\leq 10 \times 10^9$/L and platelets $> 40 \times 10^9$/L, intermediate-risk patients had leucocytes $\leq 10 \times 10^9$/L and platelets $< 40 \times 10^9$/L, and high-risk patients had leucocytes $> 10 \times 10^9$/L.

Differentiation syndrome: was diagnosed when the patient had least two of the following clinical features: unexplained fever, acute respiratory distress with interstitial pulmonary infiltrates, acute renal failure, weight gain greater than 5 kg, unexplained hypotension, and pleuropericardial effusion.

Treatment

The modified Protocol of International consortium on acute promyelocytic leukemia (IC-APL 2006)[8] and ATRA + ATO[9] were the two most commonly used protocols in this study.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25. Univariate analysis was done using Pearson's chi square analysis. Patient and disease characteristics that were examined in the prognostic factor analysis to establish their relation to induction response included age, sex, ECOG performance score, body mass index, biochemical parameters such as serum creatinine, fibrinogen and albumin, hematological variables including hemoglobin level, platelet, white blood cells (WBCs), and blast cell counts, morphological variants, PML/RARA isoforms, treatment protocol, and the presence of coagulopathy or infection at presentation. Multivariate analysis was performed using logistic regression model. A p-value of < 0.05 was considered as statistically significant.

Results

A total of 73 patients were analyzed, of which 36 (49.3%) were males and 37 (50.7%) were females. The median age at presentation was 30 years (range, 3–60) and the median duration of symptoms at presentation was 15 days (range, 3–90). The most common symptom at presentation was fever (80%), followed by fatigue (56%) and gum bleeding (37%). The majority of the patients at presentation were high risk ($n = 31$, 42.4%), followed by intermediate risk ($n = 28$, 38.4%) and low risk ($n = 14$, 19.2%). Of 73 patients, 55 (75%) patients received induction chemotherapy with ATRA and daunorubicin and 18 (25%) patients received ATRA and arsenic trioxide.

Fifty-seven (78%) patients achieved complete hematological remission and 16 (22%) succumbed during induction chemotherapy. The median time to CHR was 29 days (range, 20–40). Infection (50%), hemorrhage (37.5%), and differentiation syndrome (12.5%) were the causes of induction mortality.

Induction Mortality

On univariate analysis of prognostic factors, bcr3 variant, grade 3/4 bleeding during induction and low levels of albumin at presentation were significant for induction mortality ($p = 0.034$, 0.041, and 0.008 respectively). On multivariate analysis, only serum albumin < 3.5 g/dL predicted for induction mortality ($p = 0.043$). Univariate and multivariate analyses of variables for induction death are shown in ►Table 1.

Febrile Neutropenia

Febrile neutropenia (FN), differentiation syndrome (DS), and bleeding during induction chemotherapy were seen in 58 (81.6%), 19 (26.7%), and 15 (20.5%) patients, respectively. Other complications included benign intracranial hypertension (11.2%), leukocytosis (23.3%), and skin toxicity (80%). None of the patients had prolonged QTc interval or other cardiac events.

Of 58 patients with febrile episodes, microbiologically documented infection was seen in 17 (29%) cases, 23 (40%) patients had clinical signs of infection, and 18 (31%) patients had fever without a focus of sepsis. Gram-positive and gram-negative bacteria accounted for 50% and 38% of all blood isolates, respectively. Candidemia was documented in two patients (12%). Radiological signs of infection were identified in 18 (31%) patients, majority being pulmonary (17 patients) and sino-orbital in one patient. The median day of onset of febrile neutropenia (FN) was day 10 (range, 3–24). Of 58

