Weighting cancer drugs to make them hit tumors harder

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Scientists have devised a blueprint for boosting anti-cancer drugs' effectiveness and lowering their toxicity by attaching the equivalent of a lead sinker onto the drugs. This extra weight makes the drugs penetrate and accumulate inside tumors more effectively.

Chemotherapy drugs often fall short of achieving their full impact because the drugs diffuse in and out of the tumor too rapidly, said the scientists from Duke University Medical Center and Duke's Pratt School of Engineering.

The scientists increased the size of the drug by adding a "macromolecular weight" that increases its concentration and staying power inside the tumor. The heavier molecules are more selectively absorbed by tumors because tumor blood vessels are more permeable or "leakier" than normal blood vessels. Thus, larger molecules can pass through the tumor vessels more easily.

Drugs with a greater molecular weight also reduce chemotherapy's toxicity to healthy tissue because the large molecules cannot easily permeate normal blood vessels. As a result, normal tissue receives less of the drug than does the tumor.

Results of the study, funded by the National Institute of Biomedical Imaging and Bioengineering, a branch of the National Institutes of Health, are published in the March 1, 2006, issue of the Journal of the National Cancer Institute.

"Small molecules penetrate the tumor very efficiently, but are also removed very efficiently," said Ashutosh Chilkoti, Ph.D, a Duke biomedical engineer and senior author of the study. "Larger molecules penetrate more slowly, but they stay in the tissue longer, giving the patient a greater concentration of the drug. If you balance the two factors with a precise weight, you get optimal drug concentration."

Chilkoti said current chemotherapy drugs are so small ï¿½ molecular weight of 300 to 600 ï¿½ that they are reabsorbed into the bloodstream before their anti-cancer effects are fully achieved.

Overcoming this limitation by adding macromolecular weight is not a new concept, but determining the precise weight to achieve optimal drug concentration has proved difficult, he said. Chilkoti and his colleagues in the department of biomedical engineering and radiation oncology at Duke measured the tumor permeability, penetration and accumulation of various macromolecular weights in mouse tumors. The drug carrier they studied was dextran, essentially a chainlike string of sugar molecules.

By measuring a range of dextran molecular weights in a three-dimensional model and over 30 minutes instead of a single time point, they determined the optimal weight for tumor permeability, penetration and accumulation.

"No one has previously quantified the process of three-dimensional penetration and accumulation as it occurs -- information that is critical to achieving optimal results," said Matthew Dreher, a graduate student in biomedical engineering and lead author of the study. "We quantified tumor blood vessel permeability and we examined precisely where in the tumor the macromolecular molecules accumulated."

The optimal molecular weight for the drug's highest accumulation inside tumors was between 40,000 and 70,000, the study showed. At this

weight, a large percentage of the drug was concentrated near the blood vessels of the tumor, where cancer cells tend to proliferate more rapidly. Drugs of lower molecular weight penetrated more deeply into the tumor but exited more quickly.

"Tumor cells multiply more rapidly near the vasculature, so targeting that area is key to chemotherapy's cancer-killing effects," said Mark Dewhirst, DVM, Ph.D., a co-author of the paper who is a radiation biologist and director of the Duke Hyperthermia Program. Dewhirst's team has illuminated numerous mechanisms by which a tumor's blood vessels and oxygen levels influence its growth and its demise.

"Artificially increasing the weight of a drug gives us a means to increase the amount of drug going to the tumor while reducing toxicity to the rest of the body," said Fan Yuan, Ph.D., co-author on the paper and an associate professor of biomedical engineering at Duke. "We can adjust the weight higher or lower depending upon where we want the drug to concentrate."

Even drugs with vastly elevated molecular weights ï¿½ 2 million molecular weight -- achieved better concentrations in tumors than a lower molecular weight, the study showed.

Chilkoti said chemotherapy by itself is small enough to travel throughout the body via the bloodstream, causing toxicity to vital organs such as the liver, bone marrow and heart. Likewise, chemotherapy's stay inside tumors is brief because it flows out as rapidly as it entered.

In contrast, high molecular weight chemotherapy molecules are too large to be picked up by normal blood vessels. The drugs also remain longer in the tumor because they are not readily reabsorbed into the bloodstream, nor can they penetrate the kidneys to be cleared from the body. They must wait for the liver to break them up and dispose of them via the

intestines.

"Our goal was to increase the tumor dose and lower the systemic dose," said Chilkoti. "Macromolecular drug carriers are an attractive drug delivery system, because they target tumors and have limited toxicity in normal tissues."

Of additional benefit, macromolecular drug carriers can be substituted for the toxic substances routinely mixed with chemotherapy to make it more soluble. Macromolecular molecules can selectively carry the drug to the tumor simply due to their size and do not need such noxious carriers, said Chilkoti.

"We can increase the solubility of chemotherapy by adding it to a soluble macromolecular molecule," he said. "Then you don't have to mix it with noxious substances as a means of ensuring that chemotherapy gets into cancer cells."

Chilkoti said their findings also are important because they can be used to optimize drug delivery of all macromolecular therapeutic agents, including cytokines, antibodies and anti-angiogenic drugs."

Source: Duke University