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Tackling the Last Major Obstacle to Cure in Acute Promyelocytic Leukemia

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Abstract

Acute Promyelocytic Leukemia (APL) has become the most curable subtype of acute myeloid leukemia in adults with the advent of the differentiating agents, all-trans retinoic acid and arsenic trioxide. However, Early Death (ED) remains a challenge and represents the last major obstacle to the cure of almost every patient. An overwhelming majority of ED in APL is attributable to life-threatening bleeding, a phenomenon driven by complex alterations in the coagulation system. Therefore, prompt recognition of APL and immediate initiation of All-Trans Retinoic Acid (ATRA) in emergency departments–prior to confirmation of the diagnosis–is essential. All-trans retinoic acid must be immediately available, which is often problematic since most institutions will see very few APL patients in a year and will not find it cost-effective to maintain a supply. Aggressive management of the coagulopathy and less common causes of ED, such as the differentiation syndrome and infections, is required. Since emergency departments and immediate care healthcare professionals are often the first to encounter a patient with APL, their training should include comprehensive diagnostic and initial management details. Recent data suggest that early consultation with a colleague with expertise in APL for initial hour-by-hour management is very helpful in reducing the ED rate. Tackling this last major obstacle in the cure of all patients requires providers to astutely recognize the disease and manage patients according to recommended guidelines.

Keywords: Acute promyelocytic leukemia • All-Trans Retinoic Acid (ATRA) • Coagulation • Fibrinolysis • Proteolysis

Description

Acute Promyelocytic Leukemia (APL) is an uncommon, but highly curable subtype of Acute Myeloid Leukemia (AML). However, by almost any parameter one considers, APL differs from all other subtypes. The morphology of the malignant cells is distinctive, the pathogenesis of the disease is well understood, the most important prognostic factor for relapse is simply the presenting White Blood Cell (WBC) count, the treatment is completely different, and there is no primary resistance [1]. Furthermore, the disease is as sensitive in older adults as in younger adults, and therapy-related APL is as curable as *de novo* disease. In cooperative group studies with current therapeutic strategies, 98% of patients with low-risk disease (representing 75% of all patients) (WBC count ≤ 10,000/μL) and 90-95% of those with high-risk disease (WBC count >10,000/μL) are cured assuming that they survive Early Death (ED) defined as death within 30 days of presentation [2]. Early death occurs in 5-10% of patients in cooperative group studies where patients are necessarily selected, but in up to 30% of patients in population-based studies where every patient with the disease is included and is most often attributable to life-threatening bleeding [3] . Such bleeding is due to a complex coagulopathy caused by a combination of disseminated intravascular coagulation, fibrinolysis and proteolysis [4]. Mucocutaneous bleeding, often with multiple large ecchymoses out of proportion of the level of thrombocytopenia, is characteristic and a useful clinical pearl [5]. Thrombosis is an often underappreciated and unrecognized manifestation of the coagulopathy. Other contributors to ED–albeit at low rates in the present era–include differentiation syndrome (a hyperinflammatory state related to the use of differentiating agents such as All-Trans Retinoic Acid (ATRA) and arsenic trioxide, usually treatable with corticosteroids) and infections [6]. However, bleeding is responsible for the vast majority of ED in patients with APL. Early death, rather than resistant disease as is the case for all other subtypes of AML, has emerged as the most important obstacle to cure in APL in the modern era.

Unfortunately, some patients present with fatal (often intracranial) bleeding too far advanced to save. However, the overwhelming majority of patients can be cured with three cornerstones of treatment including early diagnosis (aided by early suspicion of the disease), aggressive blood product support, and rapid institution of appropriate treatment with ATRA and arsenic-based approaches, all carried out with a sense of urgency. Early aggressive blood product support with platelets and cryoprecipitate to correct the

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coagulopathy (maintain platelet counts ≥ 30,000–50,000/μL and fibrinogen ≥ 100–150 mg/dL). Higher transfusion targets may be needed in the presence of active bleeding depending on the site and severity of the bleeding. These measures should be instituted before transfer to the inpatient floor, before a bone marrow aspiration/biopsy is done, and before genetic confirmation of the diagnosis. This will require not only hematologists (who in effect become emergency department physicians), but also emergency medicine and immediate care healthcare professionals (who in effect become hematologists) to be adequately trained in the diagnosis and initial management of APL.

