THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 1

RESEARCH ARTICLE

Enhanced Survival in Acute Promyelocytic leukemia: A New Era of Therapeutic and Supportive Interventions

Muhammed Usman Shaikh[1], Nabiha Saeed[1]

[1]Department of Oncology, Aga Khan University Hospital, Karachi-Pakistan

OPEN ACCESS

PUBLISHED
31 January 2025

CITATION
Shaikh, MU. and Saeed, N., 2025. Enhanced Survival in Acute Promyelocytic leukemia: A New Era of Therapeutic and Supportive Interventions. Medical Research Archives, [online] 13(11). https://doi.org/10.18103/mra.v13i1.6119

DOI
https://doi.org/10.18103/mra.v13i1.6119

ISSN
2375-1924

ABSTRACT

Acute promyelocytic leukemia is a distinct subtype of acute myeloid leukemia characterized by a reciprocal chromosomal translocation involving the retinoic acid receptor-alpha (RARα) gene and exhibiting characteristic morphological and clinical features, with significant early mortality. With the advent of arsenic trioxide and all-trans retinoic acid the prognosis of acute promyelocytic leukemia has improved. However, early induction mortality remains a significant challenge, with hemorrhagic complications and differentiation syndrome being major contributors to morbidity and mortality. Management of acute promyelocytic leukemia has undergone significant advancements, resulting in improved mortality rates and enhanced five-year survival rates exceeding 80%. Despite these gains, early induction mortality and differentiation syndrome remain pressing challenges. This review underscores the importance of proactive interventions, including early administration of blood products and corticosteroids, and highlights the need for continued research into differentiation syndrome prevention strategies. Our review also underscores the need for continued research to improve outcomes in patients with APL, particularly in low- and middle-income countries where access to healthcare and treatment options are limited.

Introduction

Acute promyelocytic leukemia is a relatively uncommon type of acute myeloid leukemia, accounting for 5-8% of acute myeloid leukemia cases[1]. Patients are usually younger, with a median age at diagnosis of 44 years[2]. The diagnostic parameters stand out when compared to other variants of acute myeloid leukemia, including the characteristic morphology of leukemic cells and typical flow cytometry findings, such as CD34 and HLA-DR negativity. Acute promyelocytic leukemia was previously classified as AML-M3 in the older French-American-British (FAB) classification system[3], and with the advancement in cytogenetic and genetic studies, it was distinguished as acute promyelocytic leukemia with t(15;17)(q24.1;q21.1) and promyelocytic leukemia-retinoic acid receptor alpha (PML-RARA) by the World Health Organization[4]. The translocation of the PML gene on chromosome 15 to the RARA gene on chromosome 17 [i.e., t(15;17)(q24.1;q21.1)] produces a PML-RARA fusion gene that can be quantitatively monitored using polymerase chain reaction to document disease burden and ultimately confirm molecular remission[5].

Acute promyelocytic leukemia was first described in 1957 by Hillested and LK as a hyperacute fatal illness, with a median survival time of less than a week[6]. Although rare, even today, patients with acute promyelocytic leukemia present as an acute emergency with extremely critical conditions, such that sometimes targeted therapy cannot be administered before death. Over the last five decades, survival has improved from a median survival of less than one week to a five-year survival rate of more than 80-90%[7]. The introduction of anthracycline as a single-agent induction therapy in patients with acute promyelocytic leukemia by Bernard et al. [8], with a remission rate of approximately 50%, has significantly improved outcomes. The introduction of all-trans retinoic acid in 1980, which is probably the first well-established example of targeted therapy, opened the floodgates for other malignancies[9]. All-trans retinoic acid revolutionized the treatment of patients with acute promyelocytic leukemia, decreasing the 5-year mortality rate from 82% to 36% [10]. From 2000 onwards, the incorporation of arsenic trioxide with all-trans retinoic acid in patients with low- and intermediate-risk acute promyelocytic leukemia showed superior response rates and overall survival when compared to all-trans retinoic acid plus chemotherapy[11]. Finally, Gemtuzumab ozogamicin, an anti-CD33 monoclonal antibody, has shown significant activity against acute promyelocytic leukemia due to the marked expression of the CD33 antigen on leukemic cells. Yasmin et al. revealed an excellent long-term outcome when Gemtuzumab was added to the induction regimen along with arsenic trioxide with all-trans retinoic acid, notably in high-risk acute promyelocytic leukemia. The introduction of oral arsenic trioxide is another milestone in the management of acute promyelocytic leukemia[12]. This comprehensive review emphasizes the critical role of proactive interventions, including timely administration of blood products and corticosteroids, in improving outcomes for patients with acute promyelocytic leukemia. Furthermore, it highlights the urgent need for continued research into the prevention and management of differentiation syndrome, a potentially life-threatening complication.

