DOES DEXRAZOXANE PROVIDE CARDIAC PROTECTION AGAINST ANTHRACYCLINE-INDUCED CARDIOTOXICITY IN CHILDREN WITH HIGH-RISK ACUTE LYMPHOBLASTIC LEUKEMIA?

Dominique de Waard[1], Ketan Kulkarni, MD[2,3], Andrew Warren, MD[3,4], Mark Bernstein, MD[2,3], Tamara MacDonald, PharmD [2,3,5]

[1]Dalhousie University Medical School, Halifax, Nova Scotia, Canada;

[2]Division of Pediatric Hematology/Oncology, IWK Health Centre, Halifax, Nova Scotia, Canada;

[3]Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada;

[4]Division of Pediatric Cardiology, IWK Health Centre, Halifax, Nova Scotia, Canada;

[5]Department of Pharmacy and Pediatric Hematology/Oncology, IWK Health Centre, Halifax, Nova Scotia, Canada

Background

Anthracyclines are highly effective in the treatment of a wide variety of childhood cancers including acute lymphoblastic leukemia (ALL), the most common type of cancer in children.

Anthracyclines cause both short and long-term cardiotoxicity[1], which is suggested to be in direct correlation with cumulative dose. It is not clear at what cumulative dose cardiotoxicity occurs.

Early-onset cardiotoxicity generally occurs within the first year of anthracycline exposure and presents as heart failure and/or pericardial effusion. Late-onset anthracycline cardiotoxicity occurs a year or more after therapy and is characterized by impaired myocardial growth.

Cardiotoxicity is assessed by a range of parameters on an echocardiogram. In most protocols for the treatment of pediatric ALL ejection fraction (EF) is used for decisions to dose reduce or omit cardiotoxic therapy.

Dexrazoxane has been suggested to reduce cardiotoxicity in patients receiving anthracycline-based chemotherapy for cancer[2-6]. Most of the data on the efficacy of dexrazoxane stems from the adult literature. Data on children is limited.

Objective

Assess the role of dexrazoxane in preventing short-term cardiotoxicity in pediatric patients with high-risk acute lymphoblastic leukemia.

Design/Methods

Beginning in 2012, all patients with high-risk acute lymphoblastic leukemia (HR-ALL) treated in Nova Scotia, New Brunswick, and Prince Edward Island, Canada received dexrazoxane prior to anthracycline as a cardioprotective agent. Prior to 2012, patients with HR-ALL were treated with anthracyclines alone.

The study was designed as a case-control study using historical controls. All patients had received a baseline and follow-up echocardiogram (ECHO) or wall motion ejection fraction (WMEF) as part of standard care. The primary outcome variable was ejection fraction.

Univariate regression analysis was used to determine predictors of a higher ejection fraction in SPSS. A p-value of less than 0.05 was considered statistically significant.

IWK Health Center ethics approval was obtained. The dose of dexrazoxane:anthracycline was 10:1 for all patients.

Results

There were 16 cases (patients who received dexrazoxane + anthracycline) and 22 controls (patients who received anthracycline only) (n=38).

The cases and controls were similar with respect to age (*p=0.758*) and gender (*p=0.326*).

The mean total dose of anthracycline received was 185±64.8mg/m^2 for the cases and 187±46.2mg/m^2 for the controls (*p=0.913)*.

The mean duration from last anthracycline dose to follow-up ECHO/WMEF date was 2.26±1.3 years.

The mean baseline ejection fractions for cases (68.5±9.2) and controls (68.0±8.0) were similar (p=0.848).

The mean follow-up EFs were not significantly different between cases and controls (65.96±11 vs 68.94±6.9 respectively) (*p=0.358*).

Fifteen of the 38 patients had additional ECHOs during therapy with no evidence of cardiotoxicity.

Discussion and Limitations of the Study

A decrease in ejection fraction below 50% results in dose reduction or omission of anthracycline from most treatment protocols for pediatric acute lymphoblastic leukemia.

Dexrazoxane is a marketed cardioprotective agent indicated for use in adult breast cancer patients who receive greater than 300 mg/m^2 cumulative doxorubicin dose.

This study did not find a significant difference in the reduction of EF below 50% in patients treated on the same HR-ALL protocols who did not receive dexrazoxane and those that did.

The average cumulative dose of children treated for HR-ALL in current protocols is less than 250 mg/m^2. This dose does not appear to negatively influence the short-term cardiac function of these patients.

Limitations of the study include small sample size and incomplete data of other ECHO parameters that measure left ventricular function and left ventricular mass. Complete ECHO data may help in further validation of observations in a larger study population.

Conclusions

This study suggests that patients with HR-ALL are **NOT** at enough risk of cardiotoxicity to warrant the use of dexrazoxane.

Studies in larger populations with longer follow-up would be helpful in better defining at-risk populations.

References

1. Lipshultz SE, Franco VI, Cochran TR. Cardiotoxicity in childhood cancer survivors: a problem with long-term consequences in need of early detection and prevention. *Pediatr Blood Cancer.* 2013;60:1395-96

2. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med.* 1991;324:808-15

3. Lipshultz SE. Dexrazoxane for protection against cardiotoxic effects of anthracyclines in children. *J Clin Oncol.* 1996;14:328-31.

4. Krischer JP, Epstein S, Cuthbertson DD, Goorin AM, Epstein ML, Lipshultz SE. Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group experience. *J Clin Oncol.* 1997;15:1544–52

5. Lipshultz SE, Franco, VI, Miller TL, Colan SD, Sallan SE. Cardiovascular Disease in Adult Survivors of Childhood Cancer. *Annu Rev Med.* 2015;66:161–76

6. Lipshultz SE, Franco VI, Sallan SE, Adamson PC, Steiner RK, Swain SM, Gligorov J, Minotti, G. Dexrazoxane for reducing anthracycline-related cardiotoxicity in children with cancer: an update of the evidence. *Prog Pediatr Cardiol.* 2014;36:39–49.

Acknowledgements

IWK Hematology/Oncology McKinnon Fund,

IWK Cardiology Research Fund,

Coast to Coast Fund.

Contact Information

Dominique de Waard – dewaard.dominique@gmail.com

Tamara MacDonald – Tamara.MacDonald@iwk.nshealth.ca