Getting to the Heart of Improving Outcomes for Patients With Acute Promyelocytic Leukemia

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By David Grimwade, MD, PhD [5] and Alan K. Burnett, MD, FRCP [6]

The management of patients with acute promyelocytic leukemia (APL) has been transformed over the course of the last two decades following the introduction of successful molecularly targeted therapies—all-trans retinoic acid (ATRA) and arsenic trioxide (ATO)—which act in concert to induce degradation of the PMLRARα oncoprotein formed by the chromosomal translocation t(15;17)(q22;q21).

The review by Stein and Tallman highlights several issues that are pertinent in the management of APL, including the importance of rapid diagnosis, prompt initiation of therapy, and use of the most appropriate management strategy, given that a significant proportion of patients may be cured without the need for conventional chemotherapy.

APL is now widely considered the most treatable form of acute myeloid leukemia (AML), based upon reported overall survival rates of up to ~90% in cooperative group trials using standard ATRA and anthracycline-based protocols.[1] In these studies, approximately one-quarter of patients have high-risk disease (defined as presenting WBC > 10,000/μL) and overall death rates for patients undergoing induction are typically below 10%. However, these reports paint a somewhat rosier picture than the real-life situation, as indicated by two recent population-based studies that considered outcomes for patients diagnosed within the ATRA era.[2,3] In a Swedish leukemia study in which 105 patients had APL, a much higher proportion (41%) had high-risk disease, and 30 (29%) died within 30 days of diagnosis, mostly as a result of hemorrhage.[2] In contrast, in a US study that reviewed Surveillance, Epidemiology and End Results (SEER) registry data for 1400 APL patients, early death rates of 17% were reported.[3] Interestingly, consideration of the clinical features of 407 consecutive APL patients who were subjected to molecular diagnostics by the UK reference laboratory showed that only 20% of those randomized into the national clinical trial presented with high-risk disease, compared with 36% of those treated contemporaneously off-study (P = .009).[4] Thus, taken together, the better outcomes reported in cooperative group trials may reflect a degree of selection bias, whereby patients with high-risk disease who are at greatest risk of early death are less likely to be recruited. This may occur for a variety of reasons, including presentation of patients with severe hemorrhagic or thrombotic complications that may preclude trial entry or recognition that high-risk APL requires immediate administration of anti-leukemic therapy, with insufficient time available to obtain informed consent. The European LeukemiaNet international guidelines emphasize the importance of considering APL as a medical emergency demanding immediate commencement of ATRA and supportive care measures to reduce risk of death from the coagulopathy.[1] However, an additional factor with potential impact on induction death rates in APL trials may relate to the still not uncommon practice of confirming the molecular diagnosis before study entry. This is not recommended, and inevitably some patients will die while the laboratory tests are in progress and hence will never be registered, so true early death rates will be underestimated. Therefore, in order to help achieve further improvements in APL outcomes, it is important that clinical trials be as inclusive as possible, allowing virtually all patients to be captured. In this regard, it may be helpful to implement the promyelocytic leukemia (PML) immunofluorescence test (see below) as a rapid routine screening method for analysis of all cases of suspected AML, to pick up APL cases that might otherwise be missed. Moreover, to improve outcomes it is of critical importance that ATRA be readily available in hospital emergency departments.