Complications of treatment and therapeutic interventions:

Two notable complications commonly observed during induction therapy are coagulopathy and therapy-related differentiation syndrome, both of which are associated with high morbidity and mortality. Promyelocytes contribute to coagulopathy through two important mechanisms: one is the production of procoagulants that directly activate factor X, and the other is the expression of phospholipids that activate tissue factor, further contributing to coagulopathy[13]. Nuclear particles, present in the cell nucleus, do not have a capsule or membrane. These particles are involved in ribonucleic acid splicing and gene transcription regulation. The PML protein, which is present in these nuclear particles, fuses with the retinoic acid receptor due to the t(15;17) translocation, leading to the pathogenesis

of acute promyelocytic leukemia with defective homeostasis of leukemia growth[14]. The central nervous system and pulmonary system are the two major sites affected by hemorrhages, resulting in high morbidity and mortality[15].

The management of coagulopathy has improved over time with the prophylactic administration of blood and blood products. The European LeukemiaNet and other regional guidelines provide sufficient evidence to prevent coagulopathy, including maintaining platelets at ≥30,000/μL, fibrinogen at ≥150 mg/dL, and fresh frozen plasma for deranged prothrombin time, activated partial thromboplastin time, and d-dimer for at least two weeks[16].

The second important complication associated with arsenic trioxide with all-trans retinoic acid therapy is differentiation syndrome, which is now observed not only with arsenic trioxide with all-trans retinoic acid but also with novel IDH1 and IDH2 inhibitors[17]. The pathogenesis of differentiation syndrome is not well characterized, but the postulated mechanism likely involves capillary leak syndrome[18]. All-trans retinoic acid targets the retinoic acid receptor and induces differentiation of blast cells, causing cytokine release, especially in the pulmonary vasculature[19]. All-trans retinoic acid also alters the adhesion properties of blast cells by increasing the expression of Beta-2 integrins, further enhancing adhesion, which leads to alveolar hemorrhage in the lungs[20].

Common symptoms reported in differentiation syndrome include shortness of breath (84–100%), fever (74–100%), pulmonary infiltrates (52–100%), weight gain (50–100%), and effusions (36–100%)—all of which are non-specific[17]. Because there is no single pathogenomic criterion for the diagnosis of ATRA syndrome, and because of the rarity of APL itself, there is often a delay in the proper steps to manage this complex complication.

Severe differentiation syndrome typically develops from day five onwards[21]. Laboratory abnormalities frequently seen with differentiation syndrome include leukocytosis and deranged renal function. Clinical correlation is extremely important during treatment with All-trans retinoic acid, as a transient increase in white blood cell is not uncommon. However, a cutoff of 30 × 10^9/L can be used to differentiate it from differentiation syndrome[22]. Likewise, deranged kidney function is noted in 11–66% of patients with differentiation syndrome[23].

The management of differentiation syndrome is not standardized, although steroids remain the mainstay of treatment[24]. Various formulations and dosages are used for both prevention and treatment, but the duration of steroid treatment is unclear. Prospective trials comparing the efficacy of different corticosteroid formulations, including oral prednisone versus intravenous dexamethasone and methylprednisolone, are lacking[24]. The cutoff value for WBC count, the duration of treatment, and the mode of administration are also not standardized. In the PETHEMA LPA99 trial, a 15-day duration of prophylactic prednisone was administered to all patients, regardless of white blood cells[25]. Current recommendations for corticosteroid prophylaxis for DS are for patients with white blood cells > 5 × 10^9/L and elevated creatinine (>1.4 mg/dL)[23].

Before establishing the diagnosis of differentiation syndrome, other conditions like chest infections, volume overload, and heart failure must be excluded. Recently, the response to ruxolitinib in refractory differentiation syndrome was published; however, further evidence from large clinical trials is needed[26]. Cytoreductive therapy is also indicated, but there is no consensus on the drug of choice. Some institutions use hydroxyurea, while others administer anthracycline or cytosine arabinoside[27]. Gemtuzumab ozogamicin also shows a survival advantage when used in high-risk acute promyelocytic leukemia[28]. In rare cases, if a patient develops hyperleukocytosis (typically defined as white blood cells > 100 × 10^9/L) with clinical features of leukostasis, leukapheresis is contraindicated due to the high risk of hemorrhagic death[16]. Unless there is rapidly rising creatinine and a need for ventilator support, treatment with arsenic trioxide with all-trans retinoic acid should be continued[16,18].

