How chemotherapy drugs block blood vessel growth, slow cancer spread

January 22 2009

Researchers at the Johns Hopkins University School of Medicine have discovered how a whole class of commonly used chemotherapy drugs can block cancer growth. Their findings, reported online this week at the *Proceedings of the National Academy of Sciences* Early Edition, suggest that a subgroup of cancer patients might particularly benefit from these drugs.

The anthracycline class of chemotherapeutics — doxorubicin (Adriamycin), daunorubicin, epirubicin, idarubicin — have been used for four decades to treat many types of cancer, including leukemia, lymphoma, sarcomas and carcinomas, The standard method of administration had been to use the highest tolerable dose every few weeks to kill all rapidly growing cells by preventing them from accurately copying their genetic material.

"But the late Judah Folkman discovered in 2000 that so-called metronomic treatment, giving patients lower doses of these drugs more frequently, can keep cancer growth at bay by blocking blood vessel formation, but the exact mechanism by which this occurred wasn't known," says Gregg L. Semenza, M.D., Ph.D., director of the vascular program at the Johns Hopkins Institute for Cell Engineering and a member of the McKusick-Nathans Institute of Genetic Medicine. "Now we've shown how it happens and what players are involved, which could help shape future clinical trials for patients with certain types of cancers."

Semenza and his team have long studied how the hypoxia-inducible factor, or HIF-1, protein helps cells survive under low-oxygen conditions. HIF-1 turns on genes that grow new blood vessels to help oxygen-starved cells, like those found in fast-growing solid tumors, survive.

To look for drugs that can prevent new blood vessel growth, the team tested more than 3,000 already FDA-approved drugs in the Johns Hopkins Drug Library for their ability to stop HIF-1 activity. Using modified liver cancer cells growing in low oxygen, the team treated cells with each of the drugs in the library and examined whether the drug could stop HIF-1 from turning on genes.

One drug—daunorubicin—reduced HIF-1's gene-activating ability by more than 99 percent. They tested other members of the anthracycline drug class and found that doxorubicin, epirubicin and idarubicin also blocked HIF-1 activity. But further examination showed that both drug-treated and untreated cells contained similar amounts of HIF-1 protein, leading the researchers to conclude that the drugs are not affecting whether or not HIF-1 is made.

To turn on genes, HIF-1 must bind to DNA. So the research team looked at drug-treated and untreated cells and compared regions of DNA known to be bound by HIF-1. The sites that are bound by HIF-1 in untreated cells were found unbound in anthracycline treated cells. "We know that this class of drug prefers to bind to DNA sequences that are similar to the DNA sequence bound by HIF-1, but this is the first direct evidence that anthracyclines prevent HIF-1 from binding to and turning on target genes," says Semenza.

To see if the interference with HIF-1 binding to DNA affects cancer growth, the team grew tumors in mice from human prostate cancer cells. They treated these mice with daunorubicin, doxorubicin or saline once a

day for five days and measured tumor size. Tumors in saline-treated mice nearly doubled in size in that time, whereas tumors in the drug-treated mice stayed the same size or became smaller.

When the team examined the tumors from drug-treated mice, they found that the number of blood vessels was dramatically reduced compared to mice treated with saline. Additional tests revealed that the genes that HIF-1 turns on to drive blood vessel formation were turned off in tumors from the drug-treated mice.

"What this means, we hope, is that patients with a prostate cancer that has high HIF-1 levels — which puts them at greater risk of relapse following surgery or radiation therapy — might benefit from treatment with these drugs," says Semenza. "However, clinical trials are necessary to determine whether this approach will help keep cancer patients alive."

Source: Johns Hopkins Medical Institutions