frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 15 September 2025
DOI 10.3389/fmed.2025.1651742

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OPEN ACCESS

EDITED BY
Sankaranarayanan Kannan,
University of Texas MD Anderson Cancer Center, United States

REVIEWED BY
Marco Antonio Murillo Maldonado,
Federico Gómez Children's Hospital, Mexico
Pritam Singha Roy,
Tata Medical Center, India

*CORRESPONDENCE
Mingqiang Ren
844198637@qq.com
Yan Chen
cyz600@163.com

†These authors have contributed equally to this work

RECEIVED 22 June 2025
ACCEPTED 18 August 2025
PUBLISHED 15 September 2025

CITATION
Gao L, An Y, Li Q, Shi S, Zhou J, Du Z, Huang P, Ren M and Chen Y (2025) Ultra-late relapse of acute promyelocytic leukemia 18 years after complete remission: a case report and literature review. *Front. Med.* 12:1651742. doi: 10.3389/fmed.2025.1651742

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Ultra-late relapse of acute promyelocytic leukemia 18 years after complete remission: a case report and literature review

Lu Gao[1,2,3†], Yang An[2,3†], Qian Li[2,3], Shuo Shi[2,3], Jie Zhou[4], Zuochen Du[2,3], Pei Huang[2,3], Mingqiang Ren[1*] and Yan Chen[2,3*]

[1]Department of Hematology, Affiliated Hospital of Zunyi Medical University, Zunyi, China, [2]Department of Pediatrics, Affiliated Hospital of Zunyi Medical University, Zunyi, China, [3]Guizhou Children's Hospital, Zunyi, China, [4]Department of Laboratory Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi, China

Late relapse of acute promyelocytic leukemia (APL) is associated with high mortality rates. While APL typically shows a low incidence of relapse after achieving complete remission (CR) for more than 7 years, we report a rare case of APL relapse occurring 18 years after CR was achieved. The patient was successfully treated with a combination of arsenic trioxide (ATO) and all-trans retinoic acid (ATRA), leading to favorable outcomes. Additionally, we review our treatment experience and provide a comprehensive analysis of the existing literature, summarizing the characteristics of reported APL cases that relapsed after maintaining CR for over 7 years.

KEYWORDS

acute promyelocytic leukemia, arsenic trioxide, all-trans retinoic acid, ultra-late relapse, Case Report and Literature Review

Introduction

Acute promyelocytic leukemia (APL), characterized by the t(15,17)(q22;q12) translocation, is a hematologic emergency that is associated with high early mortality due to coagulopathy (1, 2). Modern therapies combining all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) have led to complete remission (CR) rates exceeding 90% (3–6), with late relapses occurring more than 7 years post-CR being rare (7). This study presents an exceptional case of APL relapse occurring 18 years after the initial CR, successfully treated with ATO/ATRA-based therapy, and provides a comprehensive review of the current literature on ultra-late relapses in APL.

Case presentation

Initial presentation and treatment (1999)

In 1999, a 31-year-old woman was diagnosed with APL following evaluation for gingival bleeding and easy bruising. Laboratory studies at diagnosis revealed leukocytosis (white blood cell count, WBC: 13×10^9/L), thrombocytopenia (platelet count: 20×10^9/L), and bone marrow morphology showed a predominance of abnormal promyelocytes (80%). At that time, PML-RARA fusion testing was not yet part of routine clinical practice due to technological and logistical constraints, and thus molecular confirmation was not obtained. Induction

therapy with daunorubicin (45 mg/m^2/day for 3 days), cytarabine (100 mg/m^2/day for 7 days), and ATRA (25 mg/m^2/day for 28 days) led to complete hematologic remission. The patient subsequently received three cycles of consolidation chemotherapy (daunorubicin, cytarabine, and ATRA), followed by ATRA-based maintenance therapy (25 mg/m^2/day for 14 days per month) over 3 years.