The induction mortality and overall survival of patients has been improved by introducing preventive infusion of fresh frozen plasma, dexamethasone, and adequate supportive treatment during the induction chemotherapy.

Despite all the advancements in the management of acute promyelocytic leukemia, early deaths or induction mortality (usually defined as death within 30 days of starting targeted therapy) remain a concern for treating physicians. Once diagnosed, it is crucial to start all-trans retinoic acid as soon as possible, along with the prophylactic and therapeutic use of blood products.

Kantarjian et al. elaborated that the outcomes of acute myeloid leukemia are inferior in the real world when compared to results from clinical trials and academic centers[29,30]. Similarly, Lehman found that early induction deaths are approximately 30% in acute promyelocytic leukemia, despite advancements in management over the last three decades[31].

Below are table 1 and table 2, comparing early deaths in high- and low-income countries. It is worth noting that early death rates are nearly the same in both groups.

Table 1. Induction Deaths in Acute Promyelocytic Leukemia : Data from Canada and USA

Research Published	Total number of patients	Deaths	Mortality %
Canada 2014 Paulson et al [31]	399	87	22%
SEER USA 2011 Park et al [32]	1400	238	17%
Stanford USA 2012 McClellan et al [33]	70	19	26%
Georgia, USA 2014 Annand et al [34]	19	7	37%
Emory , USA 2014 Jillella et al [34]	75	19	25%

In low-income countries like Pakistan, where healthcare facilities are suboptimal, there are many hurdles to achieving the outcomes described in medical literature. Even in advanced countries like the USA and Scandinavia, real-world outcomes are inferior when compared to those published in clinical trials.

Appropriate management of acute promyelocytic leukemia requires a high index of suspicion for early diagnosis due to the more common viral hemorrhagic manifestations from dengue, malaria, and other viral syndromes in our geographical region. The availability of blood products is a major issue, as most blood donations are exchange donations, and voluntary blood donation is rare. Similarly, the management of acute leukemia is very expensive, with no insurance coverage for most of the population. Setting acute promyelocytic leukemia aside, many patients with acute leukemias present late in very critical condition and die before the administration of targeted therapies.

Table 2. Induction Deaths in Acute Promyelocytic Leukemia : Data from India and Pakistan			
Research Published	Total number of patients	Deaths	Mortality %
India 2020 Rajani et al [35]	111	23	21%
India 2021 Tejasvini et al [36]	64	9	14%
India 2011 Bajpai et al [37]	33	8	24%
India 2024 K Sindhusha [38]	64	23	38%
Pakistan 2024 Naz et al [39]	50	7	14%
Pakistan 2008 Shahid Raza etal [40]	31	10	32%
Pakistan 2020 Usman et al [41]	40	12	30%

Conclusion

In conclusion, the management of acute promyelocytic leukemia is a success story, with an improvement in mortality from a few days to now more than 80% five-year survival. Early induction mortality remains a major challenge, but trends are improving with early and prophylactic administration of blood products and corticosteroids. Despite all interventions, differentiation syndrome is still one of the major complications leading to death in acute promyelocytic leukemia. We need more answers to address preventive strategies for differentiation syndrome. Awareness and education of emergency staff, as well as sensitization about the early administration of all-trans retinoic acid and blood products, is highly recommended.

Conflicts of Interest Statement:

The authors report no conflicts of interest pertaining to this work.

Funding Statement:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References:

1. Stanley M, McKenna RW, Ellinger G, Brunning RD. Classification of 358 cases of acute myeloid leukemia by FAB criteria: analysis of clinical and morphologic features. Chronic and acute leukemias in adults: Springer; 1985. p. 147-74.

2. Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood, The Journal of the American Society of Hematology. 2009;113 (9):1875-91.

3. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposed revised criteria for the classification of acute myeloid leukemia: a report of the French-American-British Cooperative Group. Annals of internal medicine. 1985;103(4): 620-5.

