



RESEARCH ARTICLE

Acute Promyelocytic Leukemia: An Ambispective Institutional Experience

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ABSTRACT

Background: Acute promyelocytic leukemia (APL) is a hematologic emergency in which early hemorrhagic and treatment-related complications remain important determinants of outcome. Real-world institutional data can help characterize these challenges.

Methods: This ambispective, single-center observational cohort included 21 patients diagnosed with APL between 2021 and 2025 at Sri Aurobindo Institute of Medical Sciences, Indore. Clinical features, laboratory findings, molecular results, treatment, complications, induction response, and observed outcomes were summarized descriptively.

Results: Median age was 34 years (range, 5–72); 13 patients (61.9%) were male. Bleeding was reported in 14 (66.7%), and 15 (71.4%) had platelet counts below $40 \times 10^9/L$. ATO alone was used in 13 patients (61.9%) and ATO plus ATRA in 8 (38.1%). Differentiation syndrome occurred in 11 (52.4%) and QT prolongation in 8 (38.1%). Sixteen patients (76.2%) achieved documented complete remission after induction, while five (23.8%) died before post-induction response assessment. Recorded causes of death included respiratory failure in three patients, STEMI in one, and an undocumented cause in one.

Conclusion: In this small institutional cohort, ATO-based treatment was associated with documented remission in 16 of 21 patients, while induction-phase complications and mortality remained substantial. These findings underscore the importance of rapid diagnosis, intensive supportive care, and systematic documentation. Treatment-group comparisons and time-to-event estimates are limited by the sample size and incomplete dates.

Keywords: acute promyelocytic leukemia; arsenic trioxide; all-trans retinoic acid; differentiation syndrome; real-world outcomes
Indian J. Pharm. Biol. Res. (2026); <https://doi.org/10.30750/ijpbr.14.4.51>

INTRODUCTION

Acute promyelocytic leukemia (APL) is a biologically and clinically distinct subtype of acute myeloid leukemia (AML), accounting for well under 10% of AML cases in Western series. It is defined by the balanced reciprocal translocation $t(15;17)$, which fuses the PML gene on chromosome 15 to the retinoic acid receptor alpha (RARA) gene on chromosome 17. The resulting PML::RARA fusion protein sits at the center of APL pathogenesis, blocking normal myeloid differentiation. Beyond its characteristic morphology and molecular signature, APL is defined clinically by severe, often dramatic abnormalities of hemostasis. As Thomas has written, APL is a medical emergency in its own right: patients can present with consumptive, life-threatening coagulopathy and deteriorate within hours if treatment is delayed.[1,2]

The story of APL is one of the more remarkable turnarounds in oncology — from among the deadliest acute leukemias to among the most curable. Hillestad's original 1957 description captured a disease with a fulminant, frequently fatal course, dominated by abnormal promyelocytes and severe bleeding. Later reports confirmed

that this hemorrhagic diathesis, more than the leukemia itself in the conventional sense, was the principal driver of early death. Before differentiation therapy existed, outcomes were bleak: early chemotherapy series achieved complete remission in only 5–14% of patients, and survival was often measured in weeks rather than months. Anthracyclines changed that picture substantially — daunorubicin raised remission rates and revealed just how chemosensitive APL cells actually are.[2,9]

Molecular characterization advanced alongside these clinical gains. The discovery of $t(15;17)$ marked APL as genetically distinct, and subsequent work identified PML and RARA as the fusion partners. This molecular understanding also underpinned rapid diagnostic testing and, later, RT-PCR-based monitoring for measurable residual disease. Variant RARA rearrangements were recognized as well: Thomas notes that certain variants — $t(11;17)$ involving PLZF-RARA in particular — can be partially or fully resistant to ATRA, while other rare RARA partners remain ATRA-sensitive. This distinction matters clinically whenever a patient has APL-like morphology but a negative conventional PML::RARA test.[2,10-14]

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How to cite this article: Padhiar A, Asati V, Patidar R, Mishra H, Amin G, Agrawal A, Sharma R, Sami H. Acute Promyelocytic Leukemia: An Ambispective Institutional Experience. Indian J. Pharm. Biol. Res. 2026;14(4):347-357

Source of support: Nil

Conflict of interest: None.

