Potential cognitive effects of targeted drugs in children may be reversible with therapy

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Young mice that received molecularly targeted therapies used to treat brain cancer in human patients sustained cognitive and behavioral deficits, but the deficits were largely reversible through environmental stimulation and physical exercise. The study suggests that pediatric brain cancer patients may experience similar side effects of molecularly targeted therapies, and may benefit from efforts to remediate any cognitive deficits.

The research is published in *Cancer Research*, a journal of the American Association for Cancer Research, by Joseph Scafidi, DO, MS, a neonatal neurologist at Children's National Health System, in Washington, D.C.

"We've made significant progress against many childhood cancers, largely because of new, highly effective drugs," Scafidi said. "Targeted therapies currently used to treat brain cancers work because they target specific pathways in the cancer. However, these pathways are critical to the development of the brain, and so we set out to evaluate the cellular and behavioral effects of these drugs on a normal, developing brain.

"Primary central nervous system tumors continue to be the leading type of solid tumors in the pediatric oncology population," Scafidi continued. He said targeted therapies such as gefitinib (Iressa), sunitinib malate (Sutent), and rapamycin (Sirolimus) are now used to treat brain tumors, and interest in prescribing this class of drugs is growing. However, most clinical trials and pre-clinical studies on the drugs have been conducted in adults, therefore, the effects on pediatric patients are not fully known.

In this study, Scafidi and colleagues injected mice with either gefitinib, sunitinib malate, rapamycin, or a vehicle substance. One group of mice received the vehicle or drug when they were between 12 and 17 days old (analogous to early childhood); another group received the vehicle or drug when they were 17 to 22 days old (analogous to adolescence); and in a separate set of experiments, mice received the vehicle or drug when they were between 12 and 14 weeks old (analogous to adulthood).

Researchers assessed the drugs' effects on oligodendrocytes, a type of cell, in the white matter of the brain. They found that the mice that received the drugs at the youngest ages had the most significant decrease in oligodendrocytes; the mice that received the drugs as adults did not have significant changes. The researchers also analyzed myelin protein expression and again found the most significant changes in the mice that received the drugs at the youngest ages.

The researchers also measured other types of cells and found no significant changes, suggesting that the moleculary targeted therapeutics specifically target oligodendrocytes, Scafidi said.

To examine whether the drugs had behavioral effects, the researchers put the mice through a series of tasks: inclined beam-walking, novel object recognition, and maze running. The mice treated at a younger age with any of these three drugs showed the highest degree of behavioral deficits. Mice treated in adulthood showed no difference in cognitive performance.

Finally, the researchers randomized the mice to either typical housing or an "enriched environment," which included a running wheel and assorted toys. Researchers found that after about two weeks of living in the enriched environment, mice performed significantly better on the beam-walking task and the object recognition task.

Scafidi said the mice's improved performance supports the idea that the brain is plastic, and that cognitive deficits that result from childhood brain cancer treatments may be reversible. He said many cancer centers, including his own, provide different forms of cognitive and physical therapy to patients, and if this research is confirmed in further studies, it may provide a basis for making such therapy a widespread clinical practice.

"The fact is, these drugs do have an effect on the developing brain. The good news is that these effects can be attenuated by exposure to a stimulating cognitive and physical environment," Scafidi said.

Scafidi said the study's main limitation is that the research was conducted in mice, so further research would be necessary to determine whether children would experience similar effects. Also, each mouse was injected with just one drug, whereas in clinical practice, children often receive a targeted therapeutic in conjunction with other treatments.

Provided by American Association for Cancer Research

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