Potential brain cancer drug for children may damage bones

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A novel drug that fully eliminated brain tumors from mice in a dramatic 2004 study has shown a darker side—causing permanent bone damage in younger mice. The researcher who conducted both studies says the disappointing new finding raises concerns about using similar drugs to treat children's cancers, at least until there is a more thorough understanding of possible risks.

Tom Curran, Ph.D., a developmental biologist at The Children's Hospital of Philadelphia, led the study, published in the March 2008 issue of the journal *Cancer Cell*. The drug in question, HhAntag, is a signal transduction inhibitor--an agent that blocks signals along a biological pathway. In mice specially bred for these studies by Curran's research group, HhAntag specifically acts against signals on a pathway leading to medulloblastoma, a type of brain tumor found mostly in children.

Much current cancer research has focused on signal transduction inhibitors (STIs) because of their potential to interrupt specific biological pathways that give rise to cancer. To date, only one STI has been approved by the Food and Drug Administration for use in children. That drug, which acts on different biological pathways than HhAntag does, has not been associated with any developmental defects in children. However, other STIs are currently in pediatric clinical trials.

His team's new findings, says Curran, raise a strong caution. "While it is not clear that the bone defects we observed in mice would also occur in children, and while signal transduction inhibitors may still represent a

highly promising approach to treating pediatric cancer, it may be important to perform preclinical testing in young animals before moving ahead to clinical trials," he added. Young animals could provide a model of a drug's potential effects during childhood development.

The drug used by Curran's group acts on the hedgehog (Hh) pathway, which is known to play multiple roles during the development of mammals. Mutations of genes along that pathway lead to different cancers, including medulloblastoma, the most common cancerous brain tumor in children. Because conventional treatment with surgery, radiation and chemotherapy causes serious long-term side effects such as ataxia (a movement disorder) and cognitive impairments, the researchers sought novel, less toxic treatments for medulloblastoma.

In 2001, using genetic engineering, Curran bred mice to develop medulloblastoma. He then treated those mice with HhAntag, which had previously been developed by a biotech company for treating skin cancer in adults. In 2004, while at St. Jude's Children's Research Hospital, Curran reported highly promising results from the mouse studies. At high doses, the drug caused the tumors to shrink and in some cases, disappear entirely. The treated mice also survived much longer than untreated mice, with no serious side effects.

The drug seemed to be an unusually strong candidate for trials in children with the type of medulloblastoma having gene mutations on the Hh pathway—about a third of cases.

However, when Curran's group tested the agent on young mice (10 to 14 days old, in contrast to the adult mice tested previously), they found an unpleasant surprise: serious impairments to developing bones. The mice were smaller, with lower weight and shorter bones than untreated mice, and the effects were not reversible. Even four doses of the drug permanently stunted their growth. "We already knew that the same

biological pathway involved in the growth of tumors was also involved in bone development," said Curran, "but we did not expect temporary inhibition to cause an irreversible change in bone growth."

While the current studies were disappointing, said Curran, they do not totally rule out a future role for HhAntag as a treatment for medulloblastoma. "The effects we see in mice may be less dramatic in children, and there may be methods of delivering this drug directly to brain tissue, while avoiding bones. Alternatively, we might discover other drugs that act on the hedgehog pathway but selectively target brain tissue." Another approach, he adds, may be to use HhAntag only in older children who have already completed their growth, or in the admittedly small proportion of medulloblastoma patients who are adults.

"Signal transduction inhibitors such as this drug may still prove beneficial in treating children's cancers, but our findings raise questions about possible adverse effects during childhood development," said Curran.

Source: Children's Hospital of Philadelphia