Study urges caution with lenalidomide dosage

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An early phase multiple myeloma trial has unexpectedly revealed that the drug lenalidomide interacts with another protein in cells that affect its dose level in the body, say researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) who conducted the study.

Lenalidomide is an anti-inflammatory drug, and more than 390 clinical trials have been initiated to study its activity in a number of cancers and other diseases.

The study found that lenalidomide interacts with P-glycoprotein (Pgp), a molecule that pumps potentially toxic chemicals out of cells and aids in removing these chemicals from the body. Abnormally high levels of Pgp in cancer cells can be an important cause of drug resistance for many cancer patients.

The findings, published online in the *Journal of Clinical Oncology,* could lead to safer dosing of lenalidomide in a variety of diseases.

"This is the first report showing that lenalidomide interacts with Pgp, and our clinical data suggests this may be an important consideration for proper dosing of the drug," says study leader and researcher Dr. Mitch Phelps, assistant professor in Ohio State's College of Pharmacy. "Some toxicities induced by lenalidomide can be severe and life-threatening."

The phase I clinical trial, which evaluates the safety of a new drug or drug combination, involved 21 patients with relapsed multiple myeloma, a fatal disease that affects more than 20,000 Americans each year and kills more than 10,600 of them.

The trial combined lenalidomide with temsirolimus, a drug that the researchers knew from the start interacted with Pgp. During the study, lenalidomide levels in patients' blood were often higher than expected, and some patients experienced side effects such as electrolyte imbalances and rashes that were greater than expected.

To the investigators' surprise, laboratory experiments showed that lenalidomide was removed from cells by Pgp, and the rate of removal was reduced when temsirolimus was included in the experiments. That data was evidence that the two drugs interact via Pgp, which provided a potential explanation for the altered lenalidomide levels observed in patients' blood samples, Phelps explains.

"Although this was a relatively small study, we saw a significant pharmacokinetic interaction between the two agents," Phelps says. "That, along with side effects that were greater than expected, brought us to the conclusion that the interaction of the agents with Pgp may be the cause of this increased toxicity," Phelps says.

Phelps notes that many drugs interact with Pgp. "This is indicated on the labels of drugs approved by the Food and Drug Administration, which helps prevent the co-administration of drugs that interact with Pgp or inhibit Pgp, either of which could lead to adverse drug-drug interactions," Phelps says.

The Food and Drug Administration (FDA) approved lenalidomide in 2005 for treating myelodysplasia syndromes and in 2006 for multiple myeloma.

"It is unusual to discover several years after FDA approval that a drug interacts with Pgp," Phelps says. The delay probably occurred because the drug is predominantly excreted by the kidneys into the urine, Phelps says. This had been assumed to be through filtration, which is a passive process independent of Pgp or other transporter proteins. "Although the kidneys may have the primary job of eliminating lenalidomide, our findings indicate that Pgp and other factors may also significantly contribute," he says.

"We now need studies to confirm these findings and determine their significance when lenalidomide is combined with other Pgp substrates in various disease populations," Phelps says.

Provided by Ohio State University Medical Center

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