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Beyond Standard Protocols: Real-World Challenges And Innovative Solutions in Pediatric Leukemia Management. Experience from A Tertiary Oncology Center Integrating Mrd-Guided Therapy and Novel Agents

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Abstract

Background: Pediatric acute leukemias represent a heterogeneous group of malignancies with variable prognoses. Although survival rates have improved significantly with risk-adapted protocols and advances in supportive care, management becomes complicated in the presence of comorbidity, age-related challenges, or rare molecular subtypes.

Objective: To present three pediatric cases—infantile AML, ALL in a child with Down syndrome, and APML with differentiation syndrome—demonstrating diagnostic dilemmas, therapeutic challenges, and the potential of modified regimens.

Methods: Retrospective descriptive case series at a tertiary pediatric oncology unit, examining clinical profiles, treatment adaptations, and outcomes.

Results: All patients achieved remission. Two required significant modifications due to toxicity or preexisting conditions. Integration of MRD-guided strategies, novel therapeutic agents like azacitidine and venetoclax, and aggressive management of complications led to favorable outcomes.

Conclusion: Personalized protocols, vigilant monitoring, and early recognition of complications are essential in pediatric leukemia care. Incorporation of newer agents may rescue patients where traditional therapies fail or are poorly tolerated.

Introduction

Acute leukemias constitute the most common pediatric cancers, with ALL comprising nearly 75% and AML around 20% of childhood leukemia cases [1]. Despite impressive gains in survival—up to 85–90%

in ALL and around 65–70% in AML—certain subgroups, including infants, children with genetic syndromes like Down syndrome, and those with rare variants such as APML, continue to present unique diagnostic and therapeutic hurdles [2,3].

Infantile leukemia is biologically aggressive and typically harbors KMT2A rearrangements, which confer poor outcomes. Similarly, children with Down syndrome demonstrate unique drug sensitivities and comorbidities, often necessitating deviations from standard protocols [4,5]. Acute promyelocytic leukemia (APML), though curable with targeted therapy, carries a high early mortality rate due to coagulopathy and differentiation syndrome [6].

In this case series, we discuss three children with hematologic malignancies and challenging clinical backgrounds. These cases underscore the role of multidisciplinary care, flexible treatment algorithms, and integration of newer therapies to enhance survival while preserving quality of life.

Case Series

Case 1: Infantile AML Treated with Azacitidine and Venetoclax

Presentation:

A 14-month-old girl presented with high-grade fever, progressive pallor, and excessive irritability. CBC showed hemoglobin 6.2 g/dL, platelets 12,000/mm³, and leukocytosis with WBC 78,000/mm³. Peripheral smear revealed blasts with monocytic morphology. Bone marrow aspirate and immunophenotyping confirmed AML M5 with CD33, CD13, and CD14 positivity.

Initial Therapy & Complications:

She was started on the 7+3 induction regimen (cytarabine 100 mg/m² for 7 days and daunorubicin 45 mg/m² for 3 days). The child developed febrile neutropenia, mucosal bleeding, and Klebsiella sepsis requiring ICU care. Platelet count failed to recover by day 42, and hepatic dysfunction worsened. Based on this poor tolerance, standard chemotherapy was discontinued.

Modified Approach:

After detailed counseling, a low-intensity regimen was initiated. Azacitidine 75 mg/m² was administered subcutaneously for 7 days every 28 days, combined with oral venetoclax (ramped up to 200 mg/m²/day). The regimen was well tolerated, with MRD negativity achieved by the second cycle.

Outcome:

The patient remains in remission at 10 months post-therapy. She has not required transfusions for 6 months and continues to meet neurodevelopmental milestones.

Clinical Relevance:

Infant AML, particularly with KMT2A rearrangement, is associated with poor survival. Venetoclax-based combinations, although off-label in pediatrics, offer a less toxic and effective alternative, especially in fragile patients [7].

