Pitt aims to prove therapy can offer new cancer hope

2-drug combo set for human trial here
April 27, 2012 3:43 pm

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By David Templeton / Pittsburgh Post-Gazette

A human clinical trial under way at UPMC's Hillman Cancer Center in Shadyside will help determine whether a combination of approved drugs based on a new theory of cancer can "revolutionize cancer therapy."

That's the explanation of lead researcher Michael T. Lotze, who says his team has combined interleukin 2 (IL-2) with hydroxychloroquine in a new therapy designed to be more effective and less toxic in curing cancer than IL-2 alone.

The new cancer theory, how the two drugs work in tandem and how the treatment works involve complicated science. The Pitt team starts with IL-2, a drug that strengthens the immune response to cancer but doesn't work in the majority of patients, in part, due to severe toxicity. It then adds an inexpensive drug, hydroxychloroquine, to serve a different role -- to reduce the cancer drug's toxicity and

increase its cancer-killing efficiency.

IL-2, a hormone that promotes immune T cells that fight infections and cancer at local sites, is considered the only cancer cure available. But it's effective in only 10 percent of the patients with renal-cell (kidney) cancer and melanoma who qualify for the treatment.

One chief concern is IL-2's toxicity in high doses sent bodywide to fight cancer. The drug causes healthy tissue and organ cells to begin consuming themselves in a process known as autophagy -- Greek for "self-eating" -- that leads to vascular leakage among other serious side effects.

But a new Pitt theory about cancer says autophagy also helps explain how cancer cells produce tumors.

Dr. Lotze, professor of surgery, immunology and bioengineering at the University of Pittsburgh School of Medicine, said cancer patients who undergo IL-2 immunotherapy experience extreme influenza-like symptoms that many can't tolerate for the few days they receive it. But the oral medication hydroxychloroquine, originally used to treat patients with malaria and now used to treat patients with systemic lupus erythematosus, rheumatoid arthritis, HIV and other diseases, reduces IL-2 toxicity by inhibiting autophagy without hindering the drug assault on cancer.

The drug combination in mice with cancer proved to be "dramatically more effective" than IL-2 alone. Published April 3 in Cancer Research, the study was performed by Xiaoyan Liang, a UPMC scientist on the Lotze team at the cancer center.

Clinical-trial success could increase IL-2's use in treating kidney cancer and melanoma and expand that use to other major cancers.

With the two drugs already approved for use by the U.S. Food and Drug Administration, Pitt's Cancer Institute team hopes to test the new drug regimen on 60 renal-cell (kidney) patients. Those interested in participating should call 877-470-7241.

Michael Wong, professor of medicine at the Norris Comprehensive Cancer Center at the University of Southern California, said he's familiar with the study but was not involved in it.

The key problem with IL-2, he said, is that patients must be admitted to a hospital because of blood pressure problems and vascular leakage it causes, along with impacts on the liver, kidneys and other organs.

"The holy grail," he said, would be reductions in IL-2's toxic side effects so more patients could undergo the treatment.

"One in 10 people have a tremendous response from IL-2 -- a complete response where the tumor melts away," he said, describing it as a cure in that small percentage. But the1-in-10 success rate in those able to undergo the therapy has not budged for many years.

"In the Lotze trial, if they can get more patients in and move the needle to 2 out of 10 or 3 out of 10 -- if it truly works -- it's going to be dramatic," Dr. Wong said. "Any improvement would be mind-boggling because we've been stuck here for quite a while."

The traditional theory of cancer says a genetic mutation causes uncontrolled cell growth. But the Pitt team says cancer isn't just a disorder of cell growth, but just as much a disorder in cell death.

Rather than die in an organized, natural way through a process known as "apoptosis," as occurs with normal cells, a genetic mutation causes cancer cells to die through the process of necrosis following autophagy. Dr. Lotze describes necrosis as "a terrible, horrible, screaming-out-loud, blood-in-the-streets type of death."

In the process, cancer cells consume themselves and shed cellular parts into the tissue to keep other cancer cells alive. It also provides biological infrastructure to sustain tumor growth.

"Tumors just want to die," Dr. Lotze said. But those dying cancer cells promote autophagy and set the stage for their survival by recruiting immune cells and new cells to develop blood vessels. Those vessels help sustain the cancer cells that otherwise would die.

"What's new is our understanding of autophagy," he said. "Our innovation was to marry tumor immunology to autophagy."

The Pitt team's goal is to kill cancer cells naturally through immunology rather than allow autophagy to continue. Even with its toxic side effects, IL-2 remains "the closest to a [cancer] cure that we have," Dr. Lotze said.

Traditional chemotherapy, which can reduce tumor size and knock back cancer growth temporarily, also can promote rather than halt autophagy, which allows cancer to return with a vengeance, he said.

The Pitt team's theory about autophagy's role in cancer "is a novel one" that could make scientists "rethink what holds true" with cancer, Dr. Wong said. "It can shake the ground you stand on, and this is the first step in that direction."

If the clinical trial shows that the combination drug treatment is less toxic and more effective, Dr. Lotze said, "We think this can

potentially revolutionize cancer therapy."

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First Published April 27, 2012 11:41 am

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