Received: 27/08/2026 Revised: 30/09/2026 Accepted: 03/10/2026

The next breakthrough was all-trans retinoic acid (ATRA). Observations in the 1980s showed that retinoic acid could push leukemic promyelocytes toward terminal differentiation, and later trials confirmed ATRA as a highly effective way to induce complete remission. ATRA alone, however, tended to relapse within months, which is what pushed the field toward combining it with chemotherapy. Randomized trials then showed that ATRA-containing regimens meaningfully improved event-free and disease-free survival over chemotherapy alone, and the European APL group went further, showing that concurrent ATRA plus chemotherapy outperformed a sequential approach — a finding that made combined differentiation-and-cytotoxic therapy the standard for years.[2,9]

At the molecular level, ATRA acts directly on the aberrant retinoic-acid signaling created by PML::RARA. The fusion protein behaves as an abnormal transcriptional

repressor, recruiting corepressor complexes and disrupting the genes that govern granulocytic differentiation. At pharmacologic doses, ATRA changes the conformation and activity of PML::RARA, lifts that repression, and allows differentiation to proceed; it can also drive degradation of the fusion protein through proteolytic and ubiquitin-proteasome pathways. Together, these findings made APL something of a proof of concept for targeted differentiation therapy — a case where understanding the molecular lesion led directly to an effective treatment.[2,10]

Arsenic trioxide (ATO) supplied the second major advance. It targets the PML portion of the fusion oncoprotein, driving its degradation while separately promoting differentiation and apoptosis — so ATRA and ATO act on complementary parts of the same abnormal protein. Large trials went on to show that ATO-containing regimens could produce durable molecular remissions with far less reliance on conventional chemotherapy. Thomas frames this shift as a model for targeted cancer therapy more broadly, and points out that long-term remission rates with modern APL treatment now exceed 80%.[2,7,8] More recent randomized trials have cemented ATRA-ATO combinations as the central approach for non-high-risk disease and have supported chemotherapy-free strategies in appropriately selected patients.

That dramatic improvement in disease control has not come without cost. Differentiation syndrome remains a defining complication of ATRA- and ATO-based therapy, capable of producing fever, weight gain, hypotension, respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, and renal dysfunction. It tends to track with leukocytosis and is thought to stem from a systemic inflammatory response — capillary leak and altered adhesion among differentiating leukemic cells. Risk is highest, Thomas observes, in patients with an elevated white cell count at baseline, which is why early recognition and prompt corticosteroids are central to management. [1,2,15-18] ATO brings its own separate concern: QT prolongation and electrolyte disturbance, both of which require careful monitoring. So while modern regimens have eased the burden of conventional chemotoxicity, they have not removed the need for close observation and intensive supportive care during induction.

Risk stratification has evolved in parallel. Baseline white cell and platelet counts have long been used to sort patients into low-, intermediate-, and high-risk categories — Thomas summarizes the Sanz classification as low risk (WBC $\leq 10 \times 10^9/L$, platelets $>40 \times 10^9/L$), intermediate

risk ($\text{WBC} \leq 10 \times 10^9/\text{L}$, platelets $\leq 40 \times 10^9/\text{L}$), and high risk ($\text{WBC} > 10 \times 10^9/\text{L}$). High-risk disease carries greater leukocytosis, a higher rate of differentiation syndrome, and more relapse, which is why treatment strategies for this group are often intensified with additional cytreduction or chemotherapy.[1,2]

Trial outcomes, however, do not always translate cleanly into routine practice. Severe hemorrhage, coagulopathy, differentiation syndrome, infection, and organ dysfunction still account for a meaningful share of treatment failure and early death outside the trial setting. Real-world cohorts also include patients presenting outside specialized centers, facing diagnostic delay, lacking full molecular workup, or being treated under resource constraints that differ from what a randomized protocol assumes — all of which matters when interpreting institutional data of this kind. [19,24-28]

An earlier Indian institutional experience from Christian Medical College, Vellore, showed that arsenic trioxide-based treatment was feasible in newly diagnosed APL and underscored the practical value of leukocyte control — including hydroxyurea — alongside vigilant surveillance for differentiation syndrome and hepatic or cardiac toxicity. In that 72-patient series, single-agent ATO achieved durable remissions and could be given on an outpatient basis after induction in selected patients, with differentiation syndrome documented in only 5 patients (6.9%).[5,20-23] That series offers a particularly useful comparator for present-day Indian institutional data, though differences in patient selection, treatment era, and supportive-care practice need to be kept in mind.

