Evolution in treatment of acute promyelocytic leukemia: a major victory

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TITLE	Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia.
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Acute promyelocytic leukemia (APL) is the most curable subtype of acute myeloid leukemia (AML) in adults. The leukemia cells express the t(15;17)(q24;q21) leading to the formation of the *PML::RARα* fusion transcript which inhibits differentiation of the leukemia cells. During the last 50 years, treatment has progressively evolved. Approximately 98% of low-risk patients (presenting white blood cell count [WBC] </= $10x10^9$/L) and > 90% of high-risk patients (WBC > $10x10^9$/L) who survive induction are cured of their disease. The first important observation addressing treatment was made in 1973 when Bernard and colleagues reported unusual sensitivity of the leukemia cells to single agent daunorubicin which induced complete remission (CR) in 55% of patients with a longer duration of CR (median 26 months) compared to that among other subtypes of AML (median 7 months).[1] However, in a landmark publication, the most important breakthrough came in 1988 when Huang and co-workers reported stunning results among patients treated with the oral vitamin derivative all-trans retinoic acid (ATRA), an agent known to induce differentiation of leukemia cells *in vitro*.[2] Of 24 patients (8 previously treated, 16 untreated), 100% achieved CR, and remarkably, without obligatory marrow aplasia. Furthermore, cultured leukemic promyelocytes showed morphological evidence suggestive of progressive differentiation (Figure 1). Four of 6 patients maintained

