Chinese Folk Treatment Reveals Power of Arsenic To Treat Cancer, New Studies Under Way

By Karyn Hede

The medical uses of arsenic reach back more than 2,000 years, but only recently has Western medicine embraced its surprising rise from folk cure-all to proven cancer treatment.

The January announcement of positive results in a 6-year NCI-sponsored phase III clinical trial to treat a rare form of leukemia is merely the latest in a series of kudos for arsenic’s medicinal prowess. The latest study affirms that arsenic can effectively maintain remissions in acute promyelocytic leukemia (APL). But some investigators hope that arsenic could go even farther and eventually replace chemotherapy as a frontline treatment for APL.

“If you have something that will take away the potential toxicity and the potential real harm of high doses of anthracycline [chemotherapy] why not do it?” said Samuel Waxman, M.D., professor of medicine at Mount Sinai School of Medicine in New York and a professor consultant at Shanghai Second Medical University in China. “We’re way behind on this.”

While arsenic has had its greatest success in APL, it is also being tested in a variety of other cancers. There are 17 ongoing clinical trials in the United States testing arsenic trioxide to treat various forms of leukemia and cancers of the central nervous system and brain, according to the National Institutes of Health Web site http://www.clinicaltrials.gov. And many more trials are planned or under way in Europe.

Results of the current NCI study demonstrate that arsenic trioxide helps to maintain remissions in adult patients with previously untreated APL who received anthracyline-based chemotherapy to induce remission. These patients had a statistically significant improvement in event-free and overall survival compared with those who received only chemotherapy. The latest study did not address the use of arsenic to induce remissions in APL, either alone or alongside chemotherapy. The full results will be presented at the American Society of Clinical Oncology meeting in June.

“We feel like this study strongly suggests that arsenic needs to be part of the initial treatment for patients with [APL],” said Bayard Powell, M.D., of Wake Forest University in Winston-Salem, N.C., principal investigator of the study. “We do not yet have the information to answer whether it is better here [to maintain remission] or better to use as the very first treatment.”

But some investigators who have done clinical studies to test the effectiveness of arsenic trioxide as a front-line treatment for APL say that future clinical studies should now focus on its use as a first treatment.

Elihu Estey, M.D., and colleagues from the University of Texas M. D. Anderson Cancer Center in Houston administered a combination of arsenic trioxide plus all-trans-retinoic acid (ATRA), a proven treatment for APL, for both the initial phase and postremission phase of therapy in 44 patients with newly diagnosed APL. Nearly all the patients, 39 (89%), achieved complete remission after the initial treatment with ATRA plus arsenic, the authors reported last year in the journal Blood. The results included 96% of low-risk patients and 79% of high-risk patients, who also received chemotherapy to induce remission. None of the low-risk patients had relapsed after 15–24 months’ follow-up, the researchers note, but three of the 15 high-risk patients did relapse. Two of these three relapsed patients achieved a second complete remission with arsenic.

While the number of patients was small, Estey said that the results were encouraging. “The next step will be to ask if we need to give chemotherapy at all,” he added.

That result could come from much larger, controlled phase III clinical trial now under way in Europe. This trial, sponsored by the Italian cooperative group GIMEMA and the German group DSIL, will compare arsenic plus ATRA to standard anthracycline chemotherapy plus ATRA in newly diagnosed APL patients.

“If it turns out idarubicin plus ATRA is better than what we did, then that’s the end of arsenic for newly diagnosed patients,” Estey said. “But if it turns out you can do as well getting ATRA plus arsenic, then I think that will become the new standard.”

Arsenic and Old Communists

Waxman was one of the first Western physicians to see promise in a series of small studies in Chinese medical journals that reported intravenous doses of arsenic trioxide–induced long-term remission in APL patients. The medical uses of arsenic reach back at least 2,000 years, but it was political ideology that prompted its modern resurgence, Waxman explained.

Arsenic may never have entered the western pharmacopoeia were it not for the Chinese cultural revolution in the 1960s and 1970s, he said. During that time, Western
medicine virtually disappeared in China, and physicians turned to traditional Chinese herbal cures that had sustained the culture for millennia. The Chinese physician Zhang Ting-Dong of Harbin Medical University made the initial breakthrough by formulating a stable, low-dose solution of 1% arsenic trioxide in injectable form. Zhang presented his work at a Chinese medical society meeting in the early 1980s and gained interest from colleagues in Shanghai.

Around this same time, a researcher in Waxman’s lab began an exchange with Zhu Chen, M.D., Ph.D., and others at Shanghai Second Medical University in China, and thus began a decades-long collaboration between the two groups. They, along with colleagues in Europe, established that arsenic is associated with degradation of the PML-RARα oncoprotein that, in part, defines APL. The group also reported that arsenic trioxide is associated with induced apoptosis of the abnormal promyelocytic white cells.

“These cells are particularly sensitive to arsenic-induced apoptosis,” Waxman said. “Secondly, they are undergoing differentiation, so you are getting a double hit from the same drug. Thirdly, it is very well tolerated in the doses given.”

In the 6-year NCI-sponsored study led by the Cancer and Leukemia Group B (CALGB), the chief side effects included nausea, infection, and gastrointestinal side effects, but Powell reported that those side effects were not much higher than in patients who didn’t get arsenic. “We monitored patients closely because there was concern about potential cardiac side effects, because arsenic can affect heart rhythm, but we saw no serious adverse cardiac side effects,” he added.

Waxman, for one, says studies in China and Europe, as well as the small study done by Estey, are enough to convince him that arsenic is a safe and effective front-line treatment for APL. In one recent study, a team led by Chen and his colleagues randomized 61 APL patients into three groups: One received ATRA only, one received arsenic trioxide, and the third received a combination of the two. The patients also received standard chemotherapy. The group reported in the Proceedings of the National Academy of Sciences that clinical remission rates exceeded 90% in all three groups, but there were fewer side effects and a higher rate of sustained remissions for patients on the combination therapy. Those patients also had higher long-term survival rates.

“Arsenic is the single best treatment for APL,” Waxman said. “In my opinion, in this disease, at least the combination of ATRA and arsenic should be used up front.”

Beyond APL

Arsenic has also been tested to treat other forms of leukemia, such as acute myeloid leukemia, but the results have not been dramatic, and some investigators believe that its use may be restricted to APL.

“Arsenic does not seem to have a large role in other hematologic malignancies,” Estey said. “It certainly has not been as effective in the preleukemias or myelodysplasias.”

Others who have tested arsenic in small clinical studies are encouraged that it might work in other cancers, if only in some patients.

Azra Raza, M.D., chief of the division of hematology and oncology at the University of Massachusetts Medical Center in Worcester, treated 28 myelodysplastic syndrome patients with a combination of arsenic trioxide and thalidomide. Seven patients responded, including one complete response and one with regression in spleen size. In vitro studies confirmed that some patients who had high levels of the oncoprotein EVI1 were especially sensitive to arsenic therapy, Raza reported in Leukemia Research. Three of five patients who had high pretherapy EVI1 levels showed good responses, while the other two died from the disease early in the first cycle. She said this result was promising because expression of EVI1 is associated with particularly poor outcome in MDS patients.

“I think [arsenic] is a very promising agent,” Raza said. “It’s been around for centuries and centuries, but now for the first time we have a chance to see if we can match arsenic to the right patients, which means that even if 20% are responding, can we understand why those 20% are responding and preselect them for therapy? That would be a great advance.”