BATTLE links potential biomarkers to drugs for lung cancer

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The first lung cancer clinical trial to guide targeted therapies to patients based on molecular signatures in tumor biopsies is a step toward personalized care and more effective, efficient clinical trials for new drugs, study leaders reported today during the American Association for Cancer Research 101st Annual Meeting 2010.

Researchers at The University of Texas M. D. Anderson Cancer Center presented the results of the study that used an innovative statistical model to match four drugs to specific molecular signatures, or biomarkers, in the tumors of 255 stage IV non-small cell lung cancer patients who had received between one and nine previous treatments.

"New drugs that target molecular pathways help a small percentage of lung cancer patients, but right now there's no way to determine who those patients are before treatment," said Edward Kim, M.D., associate professor in M. D. Anderson's Department of Thoracic/Head and Neck Medical Oncology and principal investigator on the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) clinical trials.

"BATTLE evaluated tumor biomarkers in hopes that we can treat lung cancer, which kills more people than any other type of cancer, like we treat breast or colon cancer, using validated biomarkers to guide treatment and improve survival," Kim said. The National Cancer Institute estimates that 219,440 new cases of lung cancer were diagnosed in 2009 and 159,390 people died from the disease.

Kim said BATTLE also points the way to more precise clinical trials that will require smaller numbers of patients to test a targeted therapy rather than large trials open to all-comers. "Lung cancer research has been plagued by large, Phase III clinical trials that showed minor effects or even failed to enroll enough patients to finish," Kim said.

"Two lung cancer tumors might appear identical under a microscope and have the same staging, but they behave differently," said Waun Ki Hong, M.D., head of M.D. Anderson's Division of Cancer Medicine and principal investigator on the BATTLE grant from the U.S. Department of Defense. "The name of the game now is to treat based on the molecular defects in the tumor."

BATTLE identifies potential biomarkers

The Phase II clinical trial found evidence that each of the four drugs targets specific molecular signatures better than the other three. The drugs used in the trial were erlotinib (Tarceva), sorafenib (Nexavar), vandetanib (Zactima) and erlotinib with bexarotene (Targretin®). Each drug is designed to target specific molecular pathways; currently, none has a validated biomarker to guide its use.

BATTLE's end point was disease control at eight weeks, which recent research has found is a good indicator of overall survival. The study found, for example, that 61 percent of patients with a KRAS mutation in their tumors who took sorafenib had disease control at eight weeks, compared with 32 percent for the other three drugs. Erlotinib did best against EGFR mutations, vandetanib for high VEGFR-2 expression and the erlotinib-bexarotene fared best with Cyclin D1 defects or amplified numbers of the EGFR gene. These exploratory analyses raise interesting areas of future research.

Overall, 46 percent of patients on the trial had disease control at 8

weeks, compared with a historical experience of around 30 percent for late-stage lung cancer patients. Median overall survival was nine months, and 38 percent of patients survived to one year. Toxicities from the four drugs were minimal, with only 6.5 percent experiencing a significant side effect.

Kim cautioned that Phase II trial findings of biomarker effectiveness need to be validated in Phase III trials, which are typically sponsored by pharmaceutical companies or performed in cooperative groups.

A model for efficient clinical trials

By successfully collecting new tumor biopsies on each patient and employing a Bayesian adaptive randomization statistical model, BATTLE provides an example for improving clinical trials.

"BATTLE is an important step toward personalized medicine and marks a paradigm shift for clinical trials by demonstrating the feasibility of a biopsy-based, hypothesis-driven biomarker trial," said Roy Herbst, M.D., Ph.D., professor in the Department of Thoracic/Head and Neck Medical Oncology and co-principal investigator on the BATTLE clinical trials.

Patients agreed to have a new biopsy for the trial, Kim said, which was crucial to the study design because it provided fresh information on the tumor's molecular status that may have been altered by treatment since the patient's previous biopsy.

"BATTLE employed an adaptive randomization approach that allowed the statistical model to learn as the clinical trial progressed," said J. Jack Lee, Ph.D., professor in M. D. Anderson's Department of Biostatistics.

The first 97 patients were equally randomized to BATTLE's four arms.

As the study progressed, information from patients' biopsies and outcomes was employed by the model to guide assignment of drugs to new patients, who became more likely to receive a drug that had worked for earlier patients with the same tumor biomarkers.

The model leads to greater use of successful drugs and minimization or dropping of those less successful. While vandetanib helped those with VEGFR overexpression, it was dropped for patients with the KRAS mutation, Lee said.

By identifying biomarkers, and thus a potential patient population for a drug at Phase II, a follow-up Phase III will require smaller sample sizes and proceed more quickly than an all-comers trial with thousands of patients, Lee said.

Kim said future BATTLE trials will test combinations of therapies as well as single agents and will concentrate on the entire range of staging for lung cancer patients, including frontline therapy. Ultimately, the researchers plan to try the BATTLE approach in personalizing prevention clinical trials.

Provided by University of Texas M. D. Anderson Cancer Center