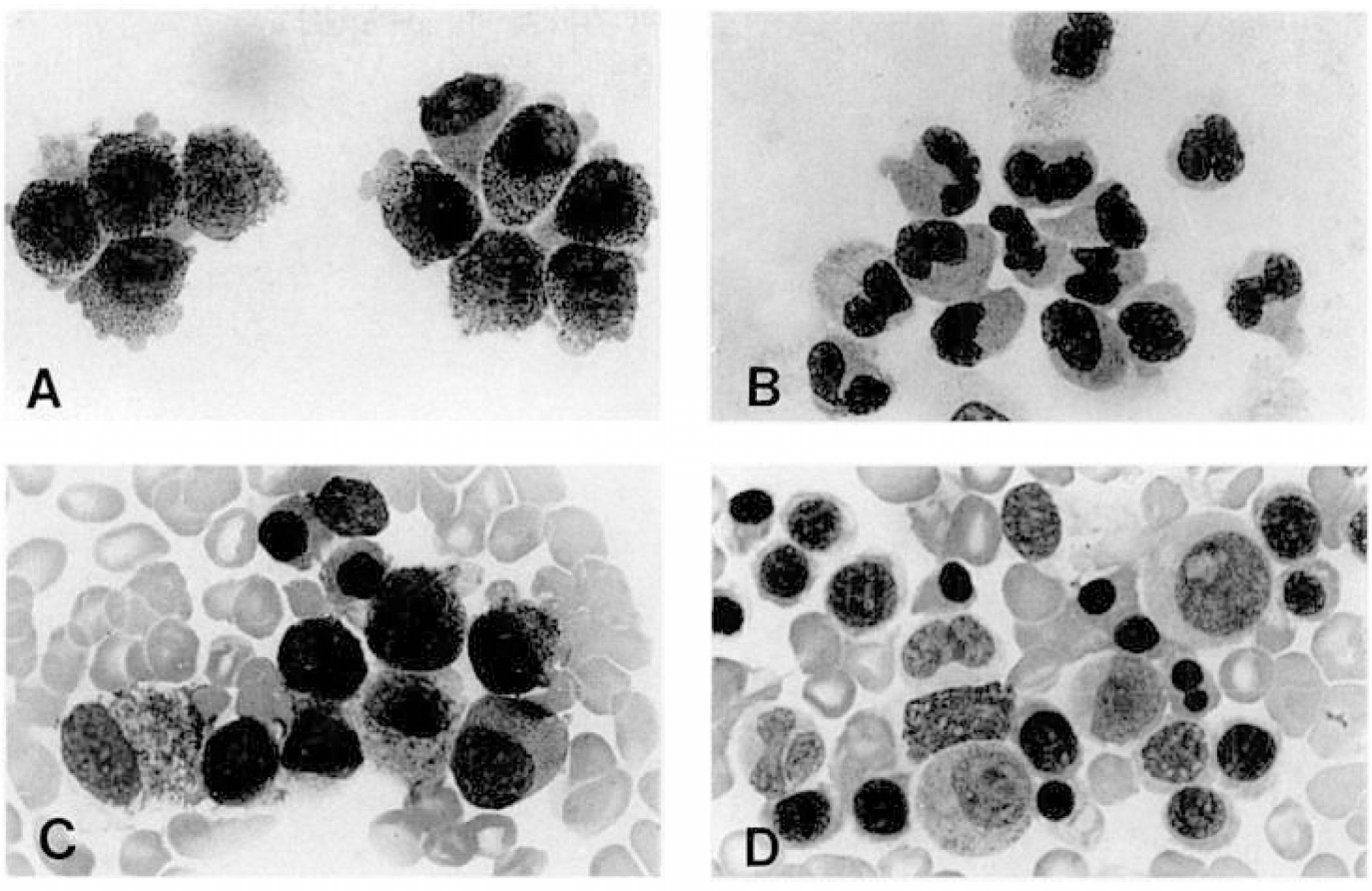

Figure 1. Morphological maturation of leukemic cells of case N. 10 *in vitro* and *in vivo*. (A) Cells cultured without retinoic acid (RA), consisting of promyelocytes with characteristic cytoplasmic granules (x1,000). (B) Cells cultured with RA, showing maturation to granulocytes (x1,000). (C) Bone marrow before RA treatment. The predominance of promyelocytes (76%) indicates typical acute promyelocytic leukemia. (D) Bone marrow after five weeks of RA treatment. Promyelocyte level <2% and restoration of normal hematopoiesis without a phase of aplasia are consistent with differentiation induction.[2] (Figure from Huang *et al.*[2] Reproduced under an Elsevier user license.)

with ATRA alone remained in CR for 5-10 months. It was subsequently demonstrated that the mature neutrophils retained the t(15;17)(q24;q21), confirming that the mechanism of successful induction is differentiation.

The introduction of ATRA represents the major turning point towards the curative treatment of APL, and also ushered in the era of effective molecularly-targeted therapy for hematologic malignancies. Given the observations of Bernard and colleagues, it was logical to combine ATRA with chemotherapy, particularly anthracyclines. Cooperative groups conducted trials of ATRA combined with either single agent anthracyclines or combination chemotherapy, yielding outstanding results. In these studies, the relapse-free survival at three years is approximately 90%. This approach established a new standard of care until a second major breakthrough came with the identification of the effectiveness of arsenic trioxide (ATO), shown to induce apoptosis with elimination of the PML-RARα fusion transcript. Lo Coco and colleagues for the GIMEMA established a new standard of care for low-risk patients combining ATRA plus ATO without chemotherapy in induction (except hydroxyurea to control the WBC), consolidation or maintenance. In this randomized trial, CR was achieved in 100% in patients treated with ATRA plus ATO and 95% in the patients treated with ATRA plus chemotherapy.[3] The 2-year event-free survival among the patients treated with ATRA plus ATO was 97% and 86% among patients treated with ATRA plus chemotherapy. The Australasian Leukemia Lymphoma Group included high-risk patients in a phase II trial of induction with ATRA, idarubicin and ATO, ATRA plus ATO for 2 cycles of consolidation and two years of maintenance with ATRA, 6-mercaptopurine and methotrexate in previously untreated patients.[4] The 2-year freedom from relapse, failure-free survival, and overall survival were 97.5%, 88.1%, and 93.2%, respectively.

The last frontier in treatment may well be incorporation of an oral formulation of arsenic. In a successful phase III non-inferiority trial, Zhu and colleagues randomized newly diagnosed patients to either an oral tetra-arsenic tetra sulfide-containing formulation plus ATRA or ATO plus ATRA for induction.[5] Subsequently, all patients were given 3 cycles of chemotherapy consolidation followed by maintenance. The major victory is that the majority of patients with APL can now be cured without chemotherapy since 75% of patients present with low-risk disease.

Disclosures

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