**Acute promyelocytic leukemia then and now**

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**INTRODUCTION**

Only a few thousand people worldwide are diagnosed each year with a rare tumour known as acute promyelocytic leukemia (APL), a subtype of acute myelogenous leukemia (AML). However, progress in the treatment of APL, leading to dramatic improvements in patient outcomes, provides a unique paradigm in the field of oncology. Once considered one of the most malignant and rapidly fatal AML subtypes, APL has been transformed over the past 2 decades into the most frequently curable. This article provides a timeline of advances in both biologic and clinical research that have enabled more precise diagnosis and highly effective treatment (Figure 1).

**UNRAVELLING THE CAUSE OF APL**

In 1957, the Norwegian hematologist Leif Hillestad first identified APL as a distinct, highly aggressive subset of AML. The disease was described in more detail in 1959 by Jean Bernard, who reported on a series of 20 cases observed at St. Louis Hospital in Paris. However, it was only in 1977 that the unique translocation between chromosomes 15 and 17 (t[15;17]) that characterizes APL was described by Janet Rowley in Chicago.1

Then, in 1990, the altered genes involved (15;17) were identified. These were PML, a newly identified gene named after promyelocytic leukemia, and RARA (retinoic acid receptor alpha), which fuse as a consequence of the translocation to form the PML-RARA hybrid gene. Interestingly, the empirical use of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) preceded by a few years the notion that these 2 agents actually target the RARA and PML moieties, respectively, of the hybrid protein.1

Progress in pinpointing the molecular features of APL also paved the way for more precise diagnosis at the genetic level. The gold standard for diagnosis today is reverse transcriptase-polymerase chain reaction (RT-PCR) from either bone marrow or peripheral blood (when infiltrated by high blast numbers), followed by fluorescence in situ hybridization (FISH) may also be used.2 White blood cell (WBC) counts are an important prognostic factor and help to determine the need for aggressive early treatment, as well as the risk of early death and relapse following initial treatment. The presence of PML/RARA fusion protein drives the disease and is predictive of favourable response to targeted treatment with ATRA and ATO.2,3

**APL TREATMENT: PAST, PRESENT AND FUTURE**

The first major breakthrough in the treatment of APL came in 1973, when the disease was found to be highly sensitive to daunorubicin. Clinical trials showed some durable responses with anthracycline chemotherapy, and this approach was adopted in Italy and Spain, where specifically tailored clinical studies were designed for APL long before the advent of ATRA.4

Chinese scientists reported in 1988 that APL was highly sensitive to ATRA, which produced terminal differentiation of leukemic cells without inducing myelosuppression.5 This finding contradicted the dogma that malignant transformation was always an irreversible condition.

In 1997, a group from Shanghai reported that APL was also highly responsive to arsenic trioxide (ATO), an old remedy used for many centuries in the treatment of various conditions, including cancer.6 The efficacy of ATO as a single agent in APL was first established in patients who relapsed after ATRA + chemotherapy.7

Studies published in the early 2000s showed improved overall and relapse-free survival with ATO + ATRA in both relapsed and newly diagnosed low-risk patients.8,9 The randomized APL0406 trial found that ATO + ATRA was noninferior to ATRA + chemotherapy in low-intermediate risk patients, with higher event-free and overall survival after 2 years, less hematologic toxicity and fewer infections.10,11 In 2015, another randomized trial reported significantly better outcomes and less hematologic toxicity for ATRA + ATO vs ATRA + chemotherapy.12 A chemotherapy-free treatment regimen also reduces the risk of developing secondary malignancies.13,14

**RECOGNIZING A MEDICAL EMERGENCY**

APL is a rare disease with early symptoms that may be attributed to other causes, increasing the risk of delayed or missed diagnosis. Comprising just 10% to 15% of all patients with newly diagnosed AML,14 only 399 cases of APL were diagnosed in Canada between 1993 and 2007.15 Clearly, many physicians will never see a case of APL. The most common symptoms include easy bleeding or bruising, pallor, dyspnea, fatigue, fever and infection. Compared to other AMLs, APL affects a younger patient population: the median age at diagnosis for APL is 44, versus 67 for AML. Men and women are affected in almost equal numbers.16,17

Prompt diagnosis is crucial, as APL frequently develops abruptly, and patients are at high risk of mortality from cerebral or pulmonary hemorrhage, which may occur in up...
to 40% of untreated patients. Hence, the disease has to be considered and managed as a medical emergency.