Case 2: Down Syndrome–Associated ALL with Congenital Heart Disease

Presentation:

A 4.5-year-old girl with trisomy 21 presented with intermittent fevers, weight loss, and fatigue. Examination revealed hepatosplenomegaly and systolic murmur. Hemogram showed Hb 7.8 g/dL, WBC 34,000/mm³ with 68% lymphoblasts, and platelets 58,000/mm³. Echocardiography identified a PDA (6 mm). Bone marrow confirmed precursor B-cell ALL.

Challenges & Treatment:
Chemotherapy was initiated using the BFM-2002 protocol. On day 5, she developed heart failure and hypotension. Chemotherapy was paused, and PDA was surgically closed. Re-induction was resumed with anthracycline sparing. Intrathecal methotrexate doses were reduced, and 6-mercaptopurine was modified. PEG-asparaginase was delayed due to grade 3 transaminitis.

Outcome:
The patient is MRD-negative and on maintenance. She is tolerating oral medications well, with regular monitoring of cardiac function and neurodevelopment. No hospital admissions were recorded in the last 6 months.

Clinical Relevance:
Children with Down syndrome have heightened chemotherapy sensitivity, particularly to methotrexate and anthracyclines. Pre-existing cardiac anomalies compound toxicity. Tailored regimens with vigilant monitoring improve tolerance and outcomes [5,6].

Case 3: Adolescent APML with Differentiation Syndrome

Presentation:
A 16-year-old boy presented with petechiae, mucosal bleeding, and low-grade fever. Blood work revealed pancytopenia with 2,800/mm³ WBC and 8,000/mm³ platelets. Bone marrow showed abnormal promyelocytes. FISH confirmed t(15;17) translocation.

Treatment & Complications:
All-trans retinoic acid (ATRA) and arsenic trioxide (ATO) were started. On day 4, the patient developed differentiation syndrome: respiratory distress, fever, and pleural effusion. Dexamethasone was initiated with temporary drug cessation. Liver enzymes elevated on day 10, and febrile neutropenia ensued. ICU support included platelet transfusions (>90 units) and IV antibiotics.

Outcome:
After completing induction and four consolidation cycles, he achieved molecular remission. Now off treatment, he has resumed school and cleared the JEE Mains exam—an indicator of restored neurocognitive function.

Clinical Relevance:
APML is curable in over 90% of cases if early death is avoided. Prompt initiation of ATRA/ATO and preemptive management of complications such as differentiation syndrome and DIC are critical [8].

Discussion
This series exemplifies the complexity of pediatric leukemia care in real-world settings and highlights how innovation and personalization can change outcomes in vulnerable populations.

Infant AML—An Aggressive Entity:
Infants with AML have lower survival due to biologically aggressive disease, increased frequency of KMT2A rearrangements, and lower tolerance to chemotherapy. Standard induction regimens often cause life-threatening toxicities. Venetoclax, a BCL-2 inhibitor, has shown synergy with hypomethylating agents such as azacitidine in adult AML and is now being trialed in children. Our patient's favorable response without myelosuppression reaffirms the utility of such regimens in high-risk infants [7].

Syndromic ALL—Tailoring Required:
Down syndrome–associated ALL carries a paradox: excellent prognosis if tolerated, but high risk of toxicity. These patients exhibit hypersensitivity to cytotoxic drugs due to altered TPMT and MTHFR activity. Standard protocols may lead to mucositis, sepsis, or cardiotoxicity. Congenital cardiac defects further complicate anthracycline use. Modified regimens with reduced doses, close echocardiographic surveillance, and delay of hepatotoxic drugs help mitigate risks and maintain efficacy [5,6].

