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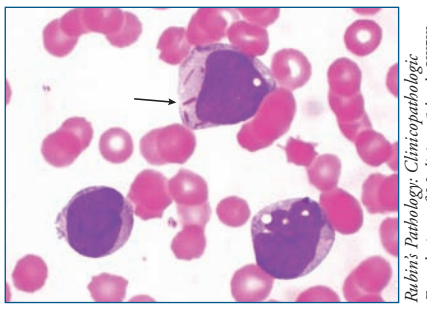
PERIODICALS

[ALSO]

ASH Plenary Study

APL: Nontoxic Cure without Chemotherapy

BY MARK FUERST



Rubin's Pathology: Clinicopathologic Foundations of Medicine, 5th ed, LWW

"Confucius said, 'Do not kill criminals; convert them to good guys.' When Chinese researchers found that malignant cells were induced to differentiate with ATRA in 1988, they transformed malignant cells into 'good guys' and demolished the dogma that tumors are irreversible… We hope that in the future, many poisons will be exploited as medical remedies by Western researchers."

ATLANTA—The first curative treatment for acute promyelocytic leukemia (APL) that does not include chemotherapy marks an important step toward frontline use of targeted therapies for acute leukemia, researchers said here at the American Society of Hematology Annual Meeting about the findings of a plenary study (***Abstract 6***) that call into question whether traditional toxic chemotherapy is still necessary to achieve high cure rates for patients with APL.

"APL is a rare leukemia that has gone from highly fatal to highly curable. Treatment has shifted from poisons to remedies," said the lead author of the study, Francesco Lo-Coco, MD, Chairman of the APL subcommittee of the Italian GIMEMA group and Professor of Hematology at University Tor Vergata in Rome.

Speaking at a news briefing that included this study as well as others in the overall category of "Personalizing Blood Cancer Treatment to Reduce Toxicity and Improve Survival," Lo-Coco said, "Cancer is not an irreversible condition—malignant cells can be transformed rather than killed. Certain poisons may be remedies. We can cure acute leukemia without chemotherapy.

"APL is a model disease that has continuously inspired investigation generating important insights, and it can be said that APL's future history may still have novel unexpected discoveries in store and so add new thrilling chapters to this revolutionary tale."

'Groundbreaking, First Example of Approach Not Using Cytotoxic Chemotherapy to Achieve Excellent Results'

ASH 2012 President Armand Keating, MD, Professor of Medicine at the University of Toronto, said: "This groundbreaking study is the first example of an approach that does not use cytotoxic chemotherapy to achieve excellent results. APL used to be a devastating disease—35 years ago there was 100 percent mortality, and most patients died in one week. Now we have made enormous progress.

"This study will spur a lot of activity in research into how non-toxic therapies work. In years to come, we will find a number of studies that will address this not just in leukemia but in other disorders as well."

In his ASH Plenary session presentation, Lo-Coco outlined the continued progression of therapy of APL from chemotherapy in 1973 to chemotherapy plus a non-chemotherapeutic agent, all—trans-retinoic acid (ATRA), a vitamin A derivative developed from ancient Chinese herbal medicine, in 1993 to ATRA plus another natural compound, arsenic trioxide (ATO), in 2012.

American Society of Hematology

FRANCESCO LO-COCO, MD: "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. Our results are an important step toward the further utilization of targeted therapies for other types of leukemia."

Early treatment regimens for APL relied heavily on anthracycline-based chemotherapy with daunorubicin or idarubicin. In the early 1990s, research supported the addition of ATRA to standard regimens. 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, ATO was integrated into APL treatment, showing higher efficacy and better tolerability when compared with conventional chemotherapy.

The combination therapy of ATRA plus ATO works by two separate mechanisms of action, he explained. ATRA induces 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). ATO works by inducing cell death via apoptosis. The altered protein present in APL cells has specific binding sites for both ATRA and ATO.

