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Prevention of Heart Failure Induced by Doxorubicin with Early Administration of Dexrazoxane (PHOENIX Study): dose response and time course of dexrazoxane-induced degradation of topoisomerase 2b

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Abstract

Background Dexrazoxane, a putative iron chelator, is effective in preventing doxorubicin-induced cardiotoxicity. However, dexrazoxane is also a catalytic inhibitor of topoisomerase 2b (Top2b), a key mediator of doxorubicin toxicity. Preclinical studies have shown that dexrazoxane induces Top2b degradation, and early administration (8 h before doxorubicin) can prevent doxorubicin-induced cardiotoxicity. In this study, we investigated the dose–response relationship and time course of dexrazoxane-induced Top2b degradation in human volunteers.

Methods Twenty-five healthy female volunteers received an intravenous infusion of dexrazoxane at doses ranging from 100 mg/m^2 to 500 mg/m^2. Blood samples were collected hourly from time zero to 12 h, as well as at 24- and 48-h post-infusion. Peripheral blood mononuclear cells (PBMCs) were isolated, nuclear fractions were extracted, and Top2b expression was analyzed by western blot using Lamin B1 as a control. A linear mixed-effects model was used to assess differences among the five dose groups.

Results Dexrazoxane infusion led to a rapid and sustained reduction of Top2b in PBMCs, lasting up to 12 h. Statistical analysis revealed a significant difference in Top2b levels among the five dose groups ($p=0.0002$). Subgroup analysis identified a significant difference between the 100 mg/m^2 and 500 mg/m^2 groups ($p=0.005$). However, topoisomerase 2a (Top2a), the molecular target of doxorubicin's tumor-killing effect, remained unchanged following dexrazoxane infusion.

Conclusions Findings from this dose–response and time-course study can inform the design of future clinical trials investigating the efficacy of early dexrazoxane administration in preventing doxorubicin-induced cardiotoxicity while minimizing the risk of tumor protection.

Trial registration (Funded by the National Institute of Health, RO1HL151993; PHOENIX trials, ClinicalTrials.gov number, NCT03930680.)

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Daunorubicin, the first anthracycline class of compounds, was discovered over 60 years ago [1, 2]. Initial study revealed its efficacy against childhood leukemias; however, a number of recipients developed congestive heart failure [3]. A retrospective analysis of 4018 patients showed that development of congestive heart failure was correlated with the total dose of doxorubicin (closely related to daunorubicin) administration [4]. Early mechanistic studies revealed a propensity for doxorubicin and other anthracyclines to induce reactive oxygen species formation in cardiac tissues [5, 6]. However, N-acetylcysteine administration (5.5 gm/m^2 PO for 30 days) failed to prevent doxorubicin-induced cardiotoxicity in sarcoma patients who have received greater than 500 mg/m^2 of doxorubicin [7]. Early animal study showed that ICRF-187 (dexrazoxane) could prevent chronic doxorubicin-induced cardiotoxicity, whereas N-acetylcysteine was not effective [8]. Dexrazoxane is hydrolyzed to ADR-925, a compound structurally similar to EDTA, a strong iron chelator, suggesting a plausible cardioprotective mechanism [9, 10]. Clinical trials in metastatic breast cancer patients demonstrated dexrazoxane's effectiveness in preventing doxorubicin-induced cardiotoxicity [11, 12]. Additionally, dexrazoxane has been extensively studied in randomized clinical trials involving pediatric patients with acute lymphoblastic leukemia/lymphoma, Hodgkin lymphoma, and osteosarcoma [13, 14] and adults with sarcoma [15, 16]. Administered as an intravenous bolus before each doxorubicin dose, dexrazoxane has shown long-term benefits; 20 years after the first anthracycline treatment, patients who received dexrazoxane maintain better left ventricular function compared to those who did not [17].

Doxorubicin and other anthracyclines kill cancer cells by targeting topoisomerase 2α (Top2a), a crucial enzyme for DNA replication [18]. Top2a is highly expressed in proliferating tissues but is undetectable in adult cardiomyocytes [19]. In contrast, the closely related isoenzyme topoisomerase 2b (Top2b) is present in adult cardiomyocytes. Doxorubicin poisons both Top2a and Top2b, suggesting that Top2b may be a key driver of doxorubicin-induced cardiotoxicity [20]. Deletion of the Top2b gene in adult cardiomyocytes prevents doxorubicin-induced DNA double-strand breaks, mitochondrial dysfunction, and ROS production [21]. This supports the Top2b hypothesis, which explains the three main hallmarks of doxorubicin-induced cardiotoxicity: DNA double-strand breaks, ROS generation, and mitochondrial dysfunction [22].

