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Gene Variant Associated With Increased Risk and Severity of Nerve Disorder Linked to Widely-Prescribed Cancer Drug

Children with acute lymphoblastic leukemia who had a certain gene variant experienced a higher incidence and severity of peripheral neuropathy, after receiving treatment with the cancer drug vincristine, according to a study in the February 24 issue of *JAMA.*

Cancer remains the leading cause of death by disease in U.S. children despite major advances in the last 20 years. Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, and as cure rates have surpassed 85 percent, it becomes increasingly important to lessen the toxicities of treatment that adversely affect quality of life and longevity. Vincristine is one of the most widely used and effective anticancer agents for treating leukemias in both adults and children. The dose-limiting toxic effect of vincristine is peripheral neuropathy (damage to the nerves), characterized by neuropathic (nerve) pain and impaired manual dexterity, balance, and altered gait. Currently, there are no reliable means of identifying patients at high risk of vincristine-induced neuropathy nor strategies to reduce this drug toxicity, according to background information in the article.

William E. Evans, Pharm.D., of St. Jude Children's Research Hospital, Memphis, and colleagues performed a genome-wide association study to determine whether there are genetic variants associated with vincristine-induced neuropathy. The study included patients in 1 of 2 prospective clinical trials for childhood ALL that included treatment with 36 to 39 doses of vincristine. Genetic analysis and vincristine-induced peripheral neuropathy were assessed in 321 patients from whom DNA was available: 222 patients (median age, 6.0 years) enrolled in 1994-1998 in a St. Jude Children's Research Hospital cohort; and 99 patients (median age, 11.4 years) enrolled in 2007-2010 in a Children's Oncology Group (COG) cohort.

Grade 2 (moderate) to 4 (life threatening) vincristine-induced neuropathy during therapy occurred in 28.8 percent of patients (64/222) in the St. Jude cohort and in 22.2 percent (22/99) in the COG cohort. The researchers found that an inherited variant in the gene *CEP72* was associated with a higher incidence and severity of vincristine-related peripheral neuropathy in children with ALL. Among patients with the gene

variant, 28 of 50 (56 percent) developed at least 1 episode of grade 2 to 4 neuropathy, compared with 21 percent (58/271) of other patients.

"If replicated in additional populations, this finding may provide a basis for safer dosing of this widely prescribed anticancer agent," the authors write.
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Editor's Note: Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, funding and support, etc.

Editorial: Precision Medicine to Improve the Risk and Benefit of Cancer Care

"The study by Diouf et al has many key elements; genome-wide discovery in patients from well-conducted clinical trials, replication in a multicenter cohort, statistical robustness, and laboratory correlative findings that contribute biologic plausibility," writes Howard L. McLeod, Pharm.D., of the Moffitt Cancer Center, Tampa, Fla., in an accompanying editorial.

"However, vincristine remains a component of the most widely accepted treatment regimens for childhood ALL, although there is variation in both dose and intensity. It is not clear that vincristine can be removed from the treatment options for a child with *CEP72* variants, although this study suggests that the resulting increase in leukemia cellular sensitivity makes vincristine dose reductions possible without compromising antileukemic effect."

"However, there is value in the association of *CEP72* with vincristine-induced peripheral neuropathy (VIPN). The ability to objectively ascribe a degree of heightened VIPN risk will allow for greater transparency in discussions of risk and benefits of therapy with patients and their family members. This also may lead to developmental therapeutic approaches to modulate *CEP72* function as either primary prevention or treatment of chronic VIPN. This study also represents an initial robust effort to generate predictors for adverse drug reactions in cancer care."
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Editor's Note: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. McLeod reports stock options for Cancer Genetics Inc.

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