Novel strategy under study for aggressive leukemia

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MCG Cancer Center director Kapil Bhalla and post-doctoral fellow Rekha Rao.Credit: Medical College of Georgia

A novel strategy to hopefully beat into oblivion one of the most aggressive forms of acute myelogenous leukemia combines the strengths of some of the newest leukemia agents, researchers say.

“These are not traditional chemotherapy regimens. These are targeted therapies that our earlier laboratory studies have shown have a synergistic effect,” says Dr. Kapil N. Bhalla, director of the Medical College of Georgia Cancer Center.

The strategy takes on the mutated protein receptor that enables the

deadly proliferation of leukemic cells by degrading it with histone deacetylase and heat shock protein 90 inhibitors. It uses protein kinase inhibitors to reduce the function of any remaining protein and kills off leukemic cells with a natural cell death mechanism called TRAIL.

Dr. Bhalla recently received a five-year, $1.3 million grant from the National Cancer Institute that will enable his research team to do more preclinical testing of the strategy in human leukemic cells and an AML animal model.

About six years ago, researchers found the mutation in the FLT-3 gene that results in the mutated protein receptor on the cell surface. This receptor usually responds to a growth factor that gives rise to normal bone marrow cell proliferation. “But in this case, this mutated protein receptor is constantly triggered, is constantly on and it drives proliferation, promotes survival and shuts down differentiation,” Dr. Bhalla says.

Within weeks, leukemic cells take over the bone marrow, then spread throughout the body. “Patients typically develop abnormalities of white blood cell count and platelet count, anemia or weakness and present with either an infection because they don’t have enough white blood cells or bleeding,” he says.

“We don’t know what causes these mutations, but if you have FLT-3 mutation – about 30 percent of AML patients do – then the leukemia is generally more aggressive,” says Dr. Bhalla. For whatever reason, this aggressive leukemia occurs most commonly in the elderly which means, with the aging population, it’s likely to become even more common.

“If you just target FLT-3 with an inhibitor of its activity, that would not be enough,” says Dr. Bhalla. “If you combine it with something that also depletes its levels, that would be better. But if you deplete its levels,

inhibit its activity and combine it with another leukemia cell death-inducing agent, it would be even better," says Dr. Bhalla, who believes the laboratory work will evolve into a strategy that can be used effectively in the clinics, maybe even before the laboratory work is done.

A big plus is that several drugs that do each of these things already are being studied in patients. However, combined effects of these drugs have not been fully studied against leukemia cells, and the drugs just haven't been used together in patients with leukemia.

For example, one of the histone deacetylase inhibitors Dr. Bhalla will study in the lab, LBH589, developed by Novartis Corp., he's also studying in an early clinical trial for patients with leukemia and lymphoma for whom standard therapies have failed. Several FLT-3 kinase inhibitors are under study for a variety of cancers and MCG will soon join one of those studies for leukemia. Apo2L/TRAIL, developed by Genetech, is under study in a variety of solid tumors and leukemia. TRAIL activates on leukemic cells the same death-inducing stimulus immune cells use to kill cancer cells. "It's a normal mechanism of killing offending cells," says Dr. Bhalla.

"We have designed combinations of agents that we will be studying in mouse models and against patient-derived leukemia cells. This grant doesn't fund a clinical trial, but it allows us to take patient samples and study them in vitro to further define why this gene confers poor survival and what combinations can work against it," says Dr. Bhalla. He notes that since the drugs are new and have not previously been used together, issues such as unforeseen toxicity will need to be explored.

"We are studying the combination and how it kills, so when the combination goes into the patient, we will be able to get samples from patients, pre- and post-treatment, to see whether what we are observing in the lab works and, if there are patients who still don't respond, why

don’t they"” says Dr. Bhalla.

Histone deacetylase and heat shock protein 90 inhibitors take direct hits at the mutant protein by targeting HSP 90, a molecular chaperone, which, in this case, improperly folds the protein, leaving it active and producing leukemic cells rather than healthy bone marrow cells as needed. Dr. Bhalla’s lab was the first to show the mutant protein kinase is particularly susceptible to depletion by targeting it with HSP 90 or histone deacetylase inhibitors. He also uncovered the synergy of kinase inhibitors.

“We are targeting HSP 90, which folds and keeps this abnormal protein in its active form,” he says. “By using this agent that targets HSP 90, you also take away many other mechanisms that drive cell proliferation and survival. Once you lower the threshold for cell death by depleting this protein, you use additional strategies to kill leukemic cells. It makes it more effective.”

Source: Medical College of Georgia