Dexrazoxane prevents doxorubicin induces DNA-double strand breaks through inhibition of Top2b in H9C2 cardiomyocytes [20]. In addition, ADR-925, a metabolite of dexrazoxane and an effective iron chelator, does not protect doxorubicin-induced cardiotoxicity in neonatal ventricular cardiomyocytes and rabbit hearts [23]. These observations suggested that dexrazoxane prevents doxorubicin-induced cardiotoxicity through Top2b inhibition, but not through iron chelation. This also make sense biochemically because dexrazoxane forms a tight complex with the ATPase domain of human Top2a and Top2b proteins [20].

A key concern is that dexrazoxane's inhibition of Top2a may compromise doxorubicin's tumoricidal activity. Although dexrazoxane has not been shown to significantly compromise the anticancer efficacy of doxorubicin in many clinical trials, a phase III trial demonstrated that dexrazoxane reduced doxorubicin's efficacy in breast cancer treatment [24, 25]. As a result, the FDA restricts its use to breast cancer patients who have received a cumulative doxorubicin dose of 300 mg/m^2 and require continued treatment for tumor control. Doxorubicin-induced cardiotoxicity is typically detected through left ventricular function assessment via echocardiography or nuclear imaging [22, 26]. However, more sensitive methods, such as cardiac biopsy, can reveal subclinical cardiotoxicity at much lower doxorubicin doses [27]. Consequently, dexrazoxane's clinical utility in breast cancer patients remains limited under its current FDA-approved indication. Nonetheless, the administration of dexrazoxane in combination with doxorubicin from day 1 in sarcoma patients did not appear to alter progression-free survival when compared with historical controls [16].Recently, we showed that dexrazoxane induces a ubiquitin/proteasome-mediated degradation of Top2b, but not Top2a in murine hearts [28]. Eight hours after intraperitoneal administration of dexrazoxane, Top2b becomes undetectable in murine heart tissue, suggesting that dexrazoxane reduces Top2b expression similarly to its genetic deletion in cardiomyocytes [21]. Given that dexrazoxane has a half-life of two hours, 93.75% is eliminated within eight hours (four half-lives) post-administration. Administering dexrazoxane eight hours before doxorubicin allows us to distinguish its effect on Top2b as degradation rather than inhibition. Notably,

in a murine model of chronic doxorubicin-induced heart failure, dexrazoxane pre-treatment eight hours before doxorubicin completely protected against doxorubicin-induced cardiotoxicity [28]. Similar observation was also made by Hasinoff et al.[29]. This strategy will be tested in human in the PHOENIX study (**P**revention of **H**eart Failure-induced by D**O**xorubicin with **E**arly Admi**NI**stration of De**X**razoxane study), funded by the National Institute of Health.

In Phase 1 of the PHOENIX study, we sought to determine the time course and dose requirement for Top2b degradation in human volunteers. It is not feasible to assess Top2b protein level in the heart following dexrazoxane administration, we choose the peripheral blood leukocyte as a surrogate tissue to study Top2a and Top2b expression following dexrazoxane administration. Top2b protein level in the peripheral blood were assessed serially after intravenous dexrazoxane in human volunteers. The effectiveness of dexrazoxane on Top2b degradation and the time course of Top2b degradation and recovery were determined.

Methods

The Phoenix 1 (Prevention of Heart Failure induced by Doxorubicin with Early Administration of Dexrazoxane) trial is a single site clinical study to investigate the degradation, time course, and dose–response of Topoisomerase 2b in peripheral blood mononuclear cells of human volunteers (NIH RO1HL151993). The study protocol (IRB#262180) is approved by the Institutional Review Board of the University of Arkansas for Medical Sciences.

Recruitment

We recruited healthy women aged 18 to 65 from community. A total of 37 individuals were screened, and 25 were enrolled in the study. Of these, 11 participants were younger than 29 years, 6 were between 30 and 49 years old, and 6 were older than 50 years. The racial distribution included 19 Caucasian participants, 3 African American participants, 1 Asian American participant, and 2 participants of mixed race.