Institutional evaluation still matters against this backdrop, because real-world outcomes reflect more than drug efficacy alone — they also capture how quickly a

patient is diagnosed, how much disease burden they carry at presentation, the quality of supportive care available, how treatment-related complications are managed, and whether induction and subsequent therapy can actually be completed. This study describes the clinical profile, laboratory and coagulation abnormalities, molecular findings, treatment patterns, complications, induction response, and outcomes of APL patients treated at our institution. By examining these parameters in an ambispective, real-world cohort, we aimed to capture the practical challenges of contemporary APL management and identify where earlier recognition, better supportive care, or treatment optimization might improve outcomes. [1,23-28]

MATERIALS AND METHODS

Study design and setting

This was an ambispective, single-institution observational cohort study of patients diagnosed with acute promyelocytic leukemia (APL) and managed at the study institution. The cohort comprised patients diagnosed between 2021 and 2025. Data were collected over a one-year data-collection period, combining retrospective review of available medical records with prospective follow-up information where this was available; the exact dates of the data-collection period should be added before submission. The study was conducted in the Department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences, Indore, Madhya Pradesh, India.

Study population

Patients with a clinical diagnosis of APL managed at the study institution during the defined period were considered for inclusion. A total of 21 patients were included in the final analysis. Both conventional APL and one patient with atypical APL were retained in the cohort; the atypical

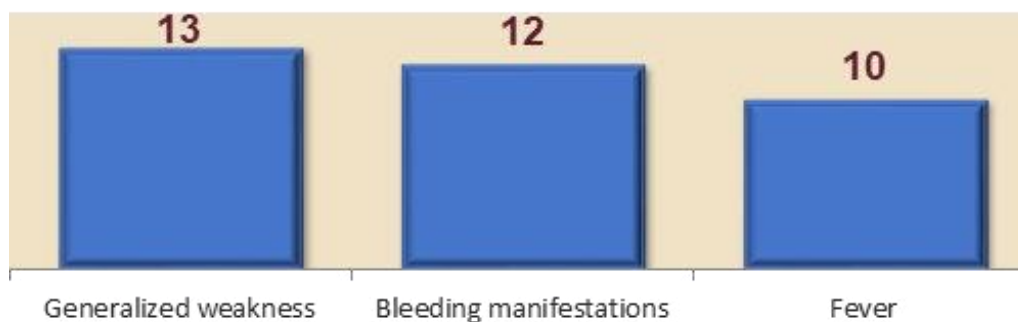


Figure 1: Presenting symptoms

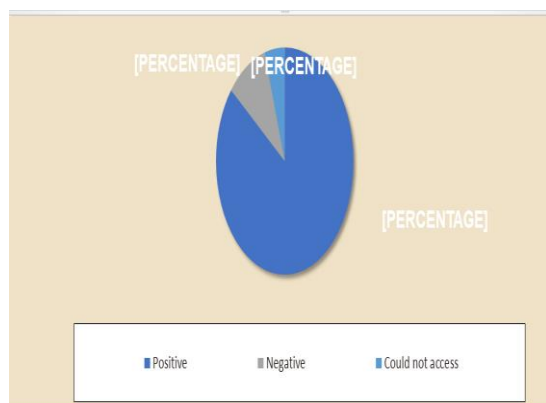


Figure 2: PML::RARA by FISH

case was identified separately during interpretation of the molecular findings.

Clinical and laboratory data collection

Data were abstracted from institutional clinical records using a predefined data collection sheet. Variables recorded included age, sex, year of diagnosis, comorbidities, bleeding symptoms, generalized weakness, visual disturbance, fever, baseline ECOG performance status, hemoglobin, WBC count, platelet count, peripheral blast and promyelocyte proportions, coagulation parameters, fibrinolysis markers, bone marrow findings, and PML::RARA FISH results. Treatment-related variables included induction regimen, daunorubicin exposure, duration of induction, treatment complications, differentiation syndrome, QT prolongation, treatment delay, induction prolongation due to complications, post-induction complete remission, consolidation regimen, and consolidation completion. Current disease status was also recorded.

Diagnostic assessment and molecular classification

The diagnosis of APL was based on the clinical, hematological, and morphological information documented in the institutional records, supplemented by molecular testing where available. PML::RARA FISH results were recorded as detected, negative, or unavailable, according to the source records. One patient with a negative PML::RARA FISH result was documented clinically as having atypical APL with t(11;17) and was therefore considered separately from conventional PML::RARA-positive APL in the analysis of molecular results. No molecular result was imputed when testing was unavailable. Current ELN guidance recommends molecular confirmation of PML::RARA or a recognized rare molecular variant.[1]

Risk classification

Risk category was recorded according to the institutional dataset and categorized as low, intermediate, or high risk where documented. For interpretation against the broader APL literature, this was considered alongside baseline WBC and platelet counts, consistent with the Sanz/ELN framework, which classifies risk primarily on these two parameters. Because the source spreadsheet already contained an institutionally recorded risk field, that recorded category was retained for the primary descriptive analysis; risk categories should be verified against individual baseline WBC and platelet values before submission.[1,2]

Treatment

Induction treatment in the cohort consisted predominantly of arsenic trioxide (ATO), given either alone or in combination with all-trans retinoic acid (ATRA). The dataset also captured daunorubicin exposure, including frequency of use. Hydroxyurea use was not captured as a dedicated variable in the final dataset and so was not included as an independent treatment exposure here. Treatment duration, treatment delay, and induction prolongation due to complications were recorded as documented in the clinical records.