Ultra-late relapse and reinduction (2017)

Eighteen years later, the patient presented with acute cutaneous ecchymosis and hemorrhagic gingivitis. Laboratory findings revealed pancytopenia (WBC 0.9 × 10^9/L with 30% blasts, platelets 41 × 10^9/L) and marked hypofibrinogenemia (0.6 g/L). Bone marrow aspiration confirmed relapsed APL (Figures 1A,B), supported by immunophenotypic markers (CD33$^+$, CD117$^+$, cMPO$^+$, HLA-DR$^-$, CD34$^-$), cytogenetic showing 46, XX, t(15,17)(q22;q12) [20 metaphases] (Figure 1D), and molecular evidence of PML-RARα fusion by FISH (Figure 1C). Reinduction therapy was initiated with ATRA (25 mg/m^2/day) and ATO (0.16 mg/kg/day). On day 5, the patient developed differentiation syndrome characterized by hypoxemia, serosal effusions, and a 5-kg weight gain due to fluid overload, necessitating ATRA discontinuation and initiation of dexamethasone. By day 10, the patient developed

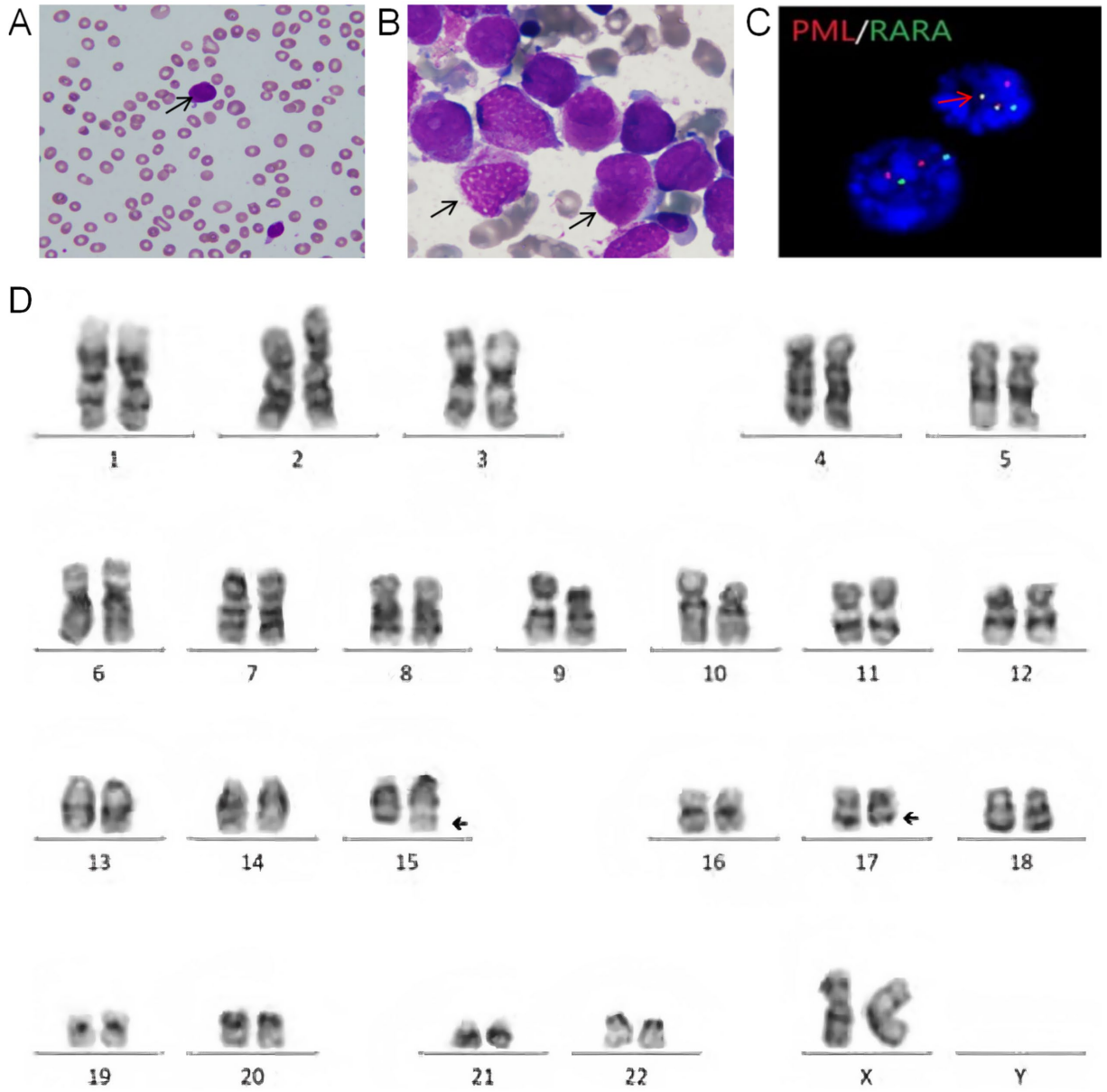

FIGURE 1
Diagnostic characteristics of late-relapse acute promyelocytic leukemia (APL). **(A)** Peripheral blood smear (Wright-Giemsa stain; 1,000 × magnification): Abnormal hypergranular promyelocytes. **(B)** Bone marrow aspirate (1,000 × magnification): Irregular promyelocytes exhibiting variable size, abundant cytoplasm, coarse azurophilic granules, and prominent Auer rods. **(C)** Fluorescence *in situ* hybridization (FISH): Positive PML-RARα fusion signals (yellow) using dual-color translocation probes. **(D)** Karyotype (G-banding): 46, XX, t(15,17)(q22;q12)—pathognomonic of APL per WHO classification.

disseminated intravascular coagulation (DIC), evidenced by severe thrombocytopenia (platelets < 20 × 10^9/L, prolonged PT/APTT, fibrinogen <0.5 g/L, and FDP 111.7 μg/mL), requiring intensive supportive management. Despite these complications, dual -agent therapy was resumed and achieved morphologic remission (3% promyelocytes) by day 30.

Consolidation and long-term outcomes

Two cycles of consolidation therapy with ATO and daunorubicin successfully eradicated detectable PML-RARα transcripts. Although the patient declined autologous hematopoietic stem cell transplantation, she completed a two-year maintenance regimen consisting of ATO and ATRA, administered in intermittent cycles as recommended for relapsed APL in published guidelines (8, 9), along with five prophylactic intrathecal administrations. Serial molecular monitoring during follow-up confirmed sustained molecular remission over a period of 8 years. This exceptional case underscores the potential for ultra-late APL relapse to remain curable with arsenic-based regimens, even 18 years of initial complete remission. A timeline summarizing the diagnostic and therapeutic course of this patient is presented in Figure 2.