Exclusion criteria included

- Pregnancy or breastfeeding
- Presence of an acute illness (participants could be re-screened after two weeks if symptoms resolved)
- Anemia (Hb < 12 g/dL)
- Calculated creatinine clearance < 60 mL/min
- Abnormal liver function tests
- Inability or unwillingness to abstain from alcohol consumption for 48 h

Participants were divided into 5 cohorts receiving 100 mg/m^2, 200 mg/m^2, 300 mg/m^2, 400 mg/m^2, or 500 mg/m^2 of dexrazoxane by IV infusion over 15 (± 5) minutes.

Bloods were drawn to purify peripheral blood leukocytes for Top2b assessment using western blot analysis. The following time points were assessed −1, 1, 2, 3, 4, 5, 6, 7, 8, 9,10,11,12, 24, and 48 h after dexrazoxane infusion.

Isolation of Peripheral Blood Mononuclear Cells (PBMCs): Blood samples collected in heparinized tubes were diluted with an equal volume of PBS containing 2% fetal bovine serum. The diluted sample was added to a SepMate tube (STEMCell Technologies) containing a density gradient medium. The tube was centrifuged at 1,200 g for 10 min with brakes on. Peripheral blood mononuclear cells (PBMCs) were harvested from the interface between the density gradient and plasma. The purified PBMCs were washed with PBS containing 2% FBS and counted before use.

Top2 protein determination and quantitation: One million PBMCs were centrifuged at 13,000 RPM for 1 min. The pellet was resuspended in Buffer A (10 mM HEPES–KOH, 1.5 mM $MgCl_2$, 10 mM KCl, 0.5 mM DTT, and 0.2 mM PMSF, pH 7.9). Triton X-100 was added to a final concentration of 0.2%. The cell lysates were centrifuged at 5,000 RPM for 5 min to obtain nuclear pellets, which were then washed with Buffer A and resuspended in 50 µL of cold Buffer B (20 mM HEPES–KOH, 1.5 mM $MgCl_2$, 420 mM NaCl, 0.5 mM DTT, 0.2 mM PMSF, 0.2 mM EDTA, and 25% glycerol, pH 7.9). The nuclear pellets were incubated on ice for 30 min with occasional mixing to extract nuclear proteins. The nuclear extract was cleared by centrifugation at 140,000 RPM for 10 min, and the supernatant was collected as the purified nuclear extract.

Next, 10 µL of 6X sample buffer was be added to the nuclear extract, which was denatured at 100 °C for 5 min. The sample was loaded onto a 12% Western blot gel, run at 100 mV for one hour, transferred, and blocked. Western blot analysis was performed using antibodies against Top2a (Proteintech 20233–1-AP), Top2b (Abcam ab72334) and Lamin B1 (Abcam ab16048), followed by Peroxidase AffiniPure Goat Anti-Rabbit IgG (H +L) (Jackson ImmunoResearch Inc., 111–035-003). The filters were scanned using LI-COR.

Statistical Analysis

A linear mixed-effects model analysis was conducted to investigate if there were significant differences in the normalized Top2b/Lamin B1 (Hr/Pre) ratio among the five dose groups. If a significant difference was detected, a subgroup analysis was used to identify specific dose groups with significant differences, using a Bonferroni-adjusted significance level to control for Type I error due

to multiple comparisons. The Kruskal–Wallis test was used to assess if there was a significant difference in the HR/Pre ratio at 24 or 48 h among the five dose groups. If a significant difference was detected, Wilcoxon rank-sum tests were conducted to identify pairs of dose groups with significant differences in the Hr/Pre ratio using a Bonferroni-adjusted significance level.

Results

Nuclear fractions of PBMCs were analyzed by Western blot as described [21]. The intensity of the Top2b and Lamin B1 bands was recorded using Li-COR, and the Top2b/Lamin B1 ratio was calculated to account for protein purification variability at each time point. The normalized Top2b/Lamin B1 ratio (Hr/Pre) was analyzed for four participants who received 100 mg/m^2, five participants each in the 200 mg/m^2, 300 mg/m^2, 400 mg/m^2, and 500 mg/m^2 cohorts. Data from participant P1001 could not be normalized due to pre-infusion sample degradation, reducing the 100 mg/m^2 cohort to four participants. Each sample was run in triplicate, and the normalized Top2b/Lamin B1 ratio at each time point after dexrazoxane infusion was divided by the pre-infusion ratio. The average of the triplicate results was plotted (Hr/Pre in Fig. 1). One hour after dexrazoxane infusion, Top2b expression in PBMCs was reduced to 3%–21% of pre-infusion levels (Pre, set as 1).

