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New drug overcomes resistance in patients with rare sarcoma

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A new targeted drug demonstrated its ability to control metastatic gastrointestinal stromal tumor, an uncommon and life-threatening form of sarcoma, after the disease had become resistant to all existing therapies, report investigators at Dana-Farber Cancer Institute who led the worldwide clinical trial.

The treatment of gastrointestinal stromal tumor, or GIST, even in its advanced metastatic stage, has been dramatically improved with two oral targeted drugs – imatinib (Gleevec) and sunitinib (Sutent). To date, these have represented the only two FDA-approved treatments with the proven ability to control GIST. However, in more than 85 percent of patients, GIST becomes resistant to these drugs after seven years and the disease worsens with fatal results.

The new study, whose results are being published in the Lancet, demonstrated that the oral drug regorafenib, which inhibits several cancer-promoting kinase enzymes, was able to control GIST for nearly four months longer than placebo in patients for whom Gleevec and Sutent were no longer effective, a result that was highly significant statistically.

"When added to best supportive care, regorafenib significantly improves disease control, as measured by progression-free survival time in patients with GIST after progression which represents failure of all other therapies," said George Demetri, MD, of Dana-Farber, principal investigator of this clinical trial.

Demonstrating the aggressive nature of this resistant disease, the study found that tumors objectively grew in less than a month, on average, in GIST patients who were initially randomized to receive a placebo. The study's "cross-over" design made it possible to treat those patients whose tumors grew, and 85 percent of the patients initially on placebo were able to receive regorafenib, which then controlled the disease in these patients as well.

Because of the study's cross-over design, Demetri said, it was not expected to prove that the patients initially randomized to receive regorafenib survived longer – the researchers would have had to withhold the drug from the placebo patients to demonstrate that difference. "But there is no question that people are living longer" with regorafenib treatment, he said, based on the results of this trial.

An application to have regorafenib approved for use in resistant GIST is under an accelerated review by the Food and Drug Administration, Demetri said.

GIST is a rare form of sarcoma that develops in the gastrointestinal tract, mainly in the stomach and small intestine. GIST is estimated to affect more than 5,000 people per year in the United States and about 8,000 in Europe.

Regorafenib is a novel rationally designed drug manufactured by Bayer HealthCare Pharmaceuticals that was FDA-approved in September 2012 to treat metastatic colon cancer after failure of standard chemotherapy. It blocks several cancer-promoting enzymes called kinases, which spur runaway growth in GIST and other cancers.

The phase 3 international trial involved 199 treatment-resistant GIST patients at 57 hospitals in 176 countries. Of the 199 patients, 133 received a regorafenib pill daily for three weeks followed by a one-week

break, while 66 received a matching placebo. The patients were monitored for at least one year after the trial began.

As for other targeted therapies, the drug did not often shrink tumors but controlled the disease for an average of 4.8 months before it progressed, while patients in the placebo group experienced less than one month (0.9 month) before the disease worsened. There was a high rate of adverse effects including high blood pressure, fatigue, diarrhea, and redness, swelling, numbness and peeling of skin on the hands and feet. These side effects were managed by reducing or interrupting the regorafenib treatment, the report said.

A companion report in The Lancet said that the drug had a "modest" benefit in patients with metastatic colon cancer. A commentary by David Cunningham, MD, of the Royal Marsden Hospital in England, said, "In the relatively rare GIST, the case for routine use of this drug in patients following failure of existing treatments is strong."

Demetri added "We know that regorafenib can inhibit many of the mutated proteins and abnormal signals that cause this cancer, and the next step will be to investigate the molecular mechanisms by which this new treatment can control GIST after resistance appears to other 'targeted therapy' drugs for this aggressive malignancy."

The clinical trial was supported, in part, by Bayer HealthCare Pharmaceuticals, as well as the Ludwig Center at Dana-Farber/Harvard Cancer Center.

More information: www.thelancet.com/journals/lan … (12)61857-1/abstract

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