Literature review

We analyzed 11 reported cases of ultra-late APL relapse (defined as relapse ≥7 years after achieving complete remission), including the current case, to elucidate clinical and therapeutic characteristics (Table 1) (7, 10–16). The cohort consisted of 5 male and 6 female patients, with a median age at relapse of 34 years (range: 15–52 years). All patients had received induction and consolidation therapy incorporating ATRA at the time of initial diagnosis, in accordance with standard APL treatment principles. However, only two patients received ATRA-based maintenance therapy, while the remaining nine did not undergo maintenance treatment.

The mean interval from initial diagnosis to relapse was 12.3 years (range: 7–18 years), with the longest latency period being 18 years. All patients harbored the hallmark t(15,17)(q22;q12)/PML-RARα fusion gene characteristic of APL. Relapse site analysis revealed that eight patients experienced bone marrow relapse, while three presented with extramedullary relapse (one involving intraparotid lymph nodes, one in the mastoid cavity, and one in the right mastoid process). Immunophenotypic analysis, reported for six patients, demonstrated the classical APL profile: $CD33^+$, $CD117^+$, $cMPO^+$, $HLA\text{-}DR^-$, and $CD34^-$. Notably, one patient exhibited an FLT3 mutation, transitioning from FLT3-ITD at initial diagnosis to FLT3-D835 at relapse, potentially contributing to leukemic persistence and clonal evolution.

In this limited cohort of ultra-late APL relapses, 10 out of 11 patients achieved remission following a variety of salvage regimens. Notably, all five patients who received arsenic-containing therapies (ATO ± ATRA) attained remission while other protocols, such as ATRA combined with chemotherapy demonstrated effectiveness. In 11 cases of late-relapsed APL, the duration of remission after achieving re-remission averaged 29.2 months (range: 0.2–96 months). Remarkably, the patient presented in our case report has remained in sustained remission for 8 years following reinduction therapy. To our knowledge, such long-term follow-up has not been previously documented in the context of ultra-late relapse, highlighting a significant gap in the existing literature regarding remission durability in this rare clinical scenario.