Table 1 Univariate analysis and multivariate analysis for induction deaths

Baseline characteristics	*N* (%)	Induction deaths *n* (%)	Univariate analysis (*p*-Value)	Multivariate analysis (*p*-Value)
Age (y)				
< 40	33 (45.2)	7 (21.2)	0.89	0.630
≥ 40	40 (54.8)	9 (22.5)		
Gender				
Male	36 (49.3)	6 (16.7)	0.453	0.592
Female	37 (50.7)	10 (27)		
Body mass index				
< 25	47 (68.4)	8 (17%)	0.174	0.264
≥25	26 (31.6)	8 (30.8%)		
ECOG PS				
< 2	53 (72.6)	10 (18.9)	0.305	0.697
≥2	20 (27.4)	6 (30)		
Infection at presentation				
Yes	12 (14%)	4 (33.3)	0.296	0.100
No	61 (86%)	12 (19.7)		
Grade 3/4 bleeding at presentation				
Yes	19 (26)	4 (21)	0.78	0.658
No	54 (74)	12 (22)		
Hemoglobin (g/dL)				
< 10	64 (86)	15 (23.4)	0.403	0.791
≥10	9 (14)	1 (11.1)		
WBC ($\times 10^9$/L)				
< 10	49 (70.2)	9 (18.4)	0.295	0.533
≥10	24 (29.8)	7 (29.2)		
Platelet ($x10^9$/L)				
< 40	42 (57.9)	9 (21.4)	0.906	0.995
≥40	31 (42.1)	7 (22.6)		
Peripheral blood blasts ($x10^9$ /L)				
< 1	57 (80.7)	11 (19.3)	0.307	0.286
≥1	16 (19.3)	5 (31.3)		
Serum fibrinogen (mg/dL)				
< 150	16 (21.1)	4 (25)	0.736	0.423
≥150	57 (78.9)	12 (21.1)		
Serum creatinine (mg/dL)				
< 1.2	66 (91.2)	14 (28.6)	0.654	0.764
≥1.2	7 (8.8)	2 (21.2)		
Serum albumin (g/dL)				
< 3.5	18 (17.5)	8 (44.4)	**0.008**	**0.043**
≥3.5	55 (82.5)	8 (14.5)		
Pathological variant				
Hypergranular	58 (78.9)	13 (22.4)	0.840	0.330
Microgranular	15 (21.1)	3 (20.0)		
Risk stratification				

Table 1 (*Continued*)

Baseline characteristics	*N* (%)	Induction deaths *n* (%)	Univariate analysis (*p*-Value)	Multivariate analysis (*p*-Value)
Low	14 (19.2)	3 (21.4)		
Intermediate	28 (38.4)	4 (14.2)	0.210	0.254
High	31 (42.4)	9 (29)		
PML RARA isoforms ($N = 40$)				
bcr1/bcr2	23 (57.5)	1 (4.3)	**0.034**	0.138
bcr3/others	17 (42.5)	4 (23.5)		
Induction protocol				
ATO + ATRA	18 (24.6)	4 (22.2)	0.971	0.817
ATRA + Daunorubicin	55 (75.4)	12 (21.8)		
Leukocytosis during induction				
Yes	17 (26.3)	2 (11.8)	0.248	0.686
No	56 (73.7)	14 (25)		
Differentiation syndrome				
Yes	18 (25)	4 (22)	0.81	0.974
No	54 (75)	12 (22)		
Febrile Neutropenia				
Yes	57 (87.7)	13 (22.8)	0.235	0.481
No	16 (12.3)	3 (18.75)		
Bleeding during induction				
Yes	15 (20.5)	7 (46.6)	**0.046**	0.184
No	58 (79.5)	9 (15.5)		

patients with FN, 8 (13.7%) patients succumbed to sepsis. On univariate analysis, high WBC at presentation ($p = 0.03$) and APL2006 protocol ($p = 0.017$) significantly predicted for febrile neutropenia. Age $\geq$ 40 years, female gender, BMI $\geq$ 25, ECOG PS $\geq$ 2, infection at presentation, hemoglobin $\leq$10 g/dL, blasts $\geq 1 \times 10^9$/L at presentation, platelet count $<$ 40000, fibrinogen $<$ 150, serum creatinine $\geq$ 1.2 mg/dL, serum albumin $<$ 3.5 g/dL, hypergranular variant, bcr3 variant, leukocytosis during induction did not significantly predict febrile neutropenia. On multivariate analysis, only APL2006 induction protocol was an independent prognostic factor for febrile neutropenia ($p = 0.033$).