Statistical analysis revealed a significant difference in the Hr/Pre ratio among the five dose groups ($p=0.0002$). Subgroup analysis identified a significant difference between the 100 mg/m^2 and 500 mg/m^2 groups ($p=0.005$). These findings indicate that dexrazoxane infusion leads to a rapid and sustained reduction of topoisomerase 2b in human PBMCs for up to 12 h, with the extent of reduction being dose dependent.

At 24 h post-dexrazoxane infusion, Top2b expression returned toward baseline in the 100–300 mg/m^2 cohorts (Fig. 2), while it remained suppressed in the 400–500 mg/m^2 groups. By 48 h, Top2b expression had returned to baseline in 12 participants from the 100–400 mg/m^2 cohorts (Fig. 3), while six participants exhibited a twofold increase above baseline. However, all participants in the 500 mg/m^2 cohort continued to show suppressed Top2b levels. In contrast, Top2a expression remained relatively stable over time following dexrazoxane infusion. A representative figure illustrating both Top2a and Top2b expression after a 500 mg/m^2 dexrazoxane infusion is shown in Fig. 4.

Seven participants experienced a drop in hemoglobin levels below 12 g/dL one week after dexrazoxane infusion and multiple blood draws. These participants initially had hemoglobin levels slightly above 12 g/dL, the lower limit of normal in our laboratory. Their hemoglobin levels returned to normal upon repeat testing one week later. White blood cell and platelet counts remained within normal limits for all participants one week after dexrazoxane infusion. There was no evidence of myelosuppression.

One participant who received 500 mg/m^2 of dexrazoxane reported experiencing coughing during the first hour of infusion. Another participant, also receiving 500 mg/m^2 of dexrazoxane, experienced calf and knee swelling along with dyspnea. However, a duplex ultrasound ruled out deep vein thrombosis, and a pulmonary CT

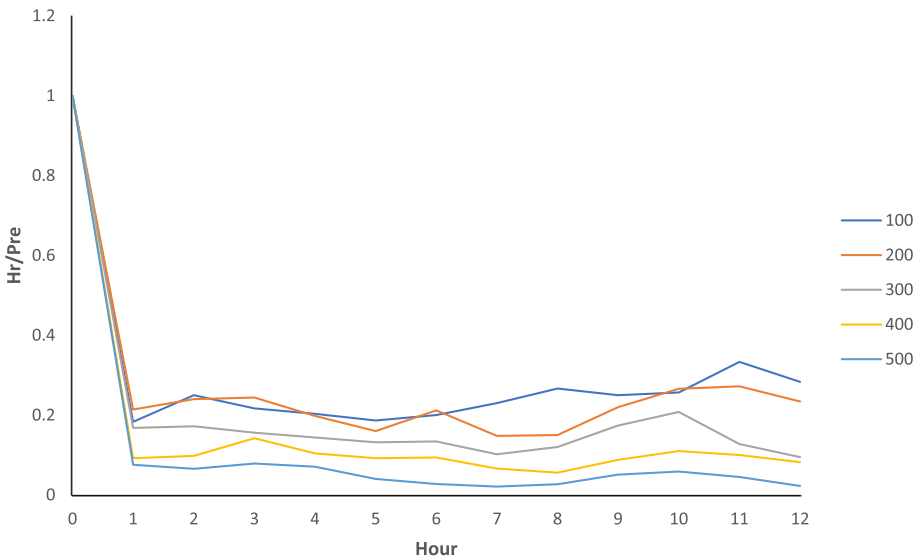
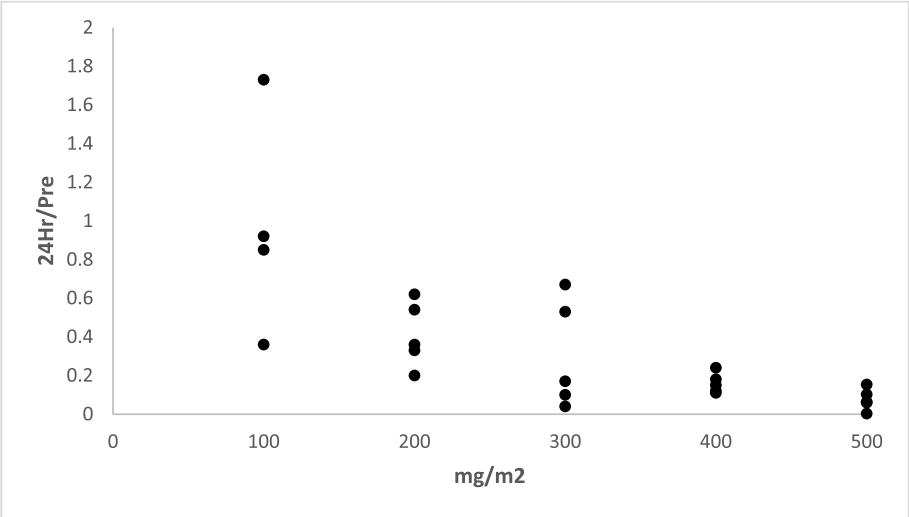