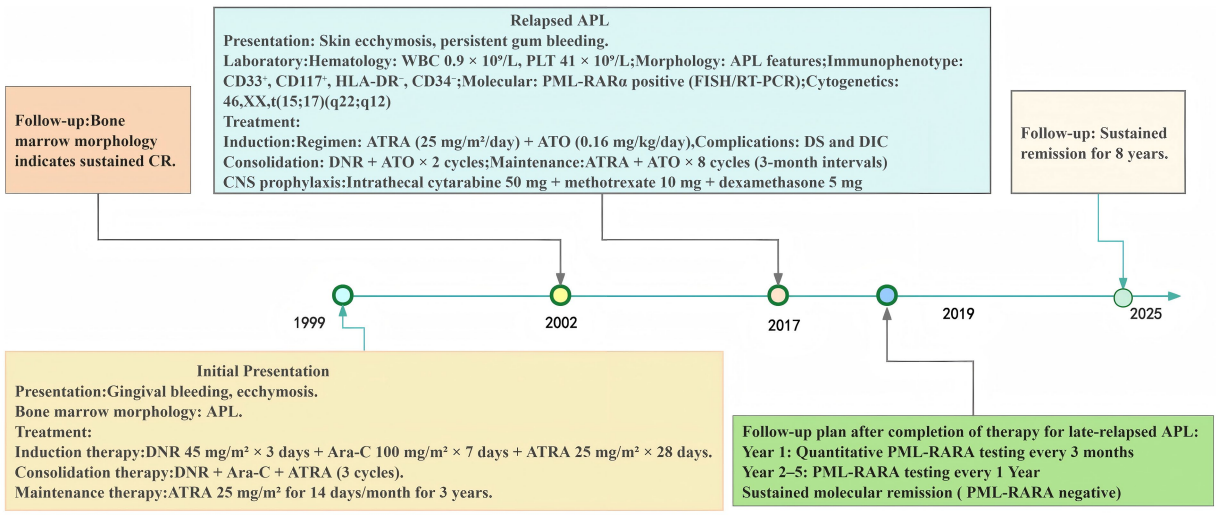

FIGURE 2
Diagnostic and therapeutic timeline for ultra-late relapsed APL. APL, acute promyelocytic leukemia; Ara-C, cytosine arabinoside; APTT, activated partial thromboplastin time; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CNSL, central nervous system leukemia; CR, complete remission; DS, differentiation syndrome; DIC, disseminated intravascular coagulation; DNR, daunorubicin; FDP, fibrin degradation products; FISH, fluorescence in situ hybridization; PLT, platelet; PT, prothrombin time; RT-PCR, reverse transcription polymerase chain reaction; WBC, white blood cell.

TABLE 1 Characteristics and outcomes of acute promyelocytic leukemia (APL) patients with ultra late relapse (>7 years post-remission).