4. McKenna R, Kyle R, Kuehl W, Grogan T, Harris N, Coupland R. WHO classification of tumours of haematopoietic and lymphoid tissues. Plasma cell neoplasms Lyon: IARC. 2008:200-13.

5. Candoni A, Damiani D, Michelutti A, Masolini P, Michieli M, Michelutti T, et al. Clinical characteristics, prognostic factors and multidrug-resistance related protein expression in 36 adult patients with acute promyelocytic leukemia. European journal of haematology. 2003;71(1):1-8.

6. Stone RM, Mayer R. The unique aspects of acute promyelocytic leukemia. Journal of Clinical Oncology. 1990;8(11):1913-21.

7. Tallman MS, Nabhan C, Feusner JH, Rowe JM. Acute promyelocytic leukemia: evolving therapeutic strategies. Blood, The Journal of the American Society of Hematology. 2002;99(3):759-67.

8. Bernard J, Weil M, Boiron M, Jacquillat C, Flandrin G, Gemon M-F. Acute promyelocytic leukemia: results of treatment by daunorubicin. Blood. 1973;41(4):489-96.

9. Zhang L, Zhu X. Epidemiology, diagnosis and treatment of acute promyelocytic leukemia in children: the experience in China. Mediterranean journal of hematology and infectious diseases. 2012;4(1).

10. Meng-Er H, Yu-Chen Y, Shu-Rong C, Jin-Ren C, Jia-Xiang L, Lin Z, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood. 1988;72(2):567-72.

11. Zx S. All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci USA. 2004;101:5328-35.

12. Abaza Y, Kantarjian H, Garcia-Manero G, Estey E, Borthakur G, Jabbour E, et al. Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab. Blood, The Journal of the American Society of Hematology. 2017;129(10):1275-83.

13. Thomas X. Acute promyelocytic leukemia: a history over 60 years—from the most malignant to the most curable form of acute leukemia. Oncology and therapy. 2019;7(1):33-65.

14. Pandolfi PP, Chen Z. Acute promyelocytic leukemia: a paradigm for oncoprotein-targeted cure. Cancer cell. 2017;32(5):552-60.

15. Kwaan HC, Weiss I, Tallman MS, editors. The role of abnormal hemostasis and fibrinolysis in morbidity and mortality of acute promyelocytic leukemia. Seminars in thrombosis and hemostasis; 2019: Thieme Medical Publishers.

16. 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, The Journal of the American Society of Hematology. 2019;133(15):1630-43.

17. Woods AC, Norsworthy KJ. Differentiation Syndrome in Acute Leukemia: APL and Beyond. Cancers. 2023;15(19):4767.

18. Stahl M, Tallman MS. Differentiation syndrome in acute promyelocytic leukaemia. British journal of haematology. 2019;187(2):157-62.

19. Luesink M, Pennings JL, Wissink WM, Linssen PC, Muus P, Pfundt R, et al. Chemokine induction

by all-trans retinoic acid and arsenic trioxide in acute promyelocytic leukemia: triggering the differentiation syndrome. Blood, The Journal of the American Society of Hematology. 2009;114(27):5512-21.

20. Taraboletti G, Borsotti P, Chirivi RG, Vergani V, Falanga A, Barbui T, et al. Effect of all trans-retinoic acid (ATRA) on the adhesive and motility properties of acute promyelocytic leukemia cells. International journal of cancer. 1997;70(1):72-7.

21. Montesinos P, Sanz MA. The differentiation syndrome in patients with acute promyelocytic leukemia: experience of the pethema group and review of the literature. Mediterranean journal of hematology and infectious diseases. 2011;3(1).

22. Yoon J-H, Kim H-J, Min GJ, Park S-S, Jeon Y-W, Lee S-E, et al. Progressive hyperleukocytosis is a relevant predictive marker for differentiation syndrome, early death, and subsequent relapse in acute promyelocytic leukemia. Scientific reports. 2019;9(1):11935.

23. Sanz MA, Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. Blood, The Journal of the American Society of Hematology. 2014;123(18):2777-82.

24. De Botton S, Dombret H, Sanz M, Miguel JS, Caillot D, Zittoun R, et al. Incidence, clinical features, and outcome of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. Blood, The Journal of the American Society of Hematology. 1998;92(8):2712-8.

25. Sanz MA, Montesinos P, Vellenga E, Rayón C, De La Serna J, Parody R, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans retinoic acid and anthracycline monochemotherapy: long-term outcome of the LPA 99 multicenter study by the PETHEMA Group. Blood, The Journal of the American Society of Hematology. 2008;112(8):3130-4.