To investigate whether a combination of ATRA plus ATO could provide the same therapeutic benefit as conventional treatment including chemotherapy, Lo-Coco and his co-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 from 67 centers with standard-risk APL were divided into two treatment arms. Most (62%) of the patients, median age about 45, were in the intermediate-risk category, and the rest were categorized as low-risk. The two treatment arms were well balanced for main baseline characteristics, Lo-Coco noted.

Patients in one arm received a regimen of ATO at 0.15/kg plus ATRA at 45 mg/m^2 daily until complete remission, then ATO for five days/week; four weeks on, four weeks off, for a total of four courses; and ATRA for two weeks on and two weeks off for a total of seven courses.

Patients in the other arm received the standard ATRA plus idarubicin (AIDA) induction followed by three cycles of anthracycline-based plus ATRA consolidation and low-dose chemotherapy and ATRA for maintenance.

After a median follow-up of 34.3 months, the results showed that the targeted ATRA plus ATO therapy 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 in the ATRA plus ATO arm and in 95 percent in the AIDA arm. Two-year, event-free survival was observed in 97 percent of patients in the ATRA-plus-ATO arm, with one death and two relapses, compared with about 86 percent in the AIDA arm, in which seven deaths and four relapses occurred.

Overall survival and cumulative incidence of relapse rates were superior in the ATRA-plus-ATO group (98.7% and 1.5%, respectively) compared with the AIDA arm (91.1% and 5.6%, respectively). The survival differences, both overall and event-free, were statistically significant; the relapse difference was not statistically significant, he reported.

Fewer side effects, including fever, low neutrophil counts, and platelet counts, were observed in the ATRA-plus-ATO arm of the study; these patients did have more hepatic toxicity, leukocytosis, and QTc prolongation, he said. Hematologic toxicities were more common in the chemotherapy arm in induction and consolidation. Other side effects including differentiation syndrome and increase of liver enzymes were recorded with similar frequency in the two study arms.

In conclusion, Lo-Coco said, "ATRA plus ATO is at least not inferior to ATRA plus chemotherapy for two-year event-free survival in low/intermediate-risk APL. The combination therapy is associated with less hematologic toxicity and more, yet manageable, hepatic toxicity and QTc prolongation. This regimen may emerge as the

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→APL

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new standard of care for low/intermediate-risk APL."

He added: "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. 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."

The Introducer at the plenary session, Pierre Fenaux, MD, PhD, of Hospital Avicenne in Bobigny, France, noted that the treatment of APL has continued to progress in the past 25 years, with ATO being the second non-toxic targeted treatment for APL.

"APL is a model disease that has continuously inspired investigation generating important insights, and it can be said that APL's future history may still have novel unexpected discoveries in store and so add new thrilling chapters to this revolutionary tale."

"The importance of the results is that this is the first highly effective treatment of acute leukemia without chemotherapy, which is applicable to 75 percent of APL patients," he said. "It has limited toxicity, allowing treatment in frail patients and in emerging countries. This paves the way for targeted therapies in other acute leukemias."

'Brilliant, First-of-Kind Study That Opens the Door to Follow-Up Studies'

Asked for his opinion for this article, the moderator of the news briefing, William Woods, MD, Hematology/Oncology Director and the Daniel P. Amos Children's Chair at Aflac Cancer Center and Blood Disorders Service at Children's Healthcare of Atlanta, said, "Lo-Coco has uncovered the first curative treatment for APL that does not include a myelosuppressive drug. This is a huge step in front-line use of targeted drugs for acute leukemia. We have been dependent on chemotherapy to cure leukemia. This is a brilliant first-in-kind study that opens the door to follow-up studies."

"APL used to be a devastating disease—35 years ago there was 100% mortality, and most patients died in one week. Now we have made enormous progress."

Noting that Chinese medicine practitioners have used herbal medicines and arsenic for thousands of years, Lo-Coco said, "Confucius said, 'Do not kill criminals; convert them to good guys.' When Chinese researchers found that malignant cells were induced to differentiate with ATRA in 1988, they transformed malignant cells into 'good guys' and demolished the dogma that tumors are irreversible."

Lo-Coco speculated that in the future, many poisons will be exploited as medical remedies by Western researchers. OT