Case no	Sex/age	Karyotype	PML/RARα type	Therapy at initial induction consolidation maintenance	Relapsed form	Time since diagnosis (years)	Immunophenotype relapse	PML/RARa type	Therapy at relapse induction consolidation maintenance	Follow-up (months)	Reference
1	F/43	t(15;17) (q22;q12)	Bcr-3	AIDA 2000 protocol ATRA+IDA 6MP+MTX+ATRA	Intra-parotid lymph nodes Molecular relapse	9	CD13+, CD33+, HLA-DR−	Bcr-3	ATO+ATRA+IDA/ RT ATRA+ATO ATO+ATRA	Remission 12	Molica et al. (7)
2	F/42	t(15;17) (q22;q12)	PML-RARa FLT3-ITD	ATRA+DNR+Ara-C DNR+Ara-C	Intramedullary	17	NA	PML-RARa FLT3-D835	ATRA+DNR+Ara-C ATRA+ATO ATO+ATRA	Molecular remission 7	Zhang et al. (10)
3	F/52	t(15;17) (q22;q12-21)	PML-RARa	ATRA DNR+Ara-C	Intramedullary	11	NA	PML-RARa	ATRA+ATO DNR+Ara-C ATRA	Molecular remission 12	Zhan et al. (11)
4	M/30	t(15;17) (q22;q12)	Bcr1–2	AIDA protocol ATRA +IDA	Intramedullary	9.25	CD13+, CD33+, HLA-DR−	Bcr1–2	ATRA+IDA ATRA+IDA ATRA	Molecular remission 11	Ferrara et al. (12)
5	M/25	t(15;17) (q22;q12)	Bcr1–2	AIDA protocol ATRA	Intramedullary	7	CD13+, CD33+, HLA-DR−	Bcr1–2	ATRA+IDA ATRA+IDA ATRA	Molecular remission 32	Ferrara et al. (12)
6	M/24	t(15;17) (q22;q12)	Bcr1–3	ATRA +IDA ATRA +IDA ATRA	Mastoid cavity	15	CD13+, CD33+, CD34-, HLA-DR−	Bcr1–3	ATRA+ATO ATRA+ATO ATRA	Remission 72	Testi et al. (13)
7	M/52	t(15;17) (q22;q12)	PML-RARa	ATRA+DNR+Ara-C JALSG AML89 protocol	Intramedullary	17	CD13+, CD33+, CD38+, CD34-	PML-RARa	ATRA+DNR ATRA+ATO ATRA	Early death Legionella pneumonia 0.2	Sakurai et al. (14)
8	F/16	NA	Bcr1–3	LAP-0389	Intramedullary right mastoid	12.9	NA	NA	LAP-0389	Remission 2	Latagliata et al. (15)
9	F/30	NA	Bcr1–3	AIDA	Intramedullary	8.4	NA	NA	prot. 0191	Remission 29	Latagliata et al. (15)
10	M/15	t(15;17) (q22;q11-12)	PML-RARα	AML-BFM 98 protocol	Intramedullary	7	NA	PML-RARα	ATO ATO ATO	Molecular remission 48	Ebinger et al. (16)
11	F/49	t(15;17) (q22;q12)	NA	ATRA+DNR+Ara-C ATRA+DNR+Ara-C ATRA	Intramedullary	18	CD117+, CD33+, HLA-DR-, CD34-	PML-RARa	ATRA+ATO+DNR DNR+ATO ATRA+ATO	Molecular remission 96	Present case

Ara-C, cytarabine; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; DNR, daunorubicin; F, female; IDA, idarubicin; M, male; 6MP, 6-mercaptopurine; MTX, methotrexate; NA, not available; RT, radiotherapy.

10.3389/fmed.2025.1651742

Discussion

This case of APL relapse occurring 18 years after initial CR, represents one of the longest intervals reported to date and provides valuable insights into the phenomenon of ultra-late APL relapse. While the majority of relapses typically occur within 2 to 5 years of achieving CR (17), recurrence after such an extended latency period suggests the presence of unique biological mechanisms.

Relapse in APL remains a significant clinical challenge, particularly among patients presenting with high-risk features such as elevated WBC counts (18), FLT3 mutations (19, 20), and specific genetic alterations (21). FLT3 mutations are among the most common genetic alterations in APL, detected in up to 40% of cases (22). These mutations are frequently associated with leukocytosis and have been implicated in promoting leukemic infiltration into extramedullary sites, including the CNS (23). At the time of initial diagnosis, our patient had a WBC count exceeding 10×10^9/L, consistent with hyperleukocytosis, which may have played a role in the eventual occurrence of ultra-late relapse.

The successful achievement of molecular remission through ATO and ATRA reinduction reaffirms this combination as the cornerstone of therapy for relapsed APL (24). Remarkably, despite an 18-year treatment-free interval, ATO and ATRA retained full therapeutic efficacy, achieving clearance of PML-RARα transcripts within two cycles of consolidation. The patient's sustained remission over 8 years without undergoing hematopoietic stem cell transplantation further supports the role of ATO and ATRA as a definitive salvage strategy, particularly for patients who are ineligible for or decline transplantation.