Initiating treatment quickly is essential in a patient suspected of having APL. Patients presenting with clinical symptoms suggestive of APL should have a blood and bone marrow smear done rapidly in conjunction with coagulation tests. Meanwhile, a sample should be sent to the reference laboratory for genetic analysis to identify the PML/RARA by RT-PCR or FISH. Simultaneously, and even before results of the RT-PCR are available, aggressive supportive care should be instituted with transfusion of platelets and fresh frozen plasma (or concentrates), and treatment with ATRA should be started.

Risk stratification is important for determining appropriate treatment and assessing the risk of relapse: patients with WBC counts ≤1x10⁹/L are considered as low-intermediate risk and are generally at risk for relapse, while those with WBC counts >10x10⁹/L are considered at high risk and are generally subjected to more intensive consolidation regimens.

CURRENT RECOMMENDATIONS
Until recently, ATRA + chemotherapy was the standard first-line therapy for APL, and it is still widely used in this setting. However, a chemotherapy-free approach has become the current standard of care for induction therapy in untreated low- to intermediate-risk APL patients.

The U.S. National Comprehensive Cancer Network (NCCN) 2016 guidelines endorse the following options for newly diagnosed low-, intermediate- and high-risk patients: ATRA + ATO (+ idarubicin for high-risk patients); ATRA + daunorubicin + cytarabine; or ATRA + idarubicin. The panel advises using patient risk group, age and cardiovascular risk to guide regimen selection, and following the chosen trial protocol consistently for both induction and consolidation. NCCN notes that all 3 combinations “will yield excellent results,” but lists ATRA + ATO as the first choice based on the APL0406 study results.

Canadian consensus guidelines released in 2014 recommend ATRA + ATO for both induction and consolidation in untreated low- to intermediate-risk APL patients and, for high-risk patients, induction with ATRA + ATO + idarubicin, followed by consolidation with ATRA + ATO.

ATO has been approved for induction of remission and consolidation in patients with APL that is refractory to or has relapsed from retinoid and anthracycline therapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML-RARA gene expression. Screening for cardiac arrhythmias is essential, along with monitoring for hemorrhage, liver function alterations and QTc prolongation.

Patients on ATRA or ATO need to be managed with vigilant monitoring for signs of potentially fatal differentiation syndrome (DS), which include: dyspnea, fever, weight gain, peripheral edema, hypotension, acute renal failure, congestive heart failure and, especially, pulmonary infiltrates or pleuropericardial effusion, with or without leukocytosis. At early signs of DS, high-dose dexamethasone should be used immediately; in certain situations, such as patients with WBC counts >10x10⁹/L, steroids may be provided prophylactically.

REAL-WORLD OUTCOMES
Survival in APL has improved dramatically over the years: 5-year relative survival was only 18% in the 1975–1990 period, compared to 64% in 2000–2008. The early death rate (≤30 days after diagnosis) is low for patients enrolled in clinical trials (5%–10%) but remains high in the “real world” (17%–29% in registry studies). Older patients have still-poorer outcomes: population-based studies in Canada have shown an early death rate of 10.6% among <50-year-olds, but a significantly higher 35.5% in patients ≥50.

CONTINUING CHALLENGES
Despite impressive progress, APL still represents a challenging disease, with many patients dying early of severe hemorrhage. It is likely that misdiagnosis, late recognition and delayed referral to secondary/tertiary care centres contribute to this situation. In addition to educational efforts, further laboratory and clinical investigation is needed to predict and prevent severe hemorrhagic and thrombotic events.

References