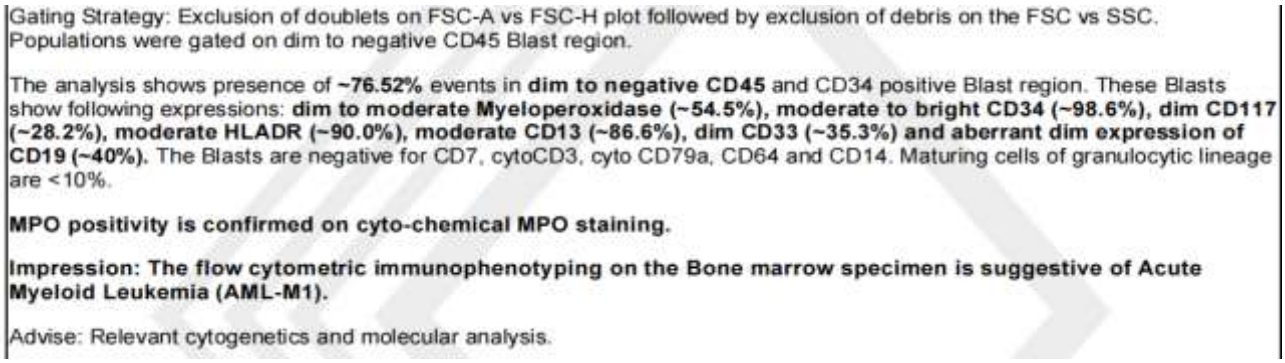
APML—A Race Against Time:
APML stands apart for its responsiveness to targeted therapy (ATRA and ATO), making it one of the few curable leukemias without conventional chemotherapy. However, early coagulopathy, DIC, and differentiation syndrome can be rapidly fatal. This case demonstrates the importance of early diagnosis, rapid initiation of ATRA, and proactive steroid use. The patient's academic success post-treatment reflects effective supportive care with preserved neurocognitive outcomes [8].
Key learning points
MRD-Guided Treatment: In all three cases, MRD assessment guided therapy decisions. It offers a robust marker for risk stratification and response, and increasingly, MRD-negative remission is used as an endpoint in clinical trials.
Novel Agents and Off-Label Use: Venetoclax and azacitidine are not standard in pediatric protocols but offer viable alternatives for fragile or refractory cases. Their role is expanding as pediatric trials catch up with adult data.
Supportive Care and Multidisciplinary Input: ICU care, cardiology input, nutritional rehabilitation, and psychological support were essential across cases. Pediatric leukemia management now demands a holistic, team-based approach.
Family Counseling and Consent: Families must be educated about the rationale behind modifications, possible side effects, and long-term monitoring needs. In our setting, shared decision-making was crucial, especially where standard protocols were deviated.
Quality of Life: Long-term outcomes must consider neurodevelopment, cardiotoxicity, secondary malignancies, and psychosocial impacts. Our patients, despite severe disease and complications, are now leading healthy lives, highlighting that cure should not come at the cost of life quality.

Conclusion
Pediatric leukemias, though often curable, demand flexibility in treatment to accommodate biological, developmental, and psychosocial nuances. This series illustrates that with MRD-based monitoring, judicious use of novel agents, and individualized therapy, even children with high-risk disease or comorbidities can achieve remission and good quality of life. Future protocols must integrate precision medicine approaches and broaden access to targeted agents within pediatric trials.

References
1. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. *N Engl J Med*. 2015;373(16):1541–1552.
2. Pui CH, et al. Pediatric ALL: from biology to therapy. *Nat Rev Clin Oncol*. 2011;8(4):191–200.
3. Rubnitz JE, et al. Favorable outcome of childhood AML with FLT3-ITD and low allelic ratio. *J Clin Oncol*. 2008;26(34):5897–5901.

4. Zwaan CM, et al. Poor prognosis in infant AML. *Blood*. 2003;102(1):199–206.
5. Taub JW, et al. Treatment strategies for ALL in Down syndrome. *J Pediatr Hematol Oncol*. 2005;27(5):273–276.
6. Rabin KR, Poplack DG. Leukemia in children with Down syndrome. *Oncologist*. 2009;14(5):548–556.
7. Karol SE, et al. Azacitidine in pediatric myeloid malignancies. *Leukemia*. 2022;36(4):897–904.
8. Sanz MA, et al. Management of APL. *Blood*. 2009;113(18):4171–4179.

Fig 1 : Flow report of child with AML -M1 in a known case of Downs Syndrome



Gating Strategy: Exclusion of doublets on FSC-A vs FSC-H plot followed by exclusion of debris on the FSC vs SSC. Populations were gated on dim to negative CD45 Blast region.