The management of relapsed APL presents a complex clinical challenge, largely due to life-threatening complications such as differentiation syndrome (DS) (25) and disseminated intravascular coagulation (DIC) (26). These conditions are critical determinants of prognosis and require vigilant monitoring and prompt intervention during reinduction therapy. DS, which occurs in approximately 25% of APL patients treated with ATRA and ATO (25, 27), is characterized by systemic inflammation and cytokine dysregulation. This proinflammatory state can exacerbate the risk of DIC, a coagulopathy marked by simultaneous thrombosis and bleeding tendencies (28). In the present case, the patient developed rapid-onset hypoxemia and serositis, necessitating the immediate discontinuation of ATRA and the initiation of high-dose dexamethasone. Concurrently, refractory coagulopathy required aggressive fibrinogen replacement to manage severe DIC. The successful resolution of these complications highlights the importance of protocol-driven crisis management, including early cytokine suppression, goal-directed transfusion strategies, and maintenance of therapeutic intensity despite hematologic instability (29). The interplay between DS and DIC during reinduction underscores the need for proactive, multidisciplinary management strategies to mitigate complications and improve survival outcomes in relapsed APL.

Building upon our literature review, this analysis confirms that ultra-laterelapse of APL (≥7 years post-remission) remains exceptionally rare (7, 10–16). This rarity notwithstanding, the possibility of relapse beyond standard surveillance periods suggests that the duration of molecular monitoring in APL should be reconsidered. Our case represents one of the longest documented relapse intervals to date at 18 years, modestly exceeding the previously reported maximum of 17 years (10, 14). Although therapeutic approaches varied across the cohort, including ATO/ATRA-based salvage therapy (7, 10, 11), chemotherapy combined with ATRA (12), and hematopoietic stem cell transplantation (13), all regimens yielded favorable outcomes, with 10 out of 11 patients achieving remission. Notably, our patient, treated with ATO/ATRA, remains in remission 8 years post-salvage therapy, underscoring the potential for durable responses even in the context of extreme relapse latency. Currently, the longest reported post-relapse follow-up duration in the literature is 6 years (13). Our case offers the longest systematically documented remission duration following an ultra-late relapse. This finding supports with existing evidence that late-relapse APL retains sensitivity to conventional salvage regimens, including arsenic-based therapy (24). However, the heterogeneity of treatments and the absence of standardized consolidation and maintenance strategies underscore the pressing need for further studies to establish structured management protocols for this distinct subset of patients.

Conclusion

This study highlights three key clinical implications. First, the duration of molecular surveillance in APL should be reconsidered, as the risk of ultra-late relapse may exceed beyond current monitoring timeframes. Second, ATO/ATRA-based regimens may be reasonably initiated empirically in cases of suspected relapse, given their efficacy in reported cases, though further validation is warranted. Third, ultra-late relapsed APL represents a distinct clinical entity, emphasizing the need for further investigation to optimize treatment strategies and define long-term management approaches. Together, these findings call for heightened clinical awareness and collaborative efforts to address the unmet needs of this rare but consequential patient subset.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Biomedical Research Ethics Committee of the Affiliated Hospital of Zunyi Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants

provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LG: Writing – original draft, Data curation, Project administration. YA: Writing – original draft, Formal analysis, Methodology. QL: Writing – review & editing, Data curation, Investigation. SS: Writing – review & editing, Investigation. JZ: Writing – review & editing, Visualization. ZD: Writing – review & editing, Conceptualization. PH: Writing – review & editing, Conceptualization, Data curation, Methodology. MR: Writing – review & editing, Supervision. YC: Writing – review & editing, Conceptualization, Methodology, Supervision.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study is supported by the National Natural Science Foundation of China (82260036), the Guizhou Provincial Health Research Project (gzwkj2025-295), the Guizhou Provincial Program on Commercialization of Scientific and Technological Achievements (QKHCG[2024]ZD012), and the key advantageous discipline construction project of Guizhou Provincial Health Commission in 2023.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Sanz MA, Fenaux P, Tallman MS, Estey EH, Löwenberg B, Naoe T, et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. *Blood*. (2019) 133:1630–43. doi: 10.1182/blood-2019-01-894980

2. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Woods WG, et al. All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the north American intergroup protocol. *Blood*. (2002) 100:4298–302. doi: 10.1182/blood-2002-02-0632