Fig. 1 Top2b level in PBMCs at various time points following dexrazoxane infusion

A. Top2b level in PBMCs 24 hours following dexrazoxane infusion.



B. Wilcoxan Scores

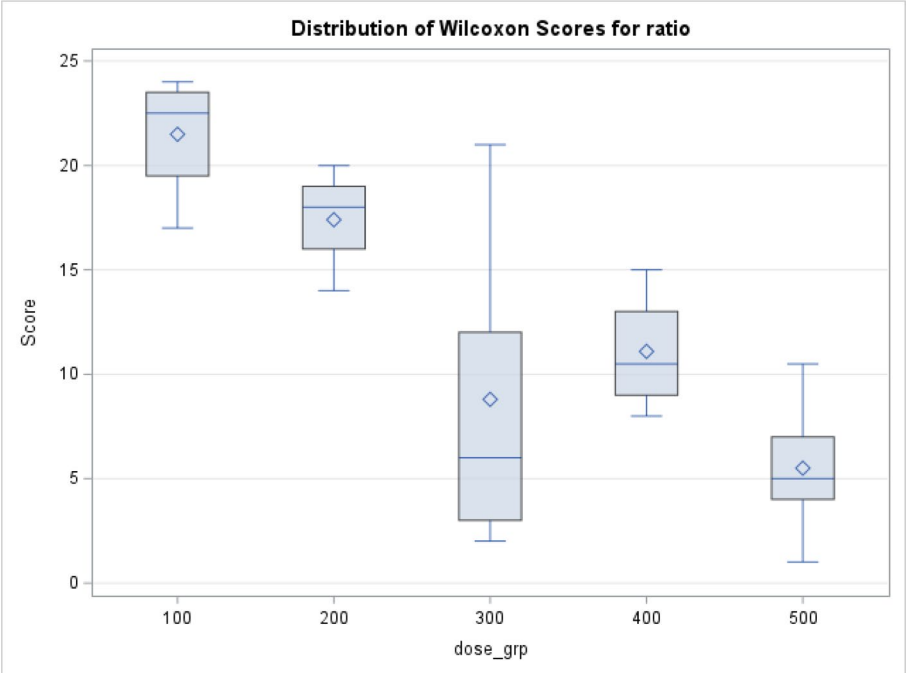


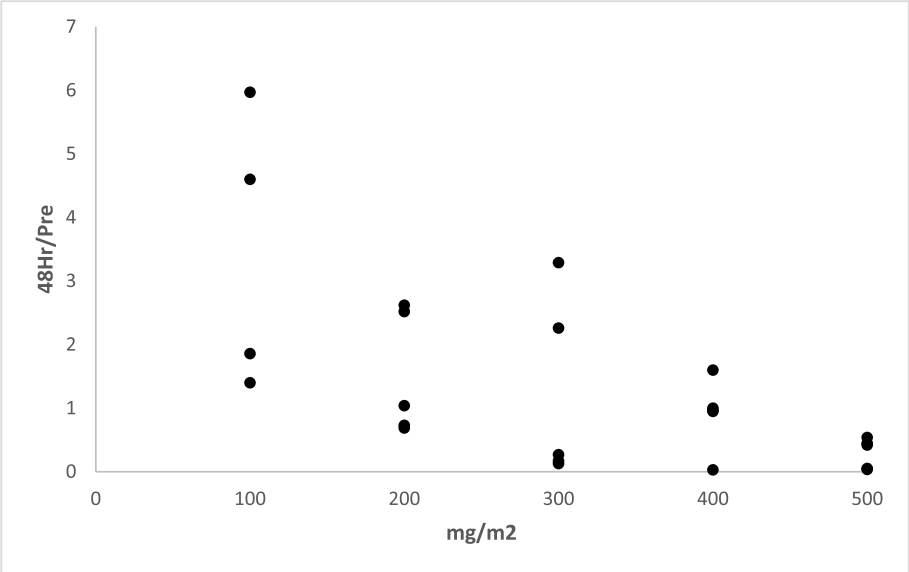
Fig. 2 A. Top2b level in PBMCs 24 h following dexrazoxane infusion

