Methotrexate exposure impacts cognitive processes cancer survivors need to multitask

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Research from St. Jude Children's Research Hospital suggests that

pediatric leukemia patients exposed to higher concentrations of the chemotherapy drug methotrexate are more likely to struggle with mental flexibility, organization and related skills as long-term survivors. The findings appear online today in an early release article in the *Journal of Clinical Oncology*.

Investigators also reported that brain imaging showed that higher blood levels of methotrexate during treatment for acute lymphoblastic leukemia (ALL) were associated with anatomical and functional changes in regions of the brain involved with mental flexibility, planning, reasoning and other skills related to executive functioning. Brain imaging documented several changes, including increased activity in the frontal lobe region. The finding suggests survivors' brains may be working harder to compensate for impaired cognitive functioning.

"With five-year survival rates for pediatric ALL approaching 95 percent, researchers are focused on better understanding and reducing the neurotoxicity patients still experience during and sometimes long after treatment," said first and corresponding author Kevin Krull, Ph.D., a member of the St. Jude Department of Epidemiology and Cancer Control. "It remains a relatively common problem even in the contemporary treatment era of chemotherapy only.

"This study is the first to show a clear dose-response effect between methotrexate concentrations in the blood during treatment and executive functioning in survivors. This information is essential for designing effective intervention to address the risk," he said.

The study included 218 long-term pediatric ALL survivors treated with multi-drug chemotherapy delivered directly to cerebrospinal fluid (intrathecal) rather than brain irradiation to prevent cancer from recurring in the central nervous system. The participants were enrolled in the St. Jude Total Therapy XV clinical trial between 2000 and 2010. All

had survived at least five years from their diagnosis and were at least 8 years old when this study was done.

Methotrexate is one of the few chemotherapy agents that cross from the blood into the brain and nervous system. Previous research into a possible association between chemotherapy agents like methotrexate and neurotoxicity used the dose patients received as a surrogate for drug exposure as measured by blood levels of the drug. Those studies yielded conflicting results, possibly due to individual differences in methotrexate metabolism.

In this study, researchers calculated methotrexate concentrations by measuring blood levels of the drug before, during and after treatment. In addition to methotrexate, investigators also checked blood levels of the amino acid homocysteine, a marker of methotrexate activity, and the chemotherapy agent dexamethasone.

Higher concentrations of methotrexate and homocysteine were associated with lower scores on measures of executive function, including mental flexibility, verbal fluency, working memory and processing speed. While the impact varied, scores suggest some survivors had executive functioning that was moderately to almost severely impaired.

Along with increased activity in regions of the brain associated with executive functioning, brain imaging showed higher methotrexate exposure was associated with thicker brain cortex in prefrontal regions, which may suggest disrupted neuronal pruning that occurs with normal aging. Methotrexate exposure was also linked to changes in the white matter that insulates neural connections in the same region.

"The neural connections remain, but as the concentrate of methotrexate in the blood increases, the integrity of the white matter breaks down,

which could affect functions like processing speed," Krull said.

The methotrexate risk was unrelated to the survivors' gender, age at diagnosis or disease risk group. In contrast, dexamethasone levels were not linked to executive function or other cognitive skills.

"Methotrexate has contributed to historically high cure rates for childhood leukemia," Krull said. "While physicians may look for opportunities to reduce concentrations of the drug in the future, interventions are already in development to enhance executive function in patients on therapy as well as long-term childhood cancer survivors."

For example, Krull is principal investigator of a pilot study into whether electrical stimulation of the prefrontal cortex combined with cognitive training will enhance executive function in adult survivors of childhood leukemia.

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