Arsenic early in treatment improves survival for leukemia patients

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Arsenic, a toxic compound with a reputation as a good tool for committing homicide, has a significant positive effect on the survival of patients with acute promyelocytic leukemia (APL), when administered after standard initial treatment, according to a new, multi-center study led by a researcher at Wake Forest University Baptist Medical Center.

While arsenic trioxide (As2O3) is known by clinicians to be a highly effective treatment for patients with relapsed APL, its benefit earlier in treatment, after first remission, has remained unknown…until now.

Researchers with the Cancer and Leukemia Group B, a group of cancer and leukemia researchers funded by the National Cancer Institute, led a study to determine if, by administering arsenic trioxide earlier – after a patient has finished standard initial treatment and reached first remission – they could improve survival rates. The results were dramatic.

"Patients with APL can achieve remission with standard treatment (chemotherapy plus ATRA, an oral vitamin A-based compound), but it often comes back," said Bayard L. Powell, M.D., a professor of hematology and oncology at Wake Forest Baptist, principal investigator and lead author on the study. "Arsenic trioxide is then used to get them back into remission, often followed by a bone marrow transplant to try to cure the patient. For this study, we used arsenic as an early "consolidation therapy" after the initial standard treatment to essentially, as one of our first patients described, 'seal the deal' the first time around. Not only did the leukemia rarely return in the patients who received the

arsenic, those patients also lived longer."

The findings appear in the November 11 issue of *Blood*.

APL accounts for about 10 to 15 percent of acute myeloid leukemia cases and presents most frequently in young adults. It is associated with a very high risk of severe bleeding complications, including early death from bleeding into the brain.

Current treatment of APL involves a combination of all-trans retinoic acid (ATRA) plus chemotherapy to induce remission, followed by additional "consolidation" chemotherapy to strengthen the remission, followed by further ATRA with or without oral chemotherapy to maintain remission. This approach yields complete remission rates of about 90 percent and improved event-free survival, with an "event" defined as failure to achieve complete remission, relapse after achieving complete remission, or death.

Those with high white blood cell counts at diagnosis have a worse prognosis, however, with higher risk of early death during initial standard treatment. If they survive initial treatment and enter remission, they are also more prone to relapse, at which point arsenic is introduced to push them back into remission.

While arsenic can be toxic and is used in potent pesticides and poisons, it also exists naturally in the environment and, when manufactured under carefully-controlled conditions and used appropriately by doctors and nurses experienced in the treatment of cancer, can provide a significant health benefit.

Arsenic has been proven effective in pushing those unresponsive to initial treatment, and those who relapse after initial response, into remission. But researchers wanted to know what would happen if they

used the arsenic trioxide after initial standard treatment, rather than wait until a patient relapses.

For the study, North American Leukemia Intergroup trial C9710, investigators randomized 481 patients with untreated APL, age 15 and older, into two groups. Both groups would receive standard treatment of ATRA plus chemotherapy, followed by standard consolidation therapy. One of the groups received an additional two 25-day courses of intravenous arsenic trioxide before administration of the standard consolidation therapy.

The patients in the investigational group received arsenic trioxide intravenously for one hour, five days a week, for five weeks, with a two-week break between courses.

After initial standard treatment, both groups experienced similar rates of remission, at about 90 percent, and there were no treatment-related deaths reported from either group during consolidation therapy, indicating that the addition of arsenic treatment earlier introduces no additional safety concerns.

Analysis of the overall results revealed that event-free survival, defined as the time from study entry to first event (defined above), was significantly better for patients randomized to receive the arsenic trioxide consolidation therapy, For example, after three years, event-free survival was 80 percent in the arsenic group versus 63 percent in the non-arsenic group. Arsenic trioxide consolidation provided significant benefit to patients in the investigational group regardless of their initial prognosis based on white blood cell count and other risk factors.

The group who received arsenic also faired better in relapse rates and overall survival, researchers found. Out of 196 study participants who received at least one dose of arsenic after initial standard treatment, only

seven individuals – four percent – relapsed within three years of follow-up.

"We think people who received the arsenic trioxide after initial standard treatment are likely cured," Powell said. "There have been no relapses in that group after 36 months. The use of arsenic earlier in treatment improves the cure rate and survival, and it does so with little or no additional toxicity."

The results are exciting, Powell said. "It gives us hope that, with the addition of arsenic trioxide earlier in treatment, we may be able to eliminate some of the chemotherapy and reduce toxicities and costs."

However, 19 patients (eight percent) in each group died during the initial standard treatment, Powell pointed out, and those who were randomized to receive the arsenic never got a chance to benefit from it, since they didn't live through the initial treatment.

"One of our next objectives is to reduce or eliminate these early deaths – most common in patients with high white blood cell counts – possibly by introducing arsenic even earlier than we did this time, as part of initial induction therapy, to help them achieve remission," Powell said. "Some of these patients are at such high risk that they may need the arsenic just to get them into remission, so they have a chance."

Provided by Wake Forest University Baptist Medical Center