

Cancer drug may help patients with heart-lung disease

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A drug developed to fight cancer is showing early promise as a treatment for pulmonary hypertension, researchers from the University of Chicago Medical Center report May 19 at the American Thoracic Society International Conference in Toronto, Canada.

In the first human trial of sorafenib (Nexavar®) as a treatment for pulmonary hypertension, eight out of the first nine patients increased their ability to exercise. Six out of nine had significant improvements in right ventricular ejection fraction, the ability of the heart to pump blood to the lungs. Four had a significant decrease in pulmonary artery pressures.

"This is not a disease where we are used to seeing people who have been stable on the strongest medications we have suddenly get better," said study author Mardi Gomberg-Maitland, MD, MSc, assistant professor of medicine at the University of Chicago. "We have drugs that may slow progression of the disease but nothing that can stop or reverse the process."

"To see these improvements in such a short time," she said, "is quite promising. Although evaluation of this drug is at a very early stage, and this study focused on safety and tolerability, we are genuinely excited about the results."

Pulmonary hypertension and cancer share certain features. Both diseases involve abnormal cellular growth. In pulmonary hypertension, these

abnormal cells line the blood vessels leading from the heart to the lungs. These abnormal cells release signals that stimulate the growth of small new blood vessels. This enables the renegade cells to grow even faster, which thickens the vessel walls and reduces blood flow.

As the arteries close off, pressures within them build up. This requires the heart to pump harder to force blood through the narrowed tubes to the lungs. Eventually the heart can no longer keep up and damage to the overworked muscle begins to accumulate. Sorafenib appears to interfere with that harmful process.

The drug was originally evaluated at the University of Chicago as a treatment for kidney cancer. Gomberg-Maitland – who is married to a member of the sorafenib-cancer team – recognized with her husband that its effects also might slow the growth and thickening of the pulmonary artery walls. In an important preclinical trial, she and colleagues demonstrated that sorafenib was effective in reducing pulmonary hypertension in a rat model. With these encouraging results, they organized this trial.

The trial enrolled patients with pulmonary hypertension who had stable disease. Patients in the study continued to take their standard medications, primarily prostacyclin, in combination with sildenafil. They also took sorafenib for 16 weeks, but at doses lower than those given to cancer patients.

"All patients had some improvement," Gomberg-Maitland said. "Some had dramatic improvement."

Most patients in the trial increased their exercise capacity, as measured by time on a treadmill or a six-minute walk test. They had an eight-percent improvement, on average, in right ventricular ejection fraction, as measured by three-dimensional echocardiography. Four patients had

significant improvements in the ability of the heart to pump blood to the lungs, as measured by cardiac catheterization.

For Martha Wheeler, 50, of Indianapolis, Indiana, the change in her lifestyle meant more than the study's quantifiable endpoints. Diagnosed 13 years ago, she hadn't been able to play with her granddaughter, ride a bicycle or walk for more than a minute or two. Now she can do all three, including walk three-quarters of a mile. "I can do more than that," she said, "if I push myself."

"Best of all," she added, "I feel like walking. When I get home from work, I want to go out for a good walk. I am thoroughly amazed by it," she said. "I'm going to buy a bike. All that from two little round pills a day."

The side effects of the drug have been relatively mild. The most common adverse effects in cancer patients were rashes, tenderness and itching on the hands and feet and some mild diarrhea and fatigue.

For patients with pulmonary hypertension, diarrhea and hair loss were often the biggest concerns. Patients taking prostacyclins often have facial rashes and flushing but the sorafenib appears to have reduced this effect. Several patients did have their doses reduced because of the skin reaction or hair loss without any detectable loss of benefit.

Wheeler had some hair thinning, "and that bothered me," she said. "But my husband just repeats: 'Grow hair, or breathe? Grow hair, or breathe?' That puts it back in perspective." She has had no other complications and her persistent rash from the prostacyclin went away after two weeks on sorafenib.

Although the trial was designed to last only 16 weeks, all of the patients enrolled continue to take the drug. Some have been on it for more than

one year.

"This was my first time in a study," said Wheeler. "Here's what it meant to me. I love to sing songs with my granddaughter, but I used to stop after one verse. Yesterday we sang six songs, long songs, with many verses."

Because of the drug's apparent potential and limited side effects, a multi-center, phase-2, placebo-controlled, cross-over study is being organized. It will likely enroll patients with stable disease on pre-existing prostacyclin-based therapy.

"This is an important first step in defining the potential of this new therapy," said pulmonary hypertension specialist Stephen Archer, MD, section chief of cardiology at the University of Chicago Medical Center.

Source: University of Chicago Medical Center

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