angiogram ruled out pulmonary embolism. The symptoms resolved without treatment. This participant had a history of heparin allergy.

Discussion

In our previous publication, administering dexrazoxane eight hours before doxorubicin infusion was shown to effectively prevent doxorubicin-induced cardiotoxicity in an animal model [28]. This strategy is based on dexrazoxane's ability to selectively induce ubiquitin-mediated degradation of Top2b while sparing Top2a. The key advantage of this approach is its differential effect on Top2 isoforms—eliminating Top2b while preserving Top2a creates an optimal clinical window in which doxorubicin can effectively target cancer cells via Top2a while minimizing Top2b-mediated

A. Top2b level in PBMCs 48 hours following dexrazoxane infusion.



B. Wilcoxon scores

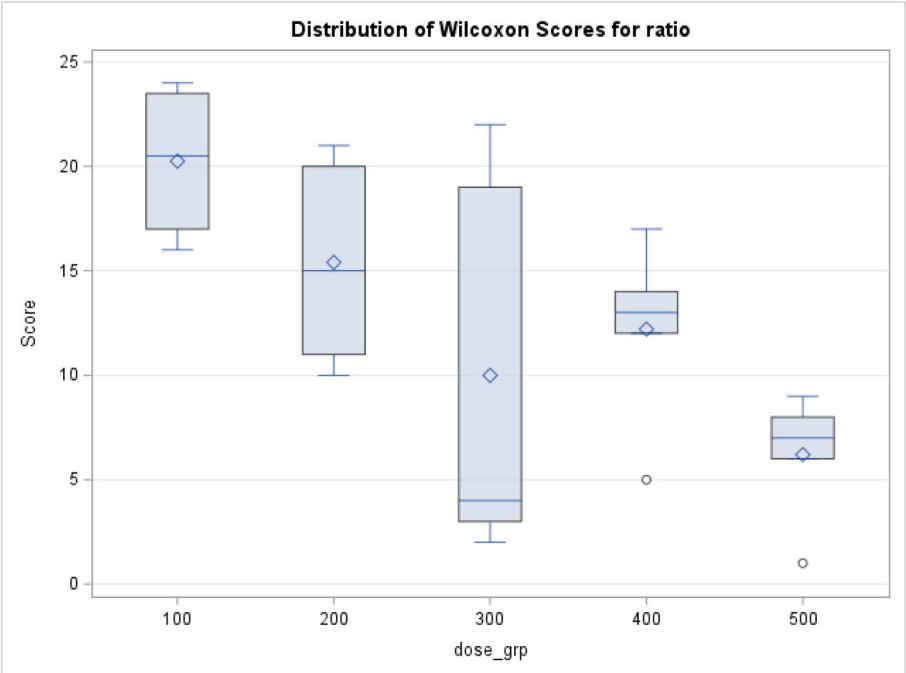


Fig. 3 A. Top2b level in PBMCs 48 h following dexrazoxane infusion

cardiotoxicity. However, the optimal dose and time course of dexrazoxane-induced Top2b degradation in humans remain unknown. This study aims to define the time course and dose–response relationship of dexrazoxane-induced Top2b degradation in humans.

