Timely diagnosis and treatment of acute promyelocytic leukemia should be available to all

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In the first report of acute promyelocytic leukemia (APL) as a discrete entity in 1957, Hillestad[1] characterized it as having "a very rapid fatal course of only a few weeks' duration", largely due to a severe bleeding tendency. He concluded that the disease "seems to be the most malignant form of acute leukemia". In the decades since that time, the treatment of APL has improved progressively with the sequential introduction of acute myeloid leukemia-type chemotherapy, all-*trans* retinoic acid (ATRA), and arsenic trioxide, such that APL is now considered one of the great successes in leukemia treatment. With the use of regimens containing ATRA plus arsenic trioxide, long-term overall survival rates of at least 95% are achievable in both low-/intermediate-[2] and high-risk[3] APL.

In the face of such results, it is sobering to remember, however, that not all patients with APL fare this well. Indeed, APL remains extremely deadly up front, with such outstanding outcomes restricted largely to those patients in whom the diagnosis is actually suspected, treatment with ATRA is started immediately at the first suspicion of APL, coagulation abnormalities are corrected aggressively, and referral/transfer to a leukemia-treating center is initiated promptly, together with timely prevention/management of APL differentiation syndrome. In the absence of such timely diagnosis and treatment, outcomes remain poor. More than 60 years after its initial description, early death remains the major problem in APL management.

Over the last 10 years, several groups, both in Europe and in North America, have confirmed that APL early death rates are higher in real life than would be suggested by clinical trial outcomes, have identified factors and management gaps potentially contributing to early death, and have suggested possible interventions to improve outcomes.[4-12] Such studies have been heterogeneous in design and execution, and have included population-based registry analyses, as well as single-centre and multiple-centre retrospective reviews, from multiple jurisdictions, so inter-study comparisons have been difficult. While there are some discrepancies among studies, triggering attempts to explain these differences,[4,5] common themes include reported early death rates ranging from 9-30%, with most early deaths occurring within the first 7-10 days, and most commonly related to hemorrhage (commonly intracerebral). In addition, some (but not all) studies have suggested that early deaths increased with delay in APL diagnosis, delay in ATRA initiation, delay in hospital admission, older age of the patients, and admission to a non-teaching hospital. Consistent with the last point, when considered together with the rarity of APL, physicians' awareness and experience have also been suggested as gaps. While delay in starting ATRA treatment was identified by some groups as a key factor in early deaths, and 30-day mortality was shown to decrease significantly from the pre-ATRA to the post-ATRA era,[7] two population-based studies did not observe decreasing early death rates over time, contrary to what would have been expected with increased ATRA usage over the same time period.[5,6] Early death in APL patients is clearly multifactorial in origin. Differences among study outcomes remain poorly explained, but are presumably related to patient, institutional, and jurisdictional differences, among others, including, speculatively, interrelated differences in healthcare availability and socio-economic status.

As a result of these reports, strategies to reduce early deaths have been introduced in many jurisdictions. The overarching goal of such initiatives has been medical provider education and mentorship, with a view towards better disease awareness and diagnosis, the early administration of ATRA at the first suspicion of APL, aggressive blood product support, early consultation and transfer (or co-management) as appropriate, and timely prevention and management of APL differentiation syndrome.[13-15] At our institution, in addition to the longstanding 24/7 access to an acute leukemia physician, a policy of recurrent community APL teaching and prompt APL transfer, and an "ATRA Program" (whereby all emergency rooms in our acute leukemia catchment area have ATRA on hand), has been in place for almost 10 years. While the outcomes of such programs are difficult to assess in the short term, early reports are promising.[14]

In the current issue of *Haematologica*, Abrahão *et al.*[15] help to clarify some of these issues. The authors previously analyzed early deaths in adolescents and young adults with APL in California,[12] and showed that among patients aged ≤39 years diagnosed with APL, 30-day mortality decreased from 26% pre-ATRA (1988-1995) to 14% post-ATRA (2004-2011). In contrast, however, 7-day mortality did not differ between pre- and post-ATRA eras. Notably, a higher risk of 30-day mortality and inferior overall survival were observed among patients without health insurance and those of Black and Hispanic race/ethnicity.[12] The authors concluded that efforts to achieve equal outcomes in young patients with APL should focus on improving access to effective treatment, mainly among these underserved groups. The authors' current report underscores this chilling recommendation.

The authors now report an update of early APL outcomes in the California group of adolescents and young adults, dividing patients into subgroups based on health insurance status. Patients could be privately insured, could be enrolled under Medicaid (a program that covers healthcare costs for non-elderly people with low incomes), or could be uninsured. With respect to Medicaid coverage, patients were divided into three time-based groups (pre-, early-, and full-) based on the introduction and adoption of the Affordable Care Act (ACA;

also known as 'Obamacare'), which expanded Medicaid eligibility. The authors report reduced early mortality in post-ACA *versus* pre-ACA patients, and also that location of care played a key role: Patients diagnosed/treated at National Cancer Institute-Designated Cancer Centers had lower mortality rates and better overall survival than did patients treated elsewhere.

This report is important in several areas that help to clarify previous observations (and the discordance among observations). First, it underscores that in APL, healthcare access is at least as important as are other factors influencing early deaths. Indeed, in the absence of timely access, none of the other factors - early diagnosis, immediate ATRA availability, vigorous correction of coagulopathy, etc. - really matters. As a Canadian enjoying universal healthcare access, I am moved by this realization. Second, treaters' experience and expertise with APL are important. This study confirms previous suggestions regarding better APL outcomes at 'teaching' or 'university' hospitals. And third, the improved outcomes over time in this report suggest that efforts to eradicate early deaths have been effective, at least in part, and provide hope that with further efforts, we can solve the problem of early deaths in patients with APL.

In the right circumstances, APL is a curable disease. Potential cure is an opportunity that should be available to all afflicted individuals.

Disclosures

No conflicts of interest to disclose.

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