Drug prevents severe cardiac events in children undergoing chemotherapy for AML

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The cardioprotective drug dexrazoxane preserved cardiac function in pediatric patients undergoing chemotherapy for acute myeloid leukemia (AML) without compromising overall patient survival and potentially improving it, according to a new study by researchers at Children's Hospital of Philadelphia (CHOP). The results suggest dexrazoxane should be considered for cardioprotection in all pediatric patients undergoing standard chemotherapy for AML.

The findings were published today in the *Journal of Clinical Oncology*.

"This study provides important evidence that using dexrazoxane helps prevent heart damage in children undergoing treatment for AML," said Richard Aplenc, Professor of Pediatrics in the Department of Pediatrics, core faculty member of the Center for Pediatric Clinical Effectiveness at CHOP, and senior author of the study. "These results have arguably changed the standard of care for pediatric AML treatment."

Anthracyclines, a class of drugs used in chemotherapy for cancers such as AML, improve survival in pediatric patients with AML, but the drugs also have cardiac side effects. The drugs generate iron-mediated free radicals and inhibit DNA replication, both of which trigger cell death and left ventricular systolic dysfunction (LVSD) and can lead to heart failure. At least 12% of AML patients experience LVSD within one year of beginning treatment and many also have lower overall rates of survival and increased mortality as a result.

Dexrazoxane is a cardioprotective drug that interferes with iron-mediated free radical formation and cell death caused by anthracyclines. Yet despite consistent evidence of dexrazoxane's cardioprotective benefits, it is used in less than 5% of pediatric AML patients in the United States.

To assess the effectiveness of dexrazoxane in pediatric AML treatment, the researchers collected information on dexrazoxane administration in the most recent clinical trial for AML by the Children's Oncology Group. Whether or not dexrazoxane was used was up to the individual treating physician. Of the 1,092 pediatric AML patients in the trial, 918 were never exposed to dexrazoxane (84%), 96 (9%) received dexrazoxane at each anthracycline administration, and 78 (7%) received dexrazoxane at some but not all of their treatments. Given the scope of their study, the researchers focused only on those patients who received dexrazoxane consistently or not at all.

Patients who received dexrazoxane had significantly lower risk for LVSD than patients who did not (26.5% vs. 42.2%). Patients in both groups had similar 5-year event free survival and overall survival rates, and the results suggest a lower treatment-related mortality among patients who received dexrazoxane (5.7% vs. 12.7%).

Based on these results, the upcoming COG Phase III AML trial will require dexrazoxane use for all patients receiving standard chemotherapy.

"To our knowledge, these data are the first demonstration of a potential survival benefit with dexrazoxane, specifically a reduction in treatment-related mortality," said Kelly D. Getz, Ph.D., MPH, Assistant Professor of Epidemiology in the University of Pennsylvania Perelman School of Medicine's Department of Biostatistics, Epidemiology, and Informatics and first author of the study. "This suggests that dexrazoxane may

directly prevent acute, severe cardiac events that contribute to early deaths. Additional research to understand the underlying biology of anthracycline-associated cardiotoxicity and effective interventions will improve both the cardiovascular and oncologic outcomes for children with cancer."

More information: Kelly D. Getz et al, Effect of Dexrazoxane on Left Ventricular Systolic Function and Treatment Outcomes in Patients With Acute Myeloid Leukemia: A Report From the Children's Oncology Group, *Journal of Clinical Oncology* (2020). DOI: 10.1200/JCO.19.02856

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