Emergency departments need to examine the CBC, coagulation profile and peripheral blood smear in any patient with an abnormal WBC count or platelet count. This can be done with the help of a hematologist, and we suggest that every hematologist should be able to recognize the morphology of APL since a hematopathologist may not be immediately available. Since ATRA should be administered at the very earliest suspicion of APL it must be available urgently in emergency departments. This often poses a conundrum. Most institutions will see very few APL patients in a year. Many may feel it is neither cost- nor administrative-effective to maintain a stock of ATRA in the pharmacy. An alternative would be to establish a network for rapid procurement of ATRA. It is important to adhere to established written guidelines such as those promulgated by the National Comprehensive Cancer Network (NCCN). Patients treated according to NCCN guidelines may fare better than those not treated in accordance with such guidelines [7]. Furthermore, recent data suggest that an effective strategy may be to contact a colleague with expertise in the care of patients with APL who can share therapeutic guidelines particularly for early hour-by-hour management of the disease [8].

The success of curative therapeutic approaches in APL has been realized by a series of successive studies carried out by cooperative groups and single institutions with worldwide collaboration [9]. Tackling ED, the last major obstacle to the cure of almost every patient with APL, will require similar collaboration and coordination among a variety of healthcare professionals.

References

1. Sanz, Miguel A., Pierre Fenaux, Martin S. Tallman and Elihu H, et al. “Management of Acute Promyelocytic Leukemia: Updated Recommendations from an Expert Panel of the European Leukemia Net.” *Blood* 133(2019): 1630-1643.
2. Cicconi, Laura, Uwe Platzbecker, Giuseppe Avvisati, Francesca Paoloni and Christian Thiede, et al. “Long-term Results of Al-Trans Retinoic Acid and Arsenic Trioxide in Non-High-Risk Acute Promyelocytic Leukemia: Update Of The APL0406 Italian-German Randomized Trial.” *Leukemia* 34(2020): 914-918.
3. Iland, Harry J, Marnie Collins, Ken Bradstock and Shane G. Supple, et al. “Australasian Leukaemia and Lymphoma Group. Use of Arsenic Trioxide in Remission Induction and Consolidation Therapy for Acute Promyelocytic Leukaemia in the Australasian Leukaemia And Lymphoma Group (ALLSG) APML4 Study: A Nonrandomized Phase 2 Trial.” *Lancet Haematol* 2(2015): 357-366.
4. Lehmann Sören, A Ravn, L Carlsson, Petar Antunovic and S. Deneberg, et al. “Continuing High Early Death Rate in Acute Promyelocytic Leukemia: A Population-Based Report from The Swedish Adult Acute Leukemia Registry.” *Leukemia* 25(2011): 1128-1134.
5. Jamy Omer H, Aditi Dhir, Luciano J Costa, and Ana C. Xavier. “Impact of Sociodemographic Factors on Early Mortality in Acute Promyelocytic Leukemia in the United States: A Time-Trend Analysis.” *Cancer* 128(2022): 292-298.
6. Hambley Bryan C, Ciprian Tomuleasa, and Gabriel Ghiaur. “Coagulopathy in Acute Promyelocytic Leukemia: Can we go Beyond Supportive Cae? ” *Frontiers in Medicine* 8(2021): 1-10.
7. Bewersdorf Jan Philipp, Stephanie Prozora, Rong Wang, Nikolai A. Podoltsev and Rory M. Shallis, et al. “Practice Patterns and Real-Life Outcomes for Patients with Acute Promyelocytic Leukemia.” *Blood Adv* 6(2022): 376-385.
8. Jillella Anand P, Sandra J Lee, Jessica K Altman, Selina M Luger and Martin S. Tallman, et al. “A Simplified Patient Care Strategy to Decrease Early Death in Acute Promyelocytic Leukemia (APL): Results Of The ECOG-ACRIN EA9131 Trial.” *Blood* 140(2022): 1101-1103.
9. Rego, Eduardo M., Haesook T. Kim, Guillermo J. Ruiz-Argüelles and Maria Soledad Undurraga, et al. ”Improving Acute Promyelocytic Leukemia (APL) Outcome in Developing Countries through Networking, Results of the International Consortium on APPL. ” *Blood* 121(2013): 1935-1943.

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