The analysis shows presence of **~76.52%** events in **dim to negative CD45** and CD34 positive Blast region. These Blasts show following expressions: **dim to moderate Myeloperoxidase (~54.5%), moderate to bright CD34 (~98.6%), dim CD117 (~28.2%), moderate HLADR (~90.0%), moderate CD13 (~86.6%), dim CD33 (~35.3%) and aberrant dim expression of CD19 (~40%).** The Blasts are negative for CD7, cytoCD3, cyto CD79a, CD64 and CD14. Maturing cells of granulocytic lineage are <10%.

MPO positivity is confirmed on cyto-chemical MPO staining.

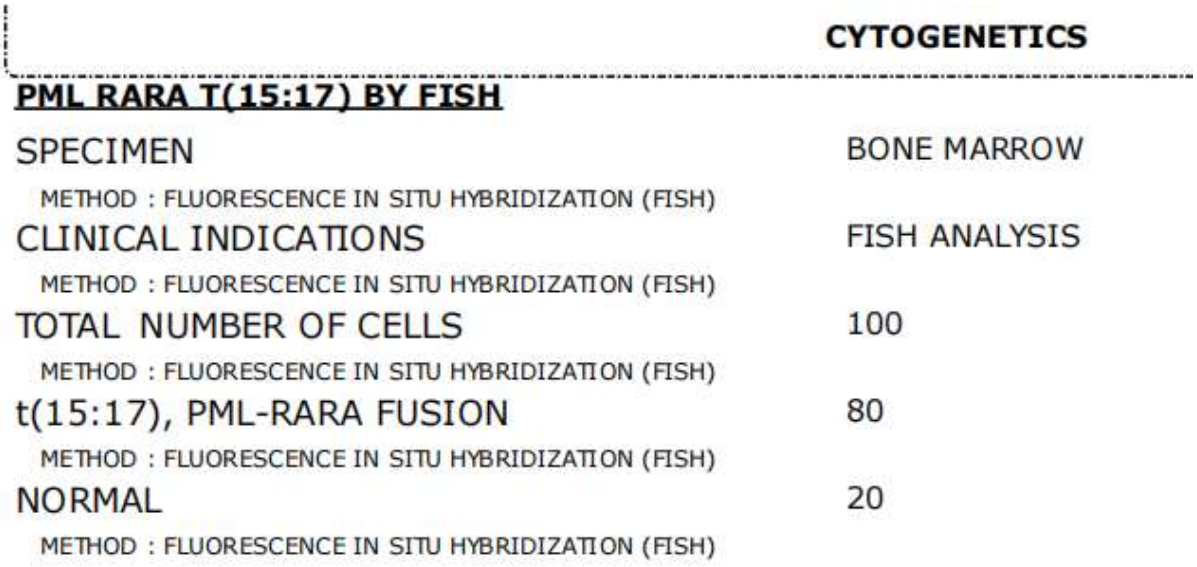
Impression: The flow cytometric immunophenotyping on the Bone marrow specimen is suggestive of Acute Myeloid Leukemia (AML-M1).

Advise: Relevant cytogenetics and molecular analysis.

Fig 2: Flow report of a child with ALL in a known case of Downs with Patent ductus arteriosus

B cell markers		
CD10	90	Bright
CD19	40	Dim
CD20	40	Heterogeneous
CD22	85	Moderate
CD66c	00	
CD73	00	
CD81	80	Dim
Cyto 79α	65	Dim

