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Lapatinib shows minimal effect against liver cancer

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Use of the molecularly targeted agent lapatinib to delay tumor growth and improve the survival of patients with inoperable hepatocellular carcinoma, or liver cancer, only benefited certain subgroups of patients. While results of this study were largely negative, patients that exhibited toxicity from the drug in the form of a skin rash appeared to have a greater tumor response and longer survival.

Findings of this phase II, multi-institutional study are published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

"These results may not be practice changing, but they do emphasize the need to continue developing strategies targeting epidermal growth factor receptor [EGFR] in hepatocellular carcinoma," said lead researcher Tanios Bekaii-Saab, M.D., assistant professor of medicine and pharmacology and medical director of gastrointestinal oncology at the Ohio State University Comprehensive Cancer Center.

The prevalence of hepatocellular carcinoma is increasing worldwide, and since this form of cancer typically responds poorly to chemotherapy, new treatments are necessary to help curb its rise. The current standard treatment for advanced hepatocellular carcinoma is sorafenib.

This study is one of the first trials to test the tolerability and efficacy of lapatinib in patients with advanced hepatocellular carcinoma. Lapatinib targets both EGFR and Human EGFR type 2 (HER2/neu) signaling

pathways. The FDA approved this drug in March of 2007 for patients with breast cancer who were already using the chemotherapeutic agent capecitabine. Lapatinib works by inhibiting the tyrosine kinase activity associated with the two oncogenes — EGFR and HER2/neu.

Twenty-six patients with advanced hepatocellular carcinoma received 1,500 mg/d of lapatinib by mouth for 28 days. Bekaii-Saab and colleagues evaluated tumor and blood specimens for expression of these signaling pathways.

Results indicated that lapatinib only benefited a subgroup of patients who developed a rash, which is an effect attributable to EGFR/HER1 inhibition. These patients tended to have a more favorable outcome and longer survival compared to the overall study population. The most common side effects were diarrhea in 73 percent of participants, nausea in 45 percent and rash in 42 percent.

"Our findings suggest a potential benefit from EGFR inhibition," said Bekaii-Saab. "Overall though, we were certainly hopeful that lapatinib would be more active and were somewhat disappointed by the results."

Samuel B. Ho, M.D., an editorial board member for *Clinical Cancer Research*, believes this study provides important information about the relevance of these signaling pathways in advanced hepatocellular carcinoma.

"The results support the fact that hepatocellular carcinomas are clinically and biochemically heterogeneous, and that certain subsets of hepatocellular carcinoma may respond differently than others, suggesting that larger trials with patients more likely to respond may show a definite survival benefit," said Ho. "However, the study failed to find a marker that could differentiate between tumors that may or may not be expected to respond."

Ho is the chief of gastroenterology section at the VA San Diego Healthcare System, and professor of medicine at the University of California, San Diego.

Furthermore, the results of this study represent an important step in the strategy for designing clinical studies for this form of cancer, according to Ho, and additional studies are needed. Specifically with lapatinib, it will be important to determine a way to identify those patients who are more likely to respond and include them in a larger trial.

"Given the complexity of the biology in hepatocellular carcinoma and essentially all other malignancies, we should not hope a single marker would be predicative; it makes more sense biologically to monitor multiple potentially relevant markers," said Ho.

Source: American Association for Cancer Research (news : web)

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