Assessment of treatment-related complications

Treatment-related complications were recorded from the institutional clinical documentation. Specific variables included differentiation syndrome, QT prolongation, and other in-treatment complications such as cerebral venous thrombosis, pseudotumor cerebri, liver function test derangement, and death during treatment. The analysis reflects clinical diagnoses as documented in the source records; complications were not retrospectively adjudicated against standardized grading criteria where the underlying information was insufficient to do so.

Response assessment and outcome definitions

The primary treatment response assessed here was

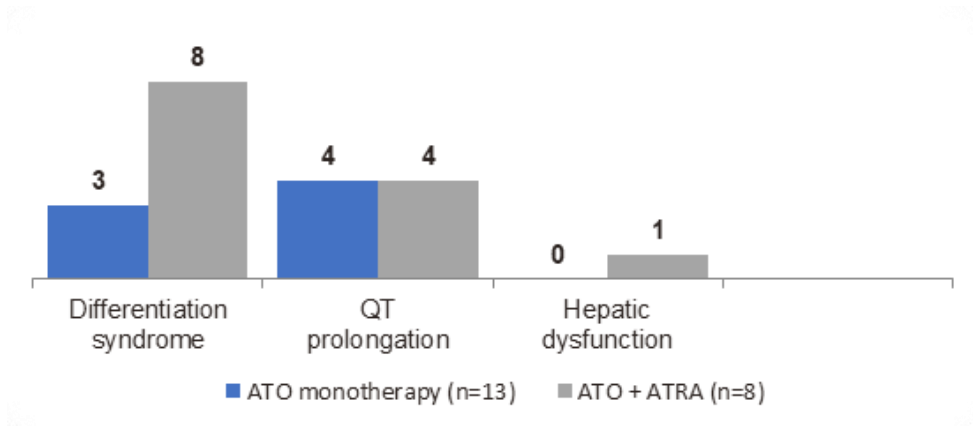


Figure 3: Treatment-related complications by induction regimen

documented complete remission following induction. Patients were classified as having achieved complete remission when a post-induction CR was recorded in the source data; those who died before a post-induction assessment were not considered response-evaluable. Secondary outcomes included treatment-related complications, observed mortality, consolidation treatment, and current disease status. Because exact dates of death and last follow-up were not uniformly available, time-to-event outcomes — 7-day or 30-day early mortality, overall survival, event-free survival, disease-free survival — were not formally estimated.

Follow-up

Follow-up information was drawn from institutional records available during the data-collection period. Patients were categorized at the time of analysis as alive/on follow-up, lost to follow-up, or deceased. Where consolidation treatment was documented, the regimen and completion status were recorded.

Statistical analysis

Continuous variables were summarized as median and range, given the small cohort size and non-normal distribution of several variables; categorical variables were summarized as frequencies and percentages. Exploratory comparisons between survivors and deceased patients, and between treatment groups, were descriptive only. Given the small sample size (n=21) and limited number of deaths, inferential testing and multivariable regression were not considered appropriate as primary analyses; any statistical comparisons in the final manuscript will be clearly labeled as exploratory.

RESULTS

Patient characteristics

Twenty-one patients with acute promyelocytic leukemia were included in the final analysis. Median age at diagnosis was 34 years (range, 5–72 years); 13 patients (61.9%) were male and 8 (38.1%) were female. Seven patients (33.3%) had a documented comorbidity, while the remaining 14 (66.7%) had none recorded. Median baseline ECOG performance status was 2.

By year of diagnosis, the cohort included 1 patient in 2021, 2 in 2022, 5 in 2023, 10 in 2024, and 3 in 2025. Bleeding symptoms were the most common presenting feature, seen in 13 patients (66.7%). Generalized weakness

Table 1: Baseline demographic and clinical characteristics of the cohort

Characteristic	n	%
Total cohort	21	100.0
Male sex	13	61.9
Female sex	8	38.1
Comorbidity present	7	33.3
Bleeding symptoms	12	57.1
Weakness	12	57.1
Visual disturbance	6	28.6
Fever	10	47.6
High TLC	9	42.9
Platelets <40 × 10 ⁹ /L	15	71.4
Coagulation abnormality	9	42.9
Fibrinolysis products elevated	21	100.0

was reported in 12 patients (57.1%), fever in 10 (47.6%), and visual disturbance in 6 (28.6%).

