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Determining genetic signature of lung tumors can help guide treatment

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The first U.S. clinical trial using genetic screening to identify lung tumors likely to respond to targeted therapies supports the use of those drugs as first-line treatment rather than after standard chemotherapy has failed. While the study led by Massachusetts General Hospital Cancer Center investigators found that upfront gefitinib (Iressa) treatment considerably improved the outcomes for non-small-cell-lung-cancer (NSCLC), additional research is required before such a strategy can be used for routine treatment planning. The report appears in the May 20 *Journal of Clinical Oncology*.

“This is a pivotal clinical trial that demonstrates the power of personalized medicine in lung cancer treatment,” says Lecia Sequist, MD, MPH, of the MGH Cancer Center, who led the study. “It is an exciting glimpse into what we hope is the future of cancer care. Instead of a ‘one size fits all’ therapy, we are moving towards finding the best treatment for each patient.”

The most common form of lung cancer, NSCLC is the leading cause of cancer deaths in the U.S. Until recently, there were no treatment options for NSCLC patients in whom chemotherapy failed. Iressa, which disables the epidermal growth factor receptor (EGFR) on the surface of lung cancer cells, was approved in 2003 for treatment of NSCLC even though it shrank tumors in less than 15 percent of patients because, in those whom it did help, responses were rapid and dramatic.

In 2004 MGH Cancer Center researchers and a team from Dana-Farber

Cancer Institute both discovered why Iressa's success was confined to a limited group of patients. Specific EGFR mutations that were probably responsible for a tumor's development also made the cancer sensitive to Iressa treatment. Subsequent to that announcement, the Laboratory for Molecular Medicine at the Harvard-Partners Center for Genetics and Genomics developed a test to screen for these sensitizing mutations.

Late in 2004 a collaborative group led by MGH investigators began the current study, designed to see whether using Iressa as an initial treatment for patients with a sensitizing EGFR mutation would improve treatment results. Out of 98 NSCLC patients screened at 11 centers – including the MGH Cancer Center and DFCI – over a two-year period, 34 had a sensitizing mutation. Of those, 31 entered the trial and began receiving daily oral doses of Iressa instead of standard chemotherapy. Iressa treatment continued indefinitely unless significant side effects occurred or tumor growth continued or resumed.

All but two of the participants responded positively to Iressa treatment, with their tumors either shrinking significantly or not growing for a month or longer. At the end of the study period, 14 patients had died but 17 remained alive. The overall survival rate and the length of time until participants' tumors resumed growing were two or three times greater than would be expected with standard chemotherapy, Sequist explains. Only one participant dropped out because of treatment side effects.

The current study also analyzed the specific EGFR mutations in participants' tumors to see if there were differences in the response to treatment. Patients with the two most typical mutations had vigorous responses to Iressa, but the seven patients found to have atypical mutations had a more limited response. None of the atypical cases had tumor shrinkage, but the majority had disease stabilization for a period of time. Two patients who experienced rapid regrowth of their cancers were found to have additional EGFR mutations that previous research

had indicated conferred resistance to the drug. It has been theorized that those resistance mutations develop in response to treatment, but this is the first observation of the mutations' being present before treatment began.

"It's starting to look like the strategy of genomically-directed cancer therapy will need to incorporate testing for multiple genotypes – screening for three, four or even more genetic markers, some of which may indicate likelihood of response to treatment, and others the chance of resistance," says Sequist. "We think these results will also apply to other effective EGFR inhibitors, and we hope they can be duplicated for other types of cancer that involve these mutations. But what is needed next is a larger-scale, randomized clinical trial comparing an EGFR blocker with standard therapy in a genotype-selected population." Sequist is an instructor in Medicine at Harvard Medical School.

Although Iressa is currently not being marketed in the U.S., the trial reported in this article was supported by AstraZeneca, the drug's manufacturer. Several other EGFR inhibitors, including Tarceva (erlotinib), are either on the market or in clinical trials.

Source: Massachusetts General Hospital