MedicalXpress

New route to killing cancer gets a test run

June 24 2010, By Sarah Avery

A targeted therapy that has generated excitement for its early success in breast cancer is now being tested in the Triangle on other cancers, including often-deadly ovarian tumors.

Doctors and patients have eagerly anticipated the drugs, which provide an entirely new route to killing tumors that is less toxic than traditional chemotherapies.

Called PARP inhibitors, after the enzyme they target, the drugs disable a key mechanism cancer cells employ to repair themselves. Used in combination with current drugs against breast cancer, PARP inhibitors were shown to add cancer-free months to patients' lives while causing few serious side effects.

Although many cancer treatments have shown early promise only to fade under wider scrutiny, the prospect of a new approach has generated buzz even in staid journals such as The New England Journal of Medicine. Last year the journal editorialized on the strength of the small breast cancer trial.

Since then, enthusiasm has only grown, with patients eagerly volunteering for limited spots in clinical trials to gain access to the treatment.

"There are a lot of patients very interested in this," said Dr. Linda Van Le, an oncologist at UNC-Chapel Hill who is helping enroll patients in a clinical trial of a PARP drug for ovarian cancer.

At least nine PARP inhibitor drugs are in different phases of the U.S. Food and Drug Administration approval process, but none is yet on the market.

As a result, patients can get the drugs only through clinical trials. In addition to the ovarian cancer study at the University of North Carolina, Chapel Hill, trials are on tap there for lung, breast and colorectal cancers. Doctors at Duke University will soon participate in a PARP inhibitor trial aimed at colon cancer.

Lynn Burrell, 44, of Clayton, was the first to enroll in the ovarian cancer study at N.C. Cancer Hospital in Chapel Hill, which was initially approved to enroll three patients. Van Le said her group quickly filled its quota and was allowed to enlist seven more patients. The trial is led by the drug's manufacturer, Abbott Laboratories.

After being diagnosed with ovarian cancer last year, Burrell had a hysterectomy and chemotherapy. When tumors recently returned in nearby tissue, she seized the chance to try the experimental treatment.

"I was excited about it," Burrell said. "Knowing there are limited chemotherapies for ovarian cancer, this was a great opportunity."

PARP inhibitors work in a way far different from traditional chemotherapies, which wipe out cancer cells but also kill or damage healthy cells. That residual damage is what causes many of chemo's dreaded side effects -- hair loss, nausea, muscle weakness and fatigue.

The new approach, which stems from discoveries about the genetic source of tumors, is much more focused.

It was initially developed to capitalize on a gene mutation evident in some inherited cancers, notably breast cancers associated with the

BRCA1 and BRCA2 genes. Women who inherit these damaged genes are five times as likely to develop breast cancer and at least 11 times as likely to have ovarian cancer. Men who inherit the mutations are at increased risk for breast, pancreatic and prostate cancers.

Both BRCA1 and BRCA2 are normally helpful genes involved in repairing damaged cells. With the harmful mutation, however, they don't function, so damaged cells grow out of control, building tumors.

Traditional chemotherapy kills most of the disease cells. The remaining stragglers are often wounded, but cannot fix themselves through the usual BRCA mechanism. Instead, a backup repair system springs to action. This second system relies on the PARP enzyme to initiate repairs. Left to regroup, tumor cells recover and multiply, causing a resurgence of the cancer.

PARP inhibitors disable that second cell repair system, so cancer cells have no way to mend after they're hit with chemotherapy. The new drugs also cause far fewer side effects, because they target only the defective cancer cells.

Initially, researchers thought the PARP inhibitors were effective only if a BRCA mutation was present. But recent studies have shown that PARP inhibitors may work regardless of that inherited defect. The UNC-CH study, for one, is exploring the effects of a PARP inhibitor on all ovarian cancers, no matter the BRCA status.

And at Duke, doctors plan to test PARP inhibitors against colon cancer, which can be caused by a genetic mutation that affects a different cell repair mechanism than the one involved in inherited breast cancers.

Dr. Alexander Starodub, an oncologist at Duke University, will enlist up to six colon cancer patients in a small national trial of a PARP inhibitor.

The approach builds on the findings from the breast cancer trials, using the new drug along with traditional chemotherapies in search of improved results, he said.

Starodub said the excitement surrounding the PARP inhibitors is in many ways typical of how all new cancer drugs are greeted.

"As oncologists, we see the world as a glass half full," he said. "Anything that potentially works, we want to advance as much as possible to help patients."

At the same time, he said, PARP inhibitors are generating an extra dose of enthusiasm. If they work as well as early tests indicate, they would add a much-needed new weapon against a deadly foe.

"This is a new direction," Starodub said, "and every time you have a new avenue, we are all excited."