Nine patients (42.9%) had a high total leukocyte count at presentation. Fifteen patients (71.4%) had a platelet count below $40 \times 10^9/L$, and 9 (42.9%) had a documented coagulation abnormality.

Hematological and laboratory parameters

Median baseline hemoglobin was 7.8 g/dL (range, 2.6–11.8 g/dL), and median baseline WBC count was $5.34 \times 10^9/L$ (range, 0.68 – $206.91 \times 10^9/L$). Median platelet count was $28 \times 10^9/L$ (range, 8 – $78 \times 10^9/L$).

The range of baseline leukocyte counts was striking, spanning from $0.68 \times 10^9/L$ to $206.91 \times 10^9/L$, and points to substantial heterogeneity in disease burden across the cohort. Fibrinolysis products were documented as elevated in all 21 patients (100%).

Peripheral blast and promyelocyte percentages were inconsistently documented, with several records lacking a quantitative figure. Bone marrow examination was documented in 10 patients; the remaining 11 had no bone marrow examination recorded in the dataset.

Risk distribution and molecular diagnosis

Using the risk category recorded in the institutional dataset, 13 patients (61.9%) were classified as low risk and 7 (33.3%) as high risk. One further patient (4.8%) had atypical APL with a documented t(11;17) abnormality and was recorded separately as high risk; including this case, 8 patients in total (38.1%) were recorded with a high-risk phenotype.

PML::RARA FISH was reported as detected in 18 patients (86.2%). 2 patients (9.0%) had no FISH result available, and one (4.8%) had a negative result — the same patient documented as having atypical APL with t(11;17), and therefore not classified as conventional PML::RARA-positive disease.

Induction treatment

Arsenic trioxide (ATO) alone was the predominant induction strategy, used in 13 patients (61.9%); the remaining 8 (38.1%) received ATO plus ATRA. Five patients (23.8%) had documented daunorubicin exposure during treatment — three in the ATO-plus-ATRA group and two in the ATO-alone group. Induction duration ranged from 6 to 61 days, with a median of approximately 30 days.

Treatment-related complications

Treatment-related complications were documented in 20 of 21 patients (95.2%). Differentiation syndrome was the most frequent, occurring in 11 patients (52.4%), followed by QT

prolongation in 8 (38.1%). Cerebral venous thrombosis, pseudotumor cerebri, and liver function test derangement were each recorded in a single patient.

Differentiation syndrome was more common with ATO alone — 8 of 13 patients (61.5%) — than with ATO plus ATRA, at 3 of 8 (37.5%). QT prolongation showed the opposite pattern: 4 of 13 patients (30.8%) on ATO alone versus 4 of 8 (50.0%) on ATO plus ATRA. Given the small, non-randomized cohort, these subgroup figures are descriptive only and should not be read as evidence of a comparative treatment effect.

Treatment delay and induction course

Induction was recorded as prolonged because of a complication in 20 of 21 patients (95.2%). Numerical treatment-delay values, where available, ranged from 2 to 25 days. In five records, the treatment-delay field instead contained a clinical outcome (respiratory failure or STEMI) rather than a number; these entries have been treated as outcomes, not delay values, and will need further cleaning before a formal delay analysis can be done.

Complete remission

Sixteen of 21 patients (76.2%) achieved documented complete remission after induction. The remaining 5 (23.8%) did not reach a documented post-induction CR — all five died during treatment or follow-up before that assessment could be made. Because these five deaths preceded any documented response assessment, the apparent 100% CR rate among response-evaluable patients reflects survivorship bias and should not be reported as the cohort's overall CR rate.

Mortality and current status

Five patients (23.8%) were deceased at the time of analysis; 16 (76.2%) remained alive. Cause of death was respiratory failure in three patients and ST-elevation myocardial infarction in one; the cause was not documented for the fifth. Exact dates of death were unavailable, so time-specific early-mortality rates could not be calculated.

Patients who died had a markedly higher median baseline WBC count than survivors ($43.0 \times 10^9/L$ versus $5.185 \times 10^9/L$) and a lower median baseline platelet count ($22 \times 10^9/L$ versus $37.5 \times 10^9/L$); all five had platelet counts below $40 \times 10^9/L$. Bleeding symptoms were present in 4 of 5 deceased patients (80.0%) versus 10 of 16 survivors (62.5%), and visual disturbance in 4 of 5 (80.0%) versus 2 of 16 (12.5%). High TLC at presentation was documented in 3 of 5 deceased patients (60.0%) versus 6 of 16 survivors (37.5%). Given the small number of deaths, these comparisons remain exploratory.

