ATRA and arsenic trioxide versus ATRA and idarubicin for newly diagnosed, non high-risk acute promyelocytic

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New research demonstrates the efficacy of the first curative treatment for acute promyelocytic leukemia (APL) that does not include chemotherapy, marking an important step toward front-line use of targeted therapies for acute leukemia.

APL is an uncommon, yet aggressive, subtype of acute myeloid leukemia (AML) in which there are too many immature white blood cells in the bone marrow, leading to a shortage of normal white and red blood cells and platelets in the blood, which is associated with clotting defects that can cause serious bleeding. Without prompt diagnosis and treatment, APL can be fatal in a matter of hours or days.

Early treatment regimens for APL relied heavily on anthracycline-based chemotherapy with daunorubicin or idarubicin. In the early 1990s, research supported the addition of a non-chemotherapeutic agent, all-trans-retinoic acid (ATRA, a vitamin A derivative developed from ancient Chinese herbal medicine), to standard regimens. ATRA causes cancer cells to develop fully into mature blood cells, which progress through full differentiation and eventually die (unlike leukemia cells that are unable to fully mature). The combination regimen of chemotherapy and ATRA dramatically improved the survival outlook for those with APL and made the disease curable in up to 80 percent of patients. More recently, another natural compound, arsenic trioxide (ATO), was integrated into APL treatment, showing higher efficacy and better

tolerability when compared with conventional chemotherapy. Today, as investigators continue to report the success of targeted cancer therapies (best exemplified by imatinib for chronic myeloid leukemia), researchers have questioned whether traditional toxic chemotherapy is still necessary to achieve high cure rates for patients with APL.

To investigate whether a combination of ATO+ATRA could provide the same therapeutic benefit as conventional treatment including chemotherapy, researchers from the Italian-German cooperative teams Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA), Study Alliance Leukemia (SAL) group, and German-Austrian AML Study Group (AMSLG) designed a multicenter, international Phase III trial in which 162 patients with standard-risk APL were divided into two treatment arms. Patients in Arm A received a regimen of ATO+ATRA, while patients in Arm B received the standard ATRA+idarubicin (AIDA) treatment regimen. The primary study objective was event-free survival (EFS) at two years, with secondary objectives including overall survival (OS), disease-free survival (DFS), cumulative incidence of relapse (CIR) rates, molecular response, and safety.

Results suggest that the targeted ATO+ATRA therapy strategy might offer similar efficacy to the chemotherapy-based regimen. In the 154 patients who were evaluable for response, complete remission was achieved in all patients (100%) in the ATO+ATRA arm and 95 percent in the AIDA arm. EFS was observed in 97 percent in the ATO+ATRA arm, with one death and two relapses, compared to 86.7 percent in the AIDA arm, in which seven deaths and four relapses were observed. Overall survival, DFS, and CIR rates were 98.7 percent, 97 percent, and 1.6 percent, respectively, in the ATO+ATRA arm, versus 91.1 percent, 91.6 percent, and 4.3 percent, respectively, in the AIDA arm. Additionally, fewer side effects (fever, low neutrophil and platelet counts) were observed in the ATO+ATRA arm.

"This is one of the first times that we can report the success of a treatment strategy for an acute leukemia that relies solely on targeted molecular therapy," said Francesco Lo-Coco, MD, lead author and Chairman of the APL subcommittee of the Italian GIMEMA group and Professor of Hematology at University Tor Vergata in Rome, Italy. "Our results are an important step toward the further utilization of targeted therapies for other types of leukemia, as we begin to focus on improving the overall treatment experience for patients by offering new strategies that deliver the same efficacy as traditional options with considerably lower toxicity."

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