Differentiation Syndrome

Leukocytosis during induction therapy was seen in 17 (23.3%) patients with a median day of onset of 6 days (range, 2–15) after initiation of therapy. The median peak of WBC count in these patients was 12.7×10^9/µL (range, 8–54.6). Nine out of 18 patients (50%) treated with ATRA and ATO and 8 out of 55 patients (14.5%) treated with APL2006 protocol had leukocytosis during induction. Nine patients (9/17, 53%) with leukocytosis developed differentiation syndrome.

Differentiation syndrome (DS) was seen in 19 (26.7%) patients. The occurrence of DS in patients treated with APL2006 protocol and ATRA plus ATO protocol is 27.3% (15/55) and 22.2% (4/18), respectively. The median day of onset was day 5 (range, 0–18). The most common presentation of differentiation syndrome was dyspnea and pulmonary infiltrates (90%), followed by weight gain (80%). Of 19 patients with DS, 17 (89.4%) responded to therapy with corticosteroids and temporary cessation of ATRA and 2 (10.6%) patients succumbed to DS. Peripheral blasts $\geq 1 \times 10^9$/L at presentation, ECOG PS $\geq$ 2, serum creatinine $\geq$ 1.2 mg/dL, and leukocytosis during induction ($p = 0.02$, 0.04, 0.01 and $p = 0.009$, respectively) significantly predicted for the development of DS on univariate analysis. Age $\geq$ 40 years, female gender, BMI $\geq$ 25, infection at presentation, hemoglobin $\leq$ 10 g/dL, WBC count $\geq$ 10,000, platelet count $<$ 40,000, fibrinogen $<$ 150, serum albumin $<$ 3.5 g/dL, hypergranular variant, bcr3 variant, and induction protocol did not significantly predicted differentiation syndrome. On multivariate analysis, leukocytosis during induction ($p = 0.01$) was the only significant independent prognostic factor.

Bleeding Manifestations

During induction chemotherapy, bleeding was seen in 15 (20.5%) patients. Common site of bleeding was from mucous membranes (53%) (oral, nasal, gastrointestinal, and genitourinary) followed by lungs (27%) and CNS (20%). Pulmonary hemorrhage and intracranial hemorrhage were the cause of mortality in four and two patients, respectively. On univariate and multivariate analyses, high WBC count at presentation was

significant for bleeding ($p = 0.04$) during induction. Age $\geq$ 40 years, female gender, BMI $\geq$ 25, ECOG PS $\geq$2, infection at presentation, hemoglobin $\leq$ 10 g/dL, blasts $\geq 1 \times 10^9$/L at presentation, platelet count < 40,000, fibrinogen < 150, serum creatinine $\geq$ 1.2 mg/dL, serum albumin < 3.5 g/dL, hypergranular variant, bcr3 variant, induction protocol, leukocytosis during induction did not significantly predicted for bleeding.

Fifty-seven (78%) patients survived induction chemotherapy. At the end of consolidation complete molecular remission was seen in 76.7% of patients. One patient who had molecular persistence of disease at the end of consolidation, received second-line chemotherapy with ATRA plus ATO and attained CMR.

Discussion

Acute promyelocytic leukemia is a clinically and biologically distinct subtype of AML. Complications during induction chemotherapy such as differentiation syndrome, bleeding, and febrile neutropenia are more fatal compromising survivals. The present study was designed to analyze the induction complications in APL patients and various predicting factors for those induction complications.

The median age at presentation in the present study was 30 years, which was similar to the study done by Bajpai et al[10] and was less compared to that by Sanz et al[11] and Mandelli et al.[4] The majority of patients in the present study were high risk (42.4%) as compared with the study by Bajpai et al[10] (23%), PETHEMA (22.9%), and GIMEMA groups (22.2%).[11] This difference could be attributed to the delay in diagnosis and referral to oncological center and hospital referral bias. ATRA and daunorubicin was the sole protocol used in the study until 2014 and after that low and intermediate risk groups received ATRA +ATO. Seven patients received daunorubicin in view of leukocytosis not controlled with hydroxyurea or cessation of ATRA. In the study done by Bajpai et al,[10] the majority of patients (78%) received ATRA plus daunorubicin, followed by single agent arsenic trioxide. Modified AIDA and AIDA were the only protocols used by Sanz et al[11] and Mandelli et al,[4] respectively.

Induction mortality of 22% in the present study was similar to the study by Bajpai et al (18.1%). Induction mortality in the present study was higher compared to Mandelli et al[4] (5%) and Sanz et al[12] (10.1%). Mathews et al[13] from India reported 14% induction mortality with single-agent arsenic trioxide. Sepsis was the most common cause of death followed by bleeding in the present study, which was similar to other study from India by Dayama et al.[14] However, the majority of studies reported hemorrhage as the major cause of early death followed by infection.[4,15] This may be due to the exclusion of early deaths (<72 h) prior to the confirmation of diagnosis or the initiation of treatment from analysis. In contrast to a study done by de la Serna et al[15] serum albumin (less than 3.5 g/dL), PML-RARA isoform (bcr3 variant), and bleeding during induction were predicted for the induction mortality in the present study. This disparity could be because of the small sample size in the present study.

Febrile neutropenia during remission induction was seen in 81.6% of patients in the present study, which was almost similar to the incidence of FN reported by Bajpai et al (91%)[10] and higher than the study by Dayama et al (64%).[14] Pneumonia represented the most common clinically documented infection in the present study. The most common site of infection in the study by Dayama et al (14) and Girmenia et al[16] was pulmonary, while that reported by Bajpai et al[10] was genitourinary. On multivariate analysis for febrile neutropenia, the use of IC-APL2006 induction protocol emerged as prognostic factor. This emphasizes the use of less intensive protocols or risk adapted protocols, thereby reducing the incidence of febrile neutropenia and death due to infection.

The incidence of DS (26.7%) in our study was comparable to the overall incidence of DS reported by Montesinos et al[17] (24.8%) and Bajpai et al[10] (33%). All patients who developed DS responded to higher doses of dexamethasone except for two deaths. In a study by Montesinos et al[17] pretreatment variables predictive of the differentiation syndrome were WBC count ($> 5 \times 10^9$/L), abnormal serum creatinine levels, whereas in the present study, leukocytosis during induction was the only factor that predicted for DS. Bleeding during induction was seen in 15 (20.5%) of patients, of which 6 patients succumbed to hemorrhage. Similar to the study done by Mantha et al,[18] high WBC of $> 10 \times 10^9$/L emerged as an independent predictor of hemorrhagic death in the present study. The overall incidence of hemorrhagic death of 8.2% (6/73) was less compared to the death due to infection 10.9% (8/73) probably because of exclusion of early deaths.

The survival rate at the end of induction therapy of 78% in the present study was close to the earlier study from north India[10] (81.8%) and far below the Western studies by Mandelli et al[4] (95%) and Sanz et al[5] (89%). This rate of survival at the end of induction in the present study reflects the high induction mortality due to several reasons described above and depicts the challenges in managing APL in the real-world scenario.

The present study is limited by the retrospective nature of data collection followed by the small sample size, which decreases the power of the study. Future prospective studies with large sample size are required to further validate the prognostic factors obtained in the present study. Pooled data from various parts of India can help us in framing uniform guidelines on this rare entity, thereby improving outcomes.

Conclusion

Majority of APL patients were at high risk at presentation. Sepsis was the most common complication during induction and the leading cause of induction death. Understanding the prognostic factors that predict the complications during induction helps in planning aggressive supportive measures improving induction outcomes, thereby further improving survival in APL.

Note
This study was orally presented at ISMPOCON 2018 in October 2018 in Jaipur.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
We would like to thank the Department of Pathology, Nizam's Institute of Medical Sciences, and the Department of Microbiology, Nizam's Institute of Medical Sciences.

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