A further pressing issue that has hitherto been largely ignored in APL clinical trials relates to the
optimal management of the coagulopathy, which remains the major cause of death from the disease. While bleeding manifestations can be devastating, some patients may present with or develop thrombotic complications, which are challenging clinically but are also likely to have been somewhat under-reported.[5] There is an urgent need to undertake studies that will lead to establishment of more tailored approaches to managing the coagulopathy, adjusted to the needs of individual patients. Moreover, there are interesting recent data that merit further investigation, associating risk of early death in APL patients treated with ATRA and anthracycline-based therapy with the presence of a common polymorphism in the CD95 promoter, which leads to decreased gene expression.[6] Intriguingly, it has been shown that PML-RARA interacts with CD95 (FAS); hence the polymorphism may affect signalling through this pathway, impairing treatment response.[7] Subject to replication of this novel finding by other groups, it will be of interest to see whether this risk factor is overcome using novel treatment protocols involving ATO and ATRA in the absence of chemotherapy. Stein and Tallman provocatively suggest that taking a bone marrow (BM) sample at suspected diagnosis of APL, which sometimes causes the patient distress, may be clinically unnecessary. This, indeed, may be the case in patients with a significant population of circulating leukemic cells, but this will not be feasible when APL presents with cytopenia with few evaluable cells in the peripheral blood (PB). A prerequisite for appropriate use of molecularly targeted therapies is routine implementation of a range of laboratory assays to identify patients who will (or will not) benefit from a given agent and to understand the limitations of each respective assay. While ATRA has activity in a number of molecular subtypes of APL, ATO is only effective in cases with the PML-RARA fusion (which account for ~98% of APL cases).[8] However, it is important to appreciate that approximately 10% of APL cases with an underlying PML-RARA fusion lack the classical t(15;17) by cytogenetics, and small insertion events can be missed by standard probes used for fluorescence in situ hybridization (FISH) analysis.[9] Such cases will, however, be detected using the PML immunofluorescence test, characterized by a microparticulate staining pattern in cells expressing the PMLRARα fusion protein.[1,9] While these tests are helpful in identifying patients likely to benefit from targeted therapies, PCR-based diagnosis should be established as a matter of routine to determine PML-RARA isoform type, which is critical for reliable detection of minimal residual disease (MRD) using the appropriate assay.[1] The favorable outcomes reported in large-scale clinical trials using ATRA and chemotherapy-based schedules have prompted interest in whether deintensified protocols might achieve similarly good outcomes, while reducing treatment-related toxicity, risk of death in remission, and rates of therapy-related myelodysplastic syndrome (MDS)/AML. Many groups risk-stratify treatment approach based on presenting WBC count, administering more intensive therapy to patients with high-risk disease, given their increased risk of disease relapse. However, the UK Medical Research Council (MRC) group adopted a different strategy, preferring not to dose-intensify; instead, it investigated use of systematic maximum repeatable dose (MRD) monitoring by standardized real-time quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) to identify the subset of patients requiring additional therapy.[4] Sequential MRD monitoring to direct pre-emptive ATO therapy in the MRC AML15 trial was associated with a significant reduction in the rate of frank relapse compared with the previous MRC AML12 trial in which no MRD monitoring was performed (5% vs 12% at 3 years, P = .02). Moreover, early treatment intervention with ATO at the point of molecular relapse was less problematic than deployment of the drug in frank relapse, without induction of significant hyperleukocytosis or the associated differentiation syndrome, which can be life-threatening, necessitating admission to an intensive care unit.[4] It is less clear, because of a paucity of data, that this improves overall survival. Overall, molecular monitoring as a tool to guide pre-emptive therapy was found to be most costeffective in patients with high-risk disease, affording a 10% survival benefit at 5 years at a cost of $2,415 per quality-adjusted life-year.[4] Importantly, in this study it was shown that while MRD results between PB and bone marrow during early phases of therapy are concordant, PB is inadequate for longitudinal MRD monitoring due to inferior sensitivity, which would not give sufficient warning to allow early treatment intervention to prevent frank relapse and the associated risk of fatal hemorrhage.[4] Stein and Tallman conclude by making a very attractive proposition that in future years it may be possible to treat APL patients with oral molecularly targeted therapies, checking an occasional blood sample to confirm molecular remission. However, the efficacy of oral arsenic remains to be confirmed in large-scale phase III trials. The main therapeutic challenge is the prevention of early death (death within 30 days), by limiting the adverse effect of a high presenting WBC count. Moreover, there remains uncertainty concerning the optimal management of APL with respect to induction, consolidation, and the role of maintenance therapy, in conjunction with a paucity of data
on late sequelae of arsenic therapy. Therefore, while a significant proportion of APL patients may be curable with molecularly targeted therapies, a cautious approach to the adoption of deintensified treatment protocols seems merited, involving the careful use of sequential MRD monitoring of serial BM samples as a safeguard to rapidly identify the subgroup of patients who require additional therapy—who currently cannot be reliably identified based on pretreatment characteristics.

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**References:**


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