26. Wu Q, Wu D-P, Chen S, Yang X, Zhang J, Xue M, et al. Improved Prevention and Treatment Strategy of Differentiation Syndrome Contribute to Reduce Early Death of Patients with Acute Promyelocytic Leukemia. Blood. 2023;142:1528.

27. LaBella D, Regan S, Konig H, Egan DN, Bailey NA, Mawad R, et al. The role of adjuvant chemotherapy in the management of acute promyelocytic leukemia differentiation syndrome. Frontiers in Oncology. 2022;12:911745.

28. Kantarjian H, Kadia T, DiNardo C, Daver N, Borthakur G, Jabbour E, et al. Acute myeloid leukemia: current progress and future directions. Blood cancer journal. 2021;11(2):41.

29. Chen Y, Kantarjian H, Wang H, Cortes J, Ravandi F. Acute promyelocytic leukemia: A population-based study on incidence and survival in the United States, 1975-2008. Cancer. 2012;118(23):5811-8.

30. Lehmann S, Ravn A, Carlsson L, Antunovic P, Deneberg S, Möllgård L, et al. Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the Swedish Adult Acute Leukemia Registry. Leukemia. 2011;25(7):1128-34.

31. Paulson K, Serebrin A, Lambert P, Bergeron J, Everett J, Kew A, et al. Acute promyelocytic leukaemia is characterized by stable incidence and improved survival that is restricted to patients managed in leukaemia referral centres: a pan-Canadian epidemiological study. British journal of haematology. 2014;166(5):660-6.

32. Park JH, Qiao B, Panageas KS, Schymura MJ, Jurcic JG, Rosenblat TL, et al. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. Blood, The Journal of the American Society of Hematology. 2011;118(5):1248-54.

33. McClellan JS, Kohrt HE, Coutre S, Gotlib JR, Majeti R, Alizadeh AA, et al. Treatment advances have not improved the early death rate in acute promyelocytic leukemia. Haematologica. 2012;97(1):133.

34. Jillella AP, Kolhe RB, Natrajan K, Kota V. A successful model to decrease early deaths in acute promyelocytic leukemia (APL) through the use of a

simplified algorithm and expert support. American Society of Clinical Oncology; 2014.

35. Yedla RP, Bala SC, Pydi VR, Kuruva SP, Chennamaneni R, Konatam ML, et al. Outcomes in adult acute promyelocytic leukemia: a decade experience. Clinical Lymphoma Myeloma and Leukemia. 2020;20(4):e158-e64.

36. Vaid T, Aggarwal M, Kumar P, Dhawan R, Dass J, Viswanathan G, et al. Clinical Profile, Complications and Outcomes of Patients with Acute Promyelocytic Leukemia: Indian Perspective. Blood. 2021;138:4385.

37. Bajpai J, Sharma A, Kumar L, Dabkara D, Raina V, Kochupillai V, et al. Acute promyelocytic leukemia: an experience from a tertiary care centre in north India. Indian journal of Cancer. 2011;48(3):316-22.

38. Sindhusha K, C Saldanha S, Abraham Jacob L, Suresh Babu M, Lokesh K, Rudresha A, et al. Clinico-Pathological Significance and Prognostic Impact of Various PML RARA Transcripts on Outcomes in Acute Promyelocytic Myeloid Leukemia (APML) Treated with Single Agent Arsenic Trioxide (ATO)-Insights from a Tertiary Cancer Center in South India. Indian Journal of Hematology and Blood Transfusion. 2024:1-6.

39. Naz S, Ghafoor T, Manzoor R, Hira B, Ahmed S, Arshed A. Outcomes of Acute Promyelocytic Leukaemia in Paediatric Patients: Insights from a Low-Middle-Income Country. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP. 2024; 34(8):974-80.

40. Raza S, Ullah K, Ahmed P, Khan B. Comparison of anthracycline-based combination chemotherapy with or without all-trans retinoic acid in acute promyelocytic leukemia. J Coll Physicians Surg Pak. 2008;18(9):546-50.

41. Shaikh MU, Ali N, Karim F, Raheem A, Sarwar S. Improved outcome in early induction deaths in patients with acute promyelocytic leukemia after therapeutic and supportive interventions: a follow up study of seven-years' experience at a tertiary care center. American Journal of Blood Research. 2020;10(4):82.