3. Asou N, Fujita H, Shinagawa K. JSH guideline for tumors of hematopoietic and lymphoid tissues: leukemia: 2. Acute promyelocytic leukemia (APL). *Int J Hematol*. (2017) 106:459–70. doi: 10.1007/s12185-017-2318-x

4. Kantarjian HM, DiNardo CD, Kadia TM, Daver NG, Altman JK, Stein EM, et al. Acute myeloid leukemia management and research in 2025. *CA Cancer J Clin*. (2025) 75:46–67. doi: 10.3322/caac.21873

5. Voso MT, Guarnera L, Lehmann S, Döhner K, Döhner H, Platzbecker U, et al. Acute promyelocytic leukemia: long-term outcomes from the HARMONY project. *Blood*. (2025) 145:234–43. doi: 10.1182/blood.2024026186

6. Scalzulli E, Costa A, Carmosino I, Musiu P, Bisegna ML, de Propris MS, et al. Different prognosis according to treatment in patients with acute promyelocytic leukemia: how the outcome changed over time. *Ann Hematol*. (2024) 103:5377–86. doi: 10.1007/s00277-024-06014-1

7. Molica M, Mazzone C, Ottone T, Niscola P, Abruzzese E, Fratoni S, et al. Case report: very late, atypical extra-medullary relapse in a patient with acute Promyelocytic leukemia (APL) rescued with a transplant-free approach. *Front Oncol*. (2021) 11:699886. doi: 10.3389/fonc.2021.699886

8. Chinese Society of Hematology, CMDA; Chinese Medical Association, CMDA. Chinese guidelines for diagnosis and treatment of acute promyelocytic leukemia (2018). *Zhonghua Xue Ye Xue Za Zhi*. (2018) 39:179–83. doi: 10.3760/cma.j.issn.0253-2727.2018.03.002

9. Zhu HH, Wu DP, Jin J, Li JY, Ma J, Wang JX, et al. Oral tetra-arsenic tetra-sulfide formula versus intravenous arsenic trioxide as first-line treatment of acute promyelocytic leukemia: a multicenter randomized controlled trial. *J Clin Oncol*. (2013) 31:4215–21. doi: 10.1200/JCO.2013.48.8312

10. Zhang X, Zhang Q, Dahlström J, Tran AN, Yang B, Gu Z, et al. Genomic analysis of the clonal origin and evolution of acute promyelocytic leukemia in a unique patient with a very late (17 years) relapse. *Leukemia*. (2014) 28:1751–4. doi: 10.1038/leu.2014.113

11. Zhan H, Rajasree R, Russo L, Patel D. Late relapse of acute promyelocytic leukemia in a patient with no maintenance therapy. *Am J Hematol*. (2007) 82:248. doi: 10.1002/ajh.20742

12. Ferrara F, Selleri C, Mele G, Serio B, Palmieri S, Pocali B, et al. Late relapse of acute promyelocytic leukemia treated with all- trans retinoic acid and chemotherapy: report of two cases. *Ann Hematol*. (2004) 83:484–6. doi: 10.1007/s00277-003-0842-7

13. Testi AM, Moleti ML, Canichella M, Mohamed S, Diverio D, de Propris MS, et al. Very late relapse in a patient with acute promyelocytic leukemia (APL) rescued with a chemotherapy-free protocol. *Leuk Lymphoma*. (2017) 58:999–1001. doi: 10.1080/10428194.2016.1222377

14. Sakurai M, Watanuki S, Kato J, Hashida R, Yamane Y, Karigane D, et al. Very late relapse of acute Promyelocytic leukemia 17 years after continuous remission. *Intern Med*. (2018) 57:3299–302. doi: 10.2169/internalmedicine.0807-18

15. Latagliata R, Carmosino I, Breccia M, Minni A, Testi A, Iorio N, et al. Late relapses in acute promyelocytic leukaemia. *Acta Haematol*. (2007) 117:106–8. doi: 10.1159/000097385

16. Ebinger M, Schwarze CP, Feuchtinger T, Scheel-Walter HG, Lang P, Hildenbrand S, et al. Long-term remission after first-line single-agent treatment with arsenic trioxide of relapsed acute promyelocytic leukemia in an 8-year-old boy. *Pediatr Hematol Oncol*. (2011) 28:334–7. doi: 10.3109/08880018.2010.542557

