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Letter to The Editor: Updated European Union Label for Dexrazoxane

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To the Editor

The important editorial by Daniel Bernstein in the January 19, 2018 issue of *Circulation Research* on pre-clinical models of anthracycline cardiotoxicity and cardioprotection,[1] contains errors that should be corrected, lest they adversely affect clinical care.

Dr. Bernstein states that "Current prevention strategies involve limiting total exposure to anthracycline to the lowest possible dose and use of the iron chelator dexrazoxane. *However, as a result of the potential for an increased risk of secondary malignancies, the European Medicines Agency has limited the indication for dexrazoxane to adult patients with advanced disease and contraindicated its use in children.* Thus, the search for a more effective preventive therapeutic is critical, and the contribution of Gupta et al. suggests a new pathway that is worth investigating."

Dr. Bernstein is of course correct in encouraging the use of preventive measures to reduce anthracycline-induced cardiotoxicity. Dexrazoxane provides substantial protection against anthracycline cardiotoxicity without reducing its oncologic efficacy, even allowing safer anthracycline dose escalation.[2,3] He is also correct in saying that dexrazoxane is approved for women with breast cancer. However, in 2014, the US Food and Drug Administration granted dexrazoxane pediatric orphan drug status,[4] and dexrazoxane has never been contraindicated in the pediatric population in the US.[4] Further, in 2017 the European Medicines Agency (EMA) issued a decision that means that children expected to receive a cumulative dose of more than 300 mg/m^2 of doxorubicin or the equivalent cumulative dose of another anthracycline are no longer contraindicated from treatment with dexrazoxane.[5,6]

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This recent decision allows virtually all children to receive dexrazoxane starting with the first dose of anthracycline at the discretion of the treating provider.

Specifically, in July 2017, the EMA concluded that dexrazoxane should not be contraindicated in children at the highest risk of cardiotoxicity.[5,6] The EMA found no data indicating that dexrazoxane was associated with an increase in second primary malignancies, interfered with chemotherapy, or increased the risk for early death in children. The changes made by the EMA in July 2017 related to dexrazoxane as an approved cardio-oncology protectant.[5,6] The label change for dexrazoxane followed a review by the EMA that, since 2016, has been posted and updated on the EMA website to help share the data and new updated label.[5,6]

New data presented to the EMA in 2016 included the results of multicenter randomized clinical trials that were published in high-impact peer reviewed journals.[2,3] Alongside the amendment of the contraindication of dexrazoxane in children was a reassessment of its overall safety profile.[5,6] In July 2017, the EMA approved a change in dexrazoxane labeling which could change clinical practice in the European Union.[5,6]

Although dexrazoxane was given pediatric orphan drug status by the US Food and Drug Administration in 2014,[4] it has been available for many years. For more than a decade, children in Brazil and other South and Central American countries have received dexrazoxane.[7,8] Patients in Mexico have also received dexraxozane.[9,10] Similarly, for children in South Korea[11,12] and Canada, dexrazoxane has been available for many years. Finally, although dexrazoxane was in fact unavailable for children in EMA countries between 2011 and 2017, this is no longer true.

Dexrazoxane is also the most consistent anthracycline cardioprotective agent identified in animal models and confirmed in clinical studies.[13] Although dexrazoxane markedly suppresses anthracycline cardiotoxicity, its cardioprotective activity is not complete, perhaps because anthracyclines have several potential cardiotoxic mechanisms.[14,15] Dexrazoxane may interfere with some, but not all, of these mechanisms.

I agree with Dr. Bernstein[1] that animal models are needed to explore these potential cardiotoxic mechanisms[14,15] and might help identify potential cardioprotective agents. To increase the likelihood of identifying such agents, pre-clinical studies searching for new cardioprotective agents should consider using procedures that can be reproduced in other experimental laboratories.[13] Dr. Bernstein and his colleagues have emphasized the importance of identifying an appropriate model of human anthracycline cardiotoxicity by stating, “This platform also holds considerable promise for the discovery of new doxorubicin-induced cardiotoxicity cardioprotectants, although our findings—that the iron-chelator dexrazoxane was not cardioprotective, whereas the antioxidant N-acetyl cysteine was—may highlight the differences between a whole-animal model and an *in vitro* isolated cardiomyocyte model.”[16] We have also emphasized the importance of pre-clinical models of anthracycline cardiotoxicity that reflect the clinical problem.[13,17]

We have summarized some of the variables affecting the reproducibility of experimentally induced anthracycline cardiotoxicity.[13,17] Further, pre-clinical studies of anthracycline

cardiotoxicity would be of more clinical value if they incorporated a chronic component because the cardiac phenotype in children with anthracycline cardiomyopathy shifts from an early dilated cardiomyopathy to a later progressive restrictive cardiomyopathy.[2,3,13] Pre-clinical models of anthracycline cardiotoxicity and cardioprotection should also incorporate multi-agent chemotherapeutic drug combinations to improve translational understanding.[13] Multi-agent anthracycline cardioprotection against multi-agent chemotherapy should be tested in preclinical models with or against dexrazoxane to determine whether cardioprotection is incremental or improved, respectively.[13] Validated cardiac biomarkers such as serum cardiac troponin-T and NT-pro-brain natriuretic peptide measurements as surrogate endpoints should be used in pre-clinical studies to assess the state of anthracycline cardiotoxicity.[13,18] The use of pre-clinical models to assess genetic susceptibility for cardiotoxicity may also help to define high-risk groups and to characterize mechanisms of anthracycline cardiotoxicity and its prevention or reduction.[13]

In conclusion, horizontally integrating pre-clinical and clinical studies of anthracyclines is important to improving and implementing cardioprotective strategies in patients at high risk for cardiovascular events with the aim to enhance their quality of life.

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