In this exploratory clinical study, dexrazoxane caused a dramatic reduction in Top2b expression within one hour of infusion. This reduction persisted for up to 12 h before gradually returning to baseline. When dexrazoxane is administered concurrently with doxorubicin, the

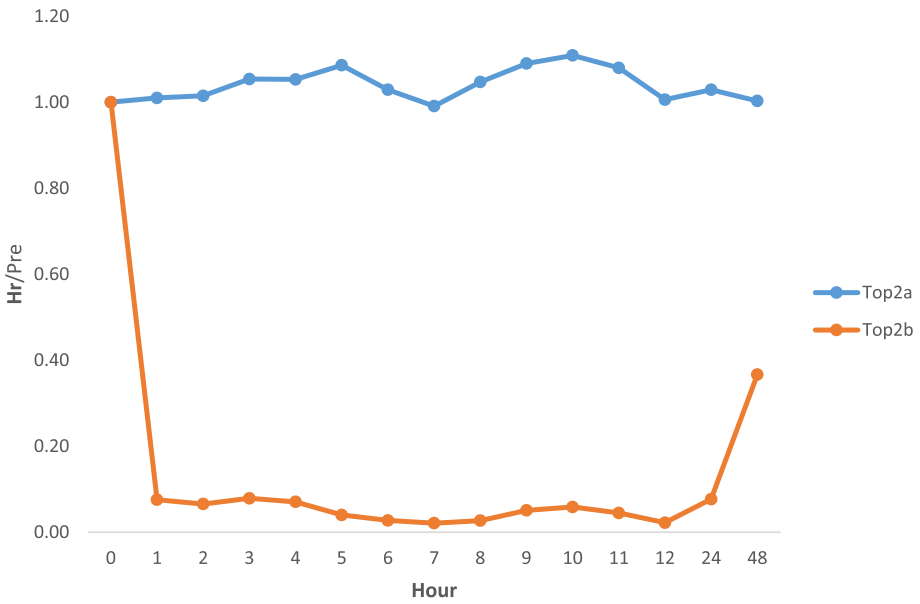


Fig. 4 Expression of Top2a (blue) and Top2b (orange) in PBMCs at various time points following 500 mg/m^2 dexrazoxane infusion. HR/Pre for each time point is the mean of five participants

FDA-recommended dose is 500 mg/m^2. However, we found that even 100 mg/m^2 significantly reduced Top2b expression, though with some variability. At higher doses, such as 400 mg/m^2 or 500 mg/m^2, Top2b reduction was more consistent and prolonged, with slower recovery compared to lower doses. In contrast, Top2a expression remained unaffected by dexrazoxane infusion, even at 500 mg/m^2. Additionally, dexrazoxane infusion in humans resulted in minimal adverse effects with doses lower than 400 mg/m^2. In the 500 mg/m^2 dose, one patient developed transient cough, and one patient developed transient knee and calf-swelling.

Clinical Implications

Dexrazoxane can inhibit or degrade Top2b to prevent doxorubicin-induced cardiotoxicity. However, because dexrazoxane also inhibits Top2a, it may compromise doxorubicin's anticancer efficacy. Consequently, many cancer patients, particularly those with breast cancer, do not benefit from dexrazoxane's cardioprotective effects at the initiation of doxorubicin therapy. Administering dexrazoxane earlier relative to doxorubicin can minimize its potential tumor-protective effect. This strategy should be tested in breast cancer patients at the inception of doxorubicin-containing regimen. Our study demonstrated that dexrazoxane rapidly and significantly reduces Top2b levels, with this effect persisting for up to 12 h. This creates a crucial clinical window to prevent Top2b-mediated cardiotoxicity while preserving Top2a-dependent tumor cell killing.

Limitation

In animal studies, Top2b expression can be directly measured in heart tissues; however, this is not feasible in human participants. Therefore, PBMCs were chosen as a surrogate tissue to assess Top2b degradation. Our study participants were adult women, so the dose–response curve and time course may not be applicable to the pediatric cancer population, where dexrazoxane is also used to prevent anthracycline-induced cardiotoxicity. Additionally, our study only evaluates the dose–response and time course of dexrazoxane's effects on Top2a and Top2b expression. Further clinical studies are needed to validate this degradation strategy by monitoring cardiac function before and after doxorubicin treatment with or without dexrazoxane protection.

Abbreviations

Top2a	Topoisomerase 2a
Top2b	Topoisomerase 2b
PBMCs	Peripheral blood mononuclear cells
Hr	Hour

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Authors'contributions

H.C. and E.Y. wrote the main manuscript. J.H. and C.A. prepared the figures. All authors reviewed the manuscript.

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Data availability
Data are available upon reasonable request and subjected to legal requirements.

Declarations

Ethics approval and consent to participate
The study protocol (IRB#262180) is approved by the Institutional Review Board of the University of Arkansas for Medical Sciences.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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