Study Title:	Prevention of Heart Failure Induced by Doxorubicin with Early Administration of Dexrazoxane (PHOENIX 1)
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Sponsor:	University of Arkansas for Medical Sciences
Study location:	University of Arkansas for Medical Sciences Winthrop P. Rockefeller Cancer Institute

Background and Rationale

Doxorubicin, an inhibitor of DNA topoisomerase 2a (Top2a), is routinely used in the treatment of breast cancer, sarcoma, and pediatric leukemia. Long-term cancer survivors who were treated with doxorubicin often suffer from dose-dependent cardiotoxicity. Of the two topoisomerase 2 isozymes, Top2a is highly expressed in cancer cells and is required for cell division. However, adult cardiomyocytes express only topoisomerase 2b(Top2b). Studies from our laboratory showed that **Top2a mediates doxorubicin's tumoricidal activity, whereas Top2b mediates doxorubicin's cardiotoxic effect**. At present, dexrazoxane is the only FDA-approved drug for cardio-protection. The cardio- protective effect of dexrazoxane is due to its ability to bind to the ATPase domain of Top2b to inhibit Top2b's catalytic cycle. Currently, dexrazoxane is administered concurrently with doxorubicin. The FDA recommended dose of Dexrazoxane is 10 times the dose of Doxorubicin. Because dexrazoxane also binds to Top2a, it has the potential to interfere with doxorubicin's tumoricidal effect. Thus, dexrazoxane has limited clinical utility as specified by FDA's approved indication. In preliminary studies, **dexrazoxane induced an ubiquitin/proteasome-mediated degradation of Top2b, but not Top2a. By administering dexrazoxane eight hours before doxorubicin, Top2b will be degraded to avoid cardiotoxicity, whereas Top2a will remain intact to preserve tumoricidal efficacy**. Because the half-life of dexrazoxane is two hours, 93.75% of dexrazoxane will be eliminated eight hours (four half-lives) after administration. Indeed, dexrazoxane pre-treatment eight hours before doxorubicin provided complete protection against doxorubicin-induced cardiotoxicity in our animal model. We propose to conduct an investigator-initiated clinical trial to test this hypothesis. We will use the results from this study to design a pilot clinical trial on breast cancer patients.

Objectives

Primary Objective: To determine the effective dose of Dexrazoxane pre-treatment in degrading topoisomerase 2 b (Top2b) in human peripheral blood.

Secondary Objectives: To determine the time course of Top2b degradation in healthy human volunteers. To determine topoisomerase 2 a (Top2a) in human peripheral blood will not be degraded by Dexrazoxane

Study Design and Procedures

This is a Phase 1 trial to determine time course and dose of dexrazoxane pre-treatment for optimal degradation of Topoisomerase 2 b (Top2b) in human volunteers. The FDA recommended dose of Dexrazoxane is 10 times the dose of Doxorubicin. All the doses in this protocol are in the FDA approved range and have been prescribed for many years.

There will be 5 cohorts for different doses: 100mg/m2, 200 mg/m2, 300 mg/m2, 400 mg/m2, or 500 mg/m2. Our plan is to enroll up to 5 subjects per cohort. We will start with 100 mg/m2 and analyze the Top2 protein level from up to five subjects. Doses will escalate to

200 mg/m2, 300 mg/m2, 400 mg/m2, and 500 mg/m2. If 100 mg/m2 dexrazoxane is insufficient, we will increase the dose to find the optimal dose.

A blood sample will be obtained at screening to rule out anemia, pregnancy and to determine liver and kidney functions. If the serum pregnancy test is not performed at the time of the initial screening blood draw and another attempt is required in order to perform this test, a urine pregnancy test can be used as a substitute. A urine pregnancy test will be done on the day of the 12-hour infusion visit, prior to infusion.

Subjects will be administered a dose of dexrazoxane by IV infusion over 15 (+/-5) minutes.

Blood will be drawn to purify peripheral blood leukocytes for Top2b and Top2a assessment using Western blot analysis. 20 mL of blood will be drawn before dexrazoxane infusion. 10 mL of blood will be drawn hourly (+/- 5 minutes) after the start of infusion for 12 hours. The final lab draw of the 12-hour infusion day may occur at 6:30 pm based on facility and staff availability. The final blood draws occur at 24 hours (+/- 2 hours); and 48 hours (+/- 2 hours) from the start of infusion. A total of 17 blood samples will be drawn for each subject.

