



Cancer therapy based on anatomical location may soon be obsolete

By Gwen Ericson

April 18, 2006 -- The results of a new study at Washington University School of Medicine in St. Louis could eventually have oncologists removing their specialties from their shingles by making therapy based on a tumor's anatomical location obsolete.

When the researchers compared eight different kinds of cancerous tumors, they saw that whether the tumor was, for instance, a breast tumor, lung tumor or colon tumor didn't correlate to how the cancers interacted with a standard anticancer drug.

Their findings suggest that traditional cancer treatments — which have established different drug regimens for brain, prostate or ovarian cancer, for example — should eventually be replaced with therapies that use drugs deemed to be of highest benefit based on the tumor's pharmacologic profile. Treatment choice would be determined by how each patient's tumor reacts to anticancer drugs, regardless of the tumor's anatomical origin.

"This study is the first time the pathway for a drug's effect has been analyzed in tumors from different anatomical locations," says Howard McLeod, Pharm.D., director of the pharmacology core at the Siteman Cancer Center and a member of the National Institutes of Health (NIH) Pharmacogenetics Research Network. "We've shown that drug effect is independent of where the tumor came from in the body. If further studies confirm that a tumor-specific approach is better than the current anatomical emphasis, oncologists may have to stop thinking of themselves as colon cancer or breast cancer specialists and let the cancer tell them which drugs to use for each specific patient."

The research team analyzed 255 samples of eight different cancers — colon, breast, prostate, ovary, lung, brain, melanoma and lymphoma — and measured the amounts of specific proteins known to influence the effect of irinotecan, a commonly used anticancer agent. Their study will appear in an upcoming issue of the *Journal of Pathology*.

The protein levels that determine irinotecan's effectiveness were found to be independent of the anatomical origin of the tumor. So, for instance, the colon tumors studied varied widely in the levels of these proteins. The same variation in protein levels held true for all of the tumor types the researchers examined.

"This study provides evidence that the pharmacological pathway of a drug is important, with significant treatment implications," says Rochelle M. Long, Ph.D., of the National Institute of General Medical Sciences and program director for the NIH Pharmacogenetics Research Network. "This work is in keeping with an overarching Network theme of selecting therapies tailored for individual patients instead of a one-size-fits-all approach."

The researchers found that, independent of anatomical origin, some tumors had high amounts of irinotecan's cellular target, a protein labeled TOP1, while other tumors had very little. Irinotecan would likely be

ineffective in tumors with low TOP1 levels. They also found that tumors varied greatly in the amounts of proteins that transport irinotecan into and out of their cells and in the amounts of proteins that break down irinotecan. These variations determine how well irinotecan will work in a particular tumor.

"Because tumor response can't be predicted from anatomical location, we should start selecting treatments based on what genes and proteins can tell us about how the tumor will respond to a drug," says McLeod, professor of medicine, of genetics, and of molecular biology and pharmacology. "If we rely just on what has clinically been shown to work in some cases for a particular anatomically defined cancer, we may not initially choose the best therapy for the individual patient. And with advanced cancer, a patient may get only one shot at the right therapy — making the wrong choice could be deadly."

According to McLeod, under current treatment selection methods virtually no chemotherapeutic drug has been successful in more than 50 percent of patients with advanced cancer. But instead of considering a drug that works only ten percent of the time a failure, he feels it would be better to consider such a drug effective for one in ten tumors and to search for the agents among the current arsenal of chemotherapeutic drugs that will work for the rest.

"We have more than 70 FDA-approved drugs that potentially could be useful for a particular tumor," McLeod says. "We are now working on methods that can be used to identify those drugs that will work for each patient's tumor."

Having a good tumor-drug match not only would improve survival rates, it would be cost-effective, according to McLeod.

"Since modern cancer therapies can be expensive — sometimes approaching the cost of a bone marrow transplant — the high cost reinforces the necessity of choosing the right therapy the first time," he says.

Zhang W, Shannon WD, Duncan J, Scheffer GL, Scheper RJ, McLeod HL. Expression of drug pathway proteins is independent of tumor type. *Journal of Pathology*, upcoming issue.

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Washington University School of Medicine's full-time and volunteer faculty physicians also are the medical staff of Barnes-Jewish and St. Louis Children's hospitals. The School of Medicine is one of the leading medical research, teaching and patient care institutions in the nation, currently ranked fourth in the nation by *U.S. News & World Report*. Through its affiliations with Barnes-Jewish and St. Louis Children's hospitals, the School of Medicine is linked to BJC HealthCare.

Siteman Cancer Center is the only NCI-designated Comprehensive Cancer Center within a 200-mile radius of St. Louis. Siteman Cancer Center is composed of the combined cancer research and treatment programs of Barnes-Jewish Hospital and Washington University School of Medicine.

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