Modern treatment of acute promyelocytic leukemia

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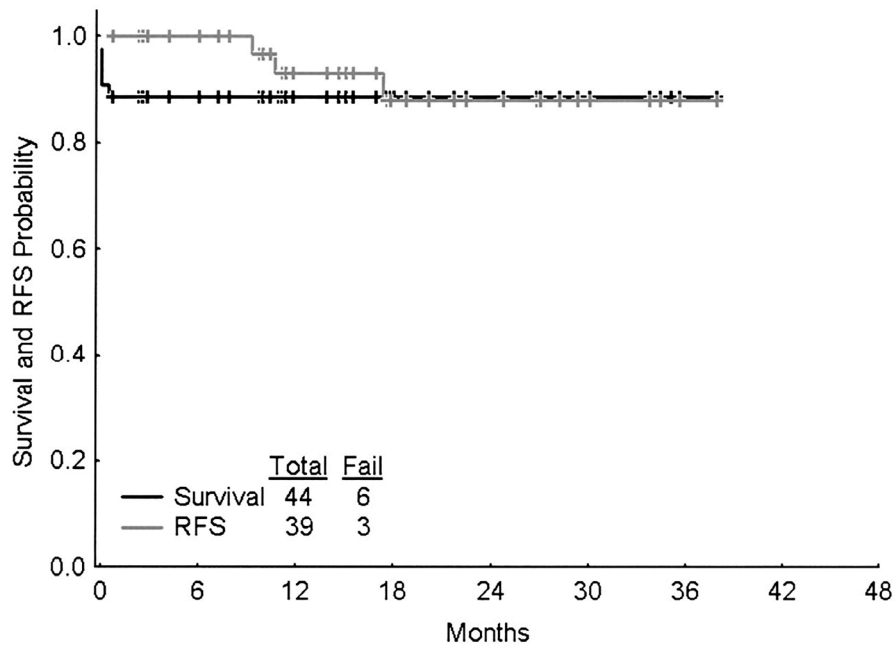
https://doi.org/10.3324/haematol.2025.289382

TITLE	Use of all-*trans* retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia.
AUTHORS	Estey E, Garcia-Manero G, Ferrajoli A, *et al.*
JOURNAL	Blood. 2006;107(9):3469-3473.

Progress in the treatment or acute promyelocytic leukemia (APL) has been one of the major successes of therapy for acute myeloid leukemia (AML) in the last two decades. Prior to that anthracycline-based chemotherapy with all-*trans* retinoic acid (ATRA) followed by 2 years of chemotherapy maintenance had been established as front-line therapy for APL with the majority of patients curable. In the interim, pioneering studies by Chinese investigators demonstrated the efficacy of arsenic trioxide (ATO) combined with ATRA in patients with relapsed APL and in a limited number of newly diagnosed patients who were also given chemotherapy in consolidation (Shen Z-X *et al.*; 2004). In 2006 investigators from the MD Anderson Cancer Center led by Dr Eli Estey published the first comprehensive report of the combination of ATRA and ATO as front-line therapy of APL with the addition of a single dose of gemtuzumab ozogamicin (GO) for patients with high-risk disease only, thus minimizing or eliminating cytotoxic chemotherapy from induction and consolidation and laying the foundations for the modern treatment approach.[1] A total of 44 patients were treated and the authors reported excellent results, particularly in low-risk patients presenting with a white count (WBC) of less than $10x10^9$/L (Figure 1). The authors suggested that the combination of ATO and ATRA could serve as a completely chemotherapy-free option for low-risk patients and, when combined with limited chemotherapy in induction, could improve the outcome in high-risk disease. These suggestions were later confirmed by two large multicenter phase III trials comparing the efficacy and safety of ATRA plus ATO compared with ATRA plus chemotherapy. One trial was conducted by the Italian Group for Adult Hematologic Diseases (GIMEMA) in collaboration with the German-Austrian AML Study Group and the Study Alliance Leukemia Cooperative Group, and randomized patients with low-risk APL (WBC count $\leq 10\times10^9$/L) to ATRA plus ATO or ATRA plus chemotherapy (AIDA regimen).[2] The other randomized trial, conducted by the National Cancer Research Institute, also included high-risk patients who also received GO given on day 1.[3] Based primarily on the results of these two randomized trials and the long-term results of the study by Estey *et al.*, the combination of ATRA plus ATO was adopted as the new standard of care for patients with non-high-risk APL (WBC count $\leq 10\times10^9$/L). More recently, the phase III APOLLO trial evaluated newly diagnosed high-risk APL patients randomized to ATRA and ATO plus idarubicin given on days 1 and 3 rather than GO, *versus* the AIDA regimen. Event-free survival was significantly improved in the ATRA and ATO arm with a significant reduction in the risk of relapse. The superiority of ATO plus ATRA, regardless of risk score and patient age, has also been confirmed by real-world data



Overall survival and relapse-free survival (RFS). Figure reproduced, with permission, from Estey *et al.*[1]

from the HARMONY project in an analysis of over 1,400 patients treated between 1999 and 2022,[4] which showed improvements in survival and reduced relapse risk for these patients compared to those treated with AIDA-like chemotherapy. Overall survival at 7 years was over 91% compared to 81% with chemotherapy. Furthermore, these studies in APL have paved the way to the development of less toxic, more targeted therapies in the treatment of other types of AML.

Disclosures

No conflicts of interest to disclose.

References

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