17. Kulkarni U, Ganesan S, Alex AA, Palani H, David S, Balasundaram N, et al. A phase II study evaluating the role of bortezomib in the management of relapsed acute promyelocytic leukemia treated upfront with arsenic trioxide. *Cancer Med*. (2020) 9:2603–10. doi: 10.1002/cam4.2883

18. Santamaría C, Chillón MC, García-Sanz R, Balanzategui A, Sarasquete ME, Alcoceba M, et al. The relevance of preferentially expressed antigen of melanoma (PRAME) as a marker of disease activity and prognosis in acute promyelocytic leukemia. *Haematologica*. (2008) 93:1797–805. doi: 10.3324/haematol.13214

19. Bochtler T, Fröhling S, Weichert W, Endris V, Thiede C, Hutter B, et al. Evolution of a FLT3-TKD mutated subclone at meningeal relapse in acute

promyelocytic leukemia. *Cold Spring Harb Mol Case Stud*. (2016) 2:a001123. doi: 10.1101/mcs.a001123

20. Jiang B, Tong H, Meng H, Xie W, Yu W, Huang J, et al. Characteristics and predictors of central nervous system relapse in newly diagnosed acute promyelocytic leukemia in the era of arsenic: a 13-year monocenter cohort study. *Blood Cancer J*. (2025) 15:39. doi: 10.1038/s41408-025-01247-3

21. Ibáñez M, Carbonell-Caballero J, García-Alonso L, Such E, Jiménez-Almazán J, Vidal E, et al. The mutational landscape of acute Promyelocytic leukemia reveals an interacting network of co-occurrences and recurrent mutations. *PLoS One*. (2016) 11:e0148346. doi: 10.1371/journal.pone.0148346

22. Lucena-Araujo AR, Kim HT, Jacomo RH, Melo RA, Bittencourt R, Pasquini R, et al. Internal tandem duplication of the FLT3 gene confers poor overall survival in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline-based chemotherapy: an international consortium on acute Promyelocytic leukemia study. *Ann Hematol*. (2014) 93:2001–10. doi: 10.1007/s00277-014-2142-9

23. Tashiro H, Shirasaki R, Oka Y, Sugao T, Mizutani-Noguchi M, Yamamoto T, et al. FLT3 internal tandem duplication is associated with a high relapse rate and central nervous system involvement in acute promyelocytic leukemia cases: single institutional analysis. *Eur J Haematol*. (2011) 86:272–3. doi: 10.1111/j.1600-0609.2010.01559.x

24. de L, Catto L, Chauffaille M, Pagnano K, Madeira M, Nunes E, et al. Diagnosis and management of acute promyelocytic leukemia: Brazilian consensus guidelines 2024 on behalf of the Brazilian Association of Hematology, Hemotherapy and cellular therapy. *Hematol Transfus Cell Ther*. (2024) 46:553–69. doi: 10.1016/j.htct.2024.05.002

25. Woods AC, Norsworthy KJ. Differentiation syndrome in acute leukemia: APL and beyond. *Cancers (Basel)*. (2023) 15:4767. doi: 10.3390/cancers15194767

26. Ten Cate H, Leader A. Management of disseminated intravascular coagulation in acute leukemias. *Hamostaseologie*. (2021) 41:120–6. doi: 10.1055/a-1393-8302

27. Issa GC, Stein EM, DiNardo CD. How I treat acute myeloid leukemia with differentiation therapy. *Blood*. (2025) 145:1251–9. doi: 10.1182/blood.2024024008

28. Yamakawa K, Okamoto K, Seki Y, Ikezoe T, Ito T, Iba T, et al. Committee of the Clinical Practice Guidelines for Management of Disseminated Intravascular Coagulation 2024, the Japanese society on thrombosis and hemostasis clinical practice guidelines for management of disseminated intravascular coagulation in Japan 2024. Part 1: sepsis. *Int J Hematol*. (2025) 121:592–604. doi: 10.1007/s12185-024-03896-9

29. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. (2022) 140:1345–77. doi: 10.1182/blood.2022016867