Consolidation and follow-up

Consolidation treatment was documented in 16 patients (76.2%); the remaining five did not proceed, having died beforehand. Among those consolidated, ATO-based regimens predominated, either alone or with ATRA; one patient received ATRA-based consolidation. Formal survival estimates were not calculated, since dates of death and last follow-up were not consistently available.

DISCUSSION

This ambispective institutional study offers a real-world picture of how acute promyelocytic leukemia (APL) presents, is treated, and evolves over the short term in a cohort of 21 patients. A few observations stand out. Bleeding was the most common presenting feature, consistent with the coagulopathy that defines APL. The cohort also included a clinically important subgroup with high-risk disease and marked leukocytosis — one patient presented with an extreme baseline white-cell count of $206.91 \times 10^9/L$. Arsenic trioxide was the dominant induction agent, used either alone or with ATRA, and differentiation syndrome and QT prolongation were both frequent, well-documented complications. Sixteen patients achieved documented complete remission, but five died before a post-induction assessment could even be made. Together, these findings underline a familiar tension in APL: the disease itself is highly curable, but patients remain vulnerable during the earliest phase of treatment.

That tension is easier to appreciate against the backdrop of what modern trials have shown is possible. ATRA- and ATO-based regimens can now achieve very high cure rates while sharply reducing exposure to conventional chemotherapy. The APL0406 trial established ATRA plus ATO as an effective, chemotherapy-free option for non-high-risk disease, with excellent long-term event-free and overall survival.[3,6] The AML17 trial extended this further, showing that ATRA plus ATO was feasible across risk groups and associated with a higher cure rate and less toxicity than ATRA plus idarubicin, though liver enzyme abnormalities were more common with ATO.[4,19] These two trials essentially define the modern treatment paradigm and explain why ATO was the backbone of therapy in our own cohort.

The burden of bleeding at presentation was one of the most striking findings. Fourteen of 21 patients (66.7%) presented with bleeding, and 15 had platelet counts below $40 \times 10^9/L$. This fits squarely with APL's underlying biology, in which abnormal promyelocytes drive a coagulopathy that is simultaneously procoagulant, fibrinolytic, and

inflammatory. Thomas's historical review makes clear that hemorrhagic diathesis was the leading cause of death before ATRA and remained a major contributor to early mortality even after chemotherapy became available.[2] That history is precisely why modern ELN guidance treats suspected APL as a medical emergency — recommending immediate ATRA and aggressive correction of coagulopathy without waiting for molecular confirmation.[1] The scale of bleeding in our cohort is a reminder of how costly delays in recognition, referral, testing, or treatment initiation can be in this disease.

High-risk disease and marked leukocytosis were also prominent. Nine patients had a high leukocyte count at presentation, including the extreme case noted above. Baseline WBC remains one of the more reliable prognostic markers in APL — the Sanz classification uses it, together with platelet count, to separate low-, intermediate-, and high-risk disease, with a WBC above $10 \times 10^9/L$ defining high risk.[1,2,23,24,26,28] Patients who died in our cohort had a substantially higher median baseline WBC than survivors (43.0 versus $5.185 \times 10^9/L$). The number of deaths is far too small to support formal inference, but the direction is biologically plausible and lines up with established evidence linking leukocytosis to differentiation syndrome, hemorrhage, and early death.[1,2,23,24,26,28] It is a clinically meaningful signal, even if it can only be described as exploratory here.

Platelet counts told a similar story. Median baseline platelets were lower among patients who died than among survivors, and all five deaths occurred in patients with platelet counts under $40 \times 10^9/L$. ELN guidance stresses maintaining adequate platelet and fibrinogen levels during induction, since bleeding risk is greatest early on.[1] In a retrospective cohort like ours, platelet count is also simply a practical, immediately available marker for flagging patients who need especially close monitoring. That said, it should not be read in isolation — coagulopathy severity, active bleeding, fibrinogen depletion, hyperleukocytosis, and organ dysfunction all interact, and any one of them alone is unlikely to fully explain outcome.

