MedicalXpress

Oncologists fight leukemia with two-pronged therapy, clinical trials to start within months

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(PhysOrg.com) -- A new therapy mounts a double-barreled attack on leukemia, targeting not just the cancer cells but also the environment in which those cells live and grow, University of Florida researchers report.

Like striking an enemy camp directly as well as cutting off its source of food and other resources, the agent, called Oxi4503, poisons leukemia cells and destroys the blood vessels that supply them with oxygen and nutrients.

Use of the treatment in mouse models of acute myelogenous leukemia, or AML, is described online and in an upcoming print issue of the journal *Blood*. The researchers plan human tests of the drug at Shands at UF later this year.

“We’ve identified a new tool to dissect out the specifics of the relationship between leukemia cells and the blood vessels that supply them,” said Dr. Christopher Cogle, the UF College of Medicine oncologist who is senior author of the paper and a member of the UF Shands Cancer Center. “What we are offering is a brand new treatment by a very different mechanism to people who desperately need something new.”

Each year, more than 120,000 people in the United States are diagnosed with a blood cancer, and about 80 percent of them die of the disease because there are no effective treatments, according to the National Cancer Institute. Some AMLs return after initially successful

chemotherapy, while others do not respond at all. In addition, chemotherapy is too toxic for some elderly people, so they need an alternative.

Many treatments and studies focus on killing cancer cells, but very few target the microenvironment in which those cells grow. That means paying attention to blood vessels, bone marrow, growth factors and cell-to-cell interaction and binding.

Existing therapies that destroy blood vessels do so by targeting a growth factor called VEGF-A, but they are not effective long term at eliminating leukemia. To try to find a strategy that attacked multiple targets, the researchers tested Oxi4503, a novel blood vessel-disrupting agent.

In mouse models, Oxi4503 killed leukemia cells in addition to destroying the blood vessels that fed and nurtured them.

“It is very exciting to find one drug that can target both the leukemic cell and the endothelium to diminish the progression of leukemias — those people who fail chemotherapy, early or late, could be treated with this drug to see whether they respond,” said Dr. Shahin Rafii, a Howard Hughes Medical Institute Investigator and director of the Ansary Stem Cell Institute at Weill Cornell Medical College, who showed that leukemia cells are dependent on activated bone marrow blood vessels for survival and proliferation. Rafii is not affiliated with the UF study.

After Oxi4503 treatment, however, the researchers found that a thin layer of viable tumor tissue remained that was fed by newly formed vessels. The cells supplied by those vessels showed increased expression of a growth factor, as is often found in oxygen-deficient areas.

To disrupt this secondary formation of blood vessels, the researchers

blocked the growth factor VEGF by administering an antibody called bevacizumab after the blood vessel-destroying agent OXi4503. The combined approach led to enhanced leukemia regression.

The research, funded by the National Institutes of Health and the Leukemia and Lymphoma Society, has implications for both basic science and clinical research, as the results suggest that potential therapies must be screened against not only leukemia cells, but also the environment with which they interact.

“It’s a major paradigm shift,” Rafii said.

Describing the studies as “elegant,” Dr. Judith Karp, a professor of oncology and medicine and director of the leukemia program of the Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University, said the findings support the notion that VEGF and the vascular milieu are extremely important in cancer cell survival, and that targeting them might be a good anti-cancer strategy. Karp pioneered the use of bevacizumab — the antibody used in the UF studies — after chemotherapy, which resulted in remission among patients with cancer that was resistant to chemotherapy or that had returned after treatment.

“The results are extremely exciting and need to be implemented clinically in a very prioritized and timely fashion,” said Karp, who was not affiliated with the study.

Indeed, the U.S. Food and Drug Administration quickly gave its approval in April for a phase 1 clinical trial. That means the treatment could be available by late 2010 or the start of 2011 to eligible study volunteers at Shands at UF, as soon as the researchers are able to obtain the necessary funding for the trial.

The initial two-year trial is not designed to determine whether the drug

works, but rather to determine the maximum tolerable dose. It will involve three dozen individuals age 18 and older whose cancer is growing despite previous treatment. Trial details are at the National Institutes of Health website clinicaltrials.gov . Search for "NCT01085656."

Provided by University of Florida