Subjects will be screened for COVID at each visit per institutional standards. Subjects who do not pass the screening will not be permitted to continue with the study.

Vital signs will be recorded at the following time points: 1) screening, 2) pre-infusion, 3) end of infusion, 4) 6 hours post-infusion, 5) 12-hours post infusion/discharge. Vital signsto be captured include: heartrate; respirations; blood pressure; temperature; pain (rate pain on scale of 1-10). Height and Weight will also be recorded at screening.

A parking voucher will be provided for each visit. During the first 12 hours after infusion, meals and a parking voucher will be provided.

Each subject will have a safety CBC one week (+/- 2 days) after dexrazoxane infusion to rule out myelosuppression. If the one-week post-study blood counts are below normal range, subject will have additional CBC two weeks post-infusion.

Treatment failure and subject removal criteria includes: subject noncompliance with blood draw, or, subject develops rare hypersensitivity reactions to dexrazoxane infusion.

Study Population

Subjects will be healthy females, ages 18 to 65 years. Up to 50 subjects will be screened in order to enroll up to 25 subjects.

Results from this protocol will be used to support future research with breast cancer patients; therefore, only women will be enrolled in the study. The protocol was approved by NIH review panel and program officer to study only female participants.

We plan to enroll 5 subjects to each of the 5 cohorts for a total of up to 25 subjects.

Participants will be recruited using the UAMS Translational Research Institute (TRI) Research Participant Registry, ARresearch.org. After the list of potential participants is obtained from TRI, we will contact the individuals via email, if indicated as their communication preference. The email we will use when communicating with potential participants is included in the IRB submission.

Participants will also be recruited using the Facebook pages of UAMS, TRI, and the Winthrop P. Rockefeller Cancer Institute. Participants may also be recruited at Community or University events, or from within UAMS via word of mouth.

Subjects will be asked to self-report on the inclusion/exclusion criteria. However, a baseline blood sample will be obtained to rule out anemia and pregnancy and to determine liver and kidney function.

Inclusion Criteria

- Female
- Age 18-65 years

Exclusion Criteria

- Women who are pregnant or breastfeeding
- Presenting with an acute illness (may re-screen again in two weeks if illness has subsided)
- Anemia (Hb < 12 g/dL for females)
- Calculated Creatinine Clearance less than 60 mL/min
- Liver function tests outside of normal range
- Unwilling to refrain from alcohol consumption for 48 hours

Participants with medical information suggestive of a chronic medical condition may be excluded from the research at the enrolling physician's discretion.

Repeat screening blood tests may be done at the discretion of the enrolling physician and/or principal investigator. All screening tests will be paid for by the research grant.

Risks and Benefits

Some subjects may experience discomforts, or pain on intravenous injection of dexrazoxane. We will minimize this risk by administering dexrazoxane as an IV infusion

over 15 (+/-5) minutes. If a participant reports pain during the infusion, the catheter will be checked to ensure it is properly inserted. If no problems are noted with the catheter, the rate of the infusion will be slowed. There is a very low probability that a subject may develop subcutaneous and cutaneous necrosis. Subjects will be informed and instructed to report to study team if she develops this side effect. PI and study team members will arrange for medical care and expect full recovery on this.

To reduce the risk of bruising and pain from multiple injections, the twelve hourly blood draws will be drawn from the IV catheter. If the initial IV line stops working for any reason, a new line will have to be placed.

There is a very low probability that a subject may develop myelosuppression. Each subject will have screening CBC one week after dexrazoxane infusion to rule out myelosuppression. The study team will arrange for medical care and expect recovery if a subject develops myelosuppression. If the one-week post-study blood counts are not within normal range, subject will have additional CBC at 2 weeks post-infusion.

The risk of allergic reaction is very low. In a rare situation, if the participant develops allergic reaction to dexrazoxane, the infusion will be stopped.

Other adverse events may include:

- Bluish color
- changes in skin color
- chest pain or tightness in the chest
- chills
- cold hands and feet
- cough, sneezing, sore throat