Fig 3A:- PML RARA Qualification report of 16 year old child at diagnosis

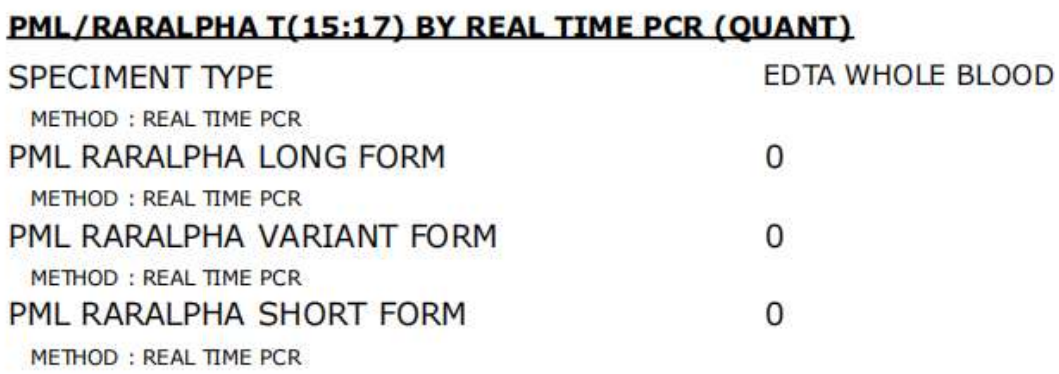


CYTOGENETICS

PML RARA T(15:17) BY FISH

SPECIMEN	BONE MARROW
METHOD : FLUORESCENCE IN SITU HYBRIDIZATION (FISH)	
CLINICAL INDICATIONS	FISH ANALYSIS
METHOD : FLUORESCENCE IN SITU HYBRIDIZATION (FISH)	
TOTAL NUMBER OF CELLS	100
METHOD : FLUORESCENCE IN SITU HYBRIDIZATION (FISH)	
t(15:17), PML-RARA FUSION	80
METHOD : FLUORESCENCE IN SITU HYBRIDIZATION (FISH)	
NORMAL	20
METHOD : FLUORESCENCE IN SITU HYBRIDIZATION (FISH)	

Fig 3 B:- PML RARA Quantifciation beforte Treatment



PML/RARALPHA T(15:17) BY REAL TIME PCR (QUANT)

SPECIMENT TYPE	EDTA WHOLE BLOOD
METHOD : REAL TIME PCR	
PML RARALPHA LONG FORM	0
METHOD : REAL TIME PCR	
PML RARALPHA VARIANT FORM	0
METHOD : REAL TIME PCR	
PML RARALPHA SHORT FORM	0
METHOD : REAL TIME PCR	

Figure 4: Clinical Management Flowchart for Pediatric APML

Initial suspicion (cytopenia + promyelocytes)

↓

Start ATRA immediately + confirm t(15;17)

↓

Assess for DIC and differentiation syndrome

↓

If DS → add steroids, hold ATRA/ATO if severe

↓

Continue ATRA + ATO until hematologic remission

↓

Molecular monitoring → confirm remission

Table 1: Clinical Summary of the Three Pediatric Cases

Parameter	Case 1: Infant AML	Case 2: Down Syndrome–ALL	Case 3: Adolescent APML
Age/Gender	14-month-old girl	4.5-year-old girl	16-year-old boy
Initial WBC Count	78,000/mm³	34,000/mm³	2,800/mm³
Diagnosis	AML M5 (monocytic)	Precursor B-cell ALL	APML (t(15;17)+)
Comorbidity	Severe sepsis, hepatic toxicity	PDA (surgically closed)	Differentiation syndrome, DIC
Standard Therapy	7+3 Induction	BFM-2002 protocol	ATRA + ATO
Complication	Refractory cytopenia, sepsis	Heart failure, hepatotoxicity	Pleural effusion, febrile neutropenia
Modified Treatment	Azacitidine + Venetoclax	Dose-modified chemo, delayed asparaginase	Temporary ATRA/ATO hold + steroids
MRD Status	Negative post 2nd cycle	Negative at day 33	Molecular remission
Current Status	In remission, transfusion-free	On maintenance, stable	Completed treatment, school resumed Cleared JEE entrance exam

Table 2: Risk-Adapted Treatment Considerations in Pediatric Leukemias

Subgroup	Challenge	Strategy
Infants (<1 year) with AML	Poor tolerance, KMT2A rearrangement	Use of low-intensity regimens like Azacitidine-Venetoclax
Children with Down Syndrome	Chemosensitivity, congenital defects	Anthracycline sparing, hepatoprotection, dose reduction
APML with Differentiation Syndrome	Early mortality from DS/DIC	Prompt ATRA initiation, dexamethasone prophylaxis