Differentiation syndrome, documented in 11 patients (52.4%), was another major finding. It is a recognized complication of both ATRA and ATO, capable of producing fever, weight gain, edema, respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, hypotension, and renal dysfunction.[1,2] Thomas describes it as a systemic inflammatory process tied to cytokine release, capillary leak, adhesion-molecule changes, and tissue infiltration by differentiating cells, with risk rising alongside

leukocyte count.[1,2,15,16] Our 52.4% rate is considerably higher than the 6.9% reported in the earlier Indian series by Mathews and colleagues, who used hydroxyurea extensively to control leukocytosis.[5] That gap should not be read as evidence of a true rise over time — diagnostic criteria, protocols, prophylactic steroid use, and patient selection could all differ between the two cohorts — but it does suggest that differentiation syndrome was a major part of the clinical burden during induction here, and it warrants closer analysis of how it relates to baseline WBC, regimen, and outcome.

QT prolongation, documented in 8 of 21 patients (38.1%), is worth flagging as well. ATO is highly effective but carries a well-known risk of QT/QTc prolongation, and current ELN guidance calls for regular ECG monitoring, correction of electrolyte disturbances, and interruption of ATO if clinically significant prolongation occurs.[1] Our dataset does not include serial QTc values, the correction formula used, electrolyte levels, or standardized grading, so this figure should be read as the frequency of documented QT prolongation rather than a measure of clinically significant cardiotoxicity — ECG changes during ATO exposure are common and do not necessarily translate into arrhythmia. The AML17 trial similarly found that ATO carries a distinct toxicity profile: less alopecia and oral toxicity, but more frequent liver enzyme elevation, compared with ATRA plus idarubicin.[4]

Perhaps the most consequential finding is the observed mortality of five patients (23.8%). APL is now considered the most curable form of adult AML, and yet early death remains a real limitation in routine practice — the updated ELN recommendations specifically call out early death before or during induction as one of the field's remaining challenges.[1] Our cohort illustrates that problem clearly:

every one of the 16 patients who reached a documented post-induction assessment achieved complete remission, while the other five died before that assessment was possible. So the main barrier to cure here was not induction resistance among survivors — it was losing patients during the vulnerable induction window before a formal response could even be measured. These cannot be labeled as 7-day or 30-day early deaths, since exact dates are not available, and that terminology should be avoided in the final manuscript — but the timing relationship between treatment start, complications, and death remains an important signal.

The recorded causes of death were respiratory failure in three patients, STEMI in one, and an undocumented cause in the fifth. Respiratory failure in APL can stem from several overlapping processes — severe differentiation syndrome,

pulmonary hemorrhage, infection, cardiopulmonary compromise, or other critical illness — so without more detailed records, it would be a stretch to attribute these deaths to differentiation syndrome on the basis of respiratory failure alone. This matters because differentiation syndrome can look clinically similar to infection or heart failure, and ELN guidance is explicit that it is a clinical diagnosis without pathognomonic features.[1] Likewise, the STEMI-related death should not automatically be read as ATO-related cardiotoxicity without ECG, troponin, electrolyte, and QTc data. Keeping documented causes separate from inferred mechanisms strengthens the credibility of what can actually be claimed here.

The complete-remission figures need similarly careful framing. Sixteen of 21 patients (76.2%) achieved documented post-induction CR, and every patient who survived to that assessment achieved it — which, taken at face value, looks like a 100% response rate among evaluable patients. But the five who died before assessment cannot simply be dropped from an intention-to-treat description of overall outcome. Clinical trials typically report very high CR rates partly because patients are managed under structured protocols with standardized evaluation and heavy supportive care.[3,4] In a real-world cohort, dying before response assessment is itself an outcome that needs reporting. The most transparent way to present this is therefore to give both figures: the overall cohort-level CR proportion (16/21) and the fact that every evaluable survivor achieved CR.

The molecular data add an interesting diagnostic angle. FISH was positive in 16 patients, unavailable in four, and negative in one — the patient later documented as atypical APL with t(11;17). Not every morphologically convincing APL case carries the canonical PML::RARA rearrangement; Thomas catalogs several rare RARA fusion partners, including PLZF-RARA in t(11;17), and notes that the specific partner can affect sensitivity to differentiation therapy.[2] ELN guidance likewise recommends confirming either PML::RARA or a recognized rare variant.[1] The atypical case in our cohort reinforces why rapid, thorough molecular workup matters — and argues against simply treating every FISH-negative but morphologically suggestive case as conventional APL without clarifying the underlying molecular lesion.

It is worth situating these findings against the earlier Indian experience reported by Mathews and colleagues. In their 72-patient cohort, treated predominantly with single-agent ATO, hematologic CR reached 86.1%, with 3-year EFS, DFS, and OS of 74.9%, 87.2%, and 86.1%

respectively.[5,20-23] Hydroxyurea was used in 73.6% of their patients to control leukocytosis, which the authors suggested may explain their comparatively low rate of differentiation syndrome.[5,20-23] Our cohort is much smaller, drawn from a later treatment era, and used a mix of ATO alone and ATO-plus-ATRA — and we lack the longitudinal molecular and survival data needed for a meaningful long-term comparison. Still, the contrast between the two series is a useful reminder of how much institutional factors, supportive-care practice, cytoreduction strategy, and patient selection can shape outcomes even when ATO sits at the center of treatment in both. A larger, more recent Northern Indian tertiary-center cohort (n=102) reported a CR rate of 76.4% and induction mortality of 24.5%, with differentiation syndrome in 56% of adults — figures that line up closely with our own CR (76.2%) and mortality (23.8%).[23] The cohorts differ in size, protocol, and completeness of follow-up, but that concordance strengthens the case that our institutional findings reflect broader patterns in contemporary Indian real-world practice.

Treatment delay is another area worth attention, though the underlying variable needs cleaning before publication, since some entries mix numerical delays with descriptions of adverse outcomes. APL is uniquely sensitive to diagnostic and therapeutic delay, because coagulopathy can turn fatal before leukemia-directed therapy has had time to work. That is why ELN guidance emphasizes starting ATRA at the first clinical suspicion of APL, alongside transfusion support and rapid molecular confirmation. [1,24-28] Thomas's historical account makes essentially the same point in a different way: the major survival gains in APL came not only from better drugs, but from recognizing the urgency of the coagulopathy and the need for early differentiation therapy.[2] In a tertiary-care setting, cutting down delays in referral, diagnosis, molecular testing, and treatment initiation may matter just as much as the choice of regimen itself.

The main strength of this study is that it reflects routine institutional practice rather than a curated trial population. The cohort spans pediatric and adult patients, a wide range of WBC counts, both low- and high-risk disease, conventional and atypical APL, and more than one ATO-based treatment approach — giving a realistic picture of how APL actually presents and is managed day to day. It also captures the complications that tend to dominate APL care in practice: differentiation syndrome, QT prolongation, and bleeding. That kind of information is useful precisely because it can point to where institutional protocols and supportive-care pathways need strengthening.

There are, however, real limitations to keep in mind. The sample is small — 21 patients and five deaths — which limits statistical power and rules out reliable multivariable analysis. The study is observational, and treatment was not randomized, so comparisons between ATO alone and ATO plus ATRA remain vulnerable to confounding by indication. Molecular confirmation was incomplete, and the atypical APL case sits in a genuinely different genetic category. Definitions and grading for complications like differentiation syndrome and QT prolongation were not standardized in the source data, which likely affects the incidence figures. Exact dates of death and last follow-up were not consistently recorded, ruling out formal Kaplan-Meier survival estimates or precise 7-day/30-day mortality figures. Some variables — the risk category field and the treatment-delay field in particular — need harmonization before formal statistical analysis. And because this is a single-institution cohort, how far these findings generalize is inherently limited.

Even with those caveats, the findings have practical implications. Frequent bleeding at presentation, a substantial high-risk subgroup, high rates of differentiation syndrome and QT prolongation, and mortality occurring before documented remission all point toward the induction period — rather than later disease control — as the more urgent quality-improvement target. A standardized institutional APL pathway might include immediate ATRA at the first suspicion of the diagnosis, rapid molecular confirmation, protocolized blood-product support, close monitoring of WBC trajectory and differentiation syndrome, structured corticosteroid initiation, frequent electrolyte and QTc checks during ATO therapy, and clear documentation of when complications occur and why. Prompt cytoreduction and close monitoring matter especially for high-risk disease. These steps align with current ELN recommendations and could plausibly reduce preventable treatment-related morbidity.[1,23,25-28]

In short, this institutional experience reflects the central paradox of modern APL: it is a highly curable disease, provided patients survive the vulnerable early phase of treatment. In our cohort, ATO-based therapy produced a high rate of documented complete remission among patients who reached response assessment, but treatment-related morbidity and mortality remained substantial. Bleeding at presentation, hyperleukocytosis, differentiation syndrome, and cardiac monitoring issues were all prominent features. Taken together, these findings support continued emphasis on rapid diagnosis, immediate disease-directed therapy, and meticulous supportive care. Future institutional work should

prioritize prospectively capturing treatment-initiation times, detailed grading of differentiation syndrome and cardiotoxicity, complete molecular response assessment, exact death dates, and standardized long-term follow-up — improvements that would let future cohorts move past descriptive reporting and start identifying which modifiable factors most strongly influence survival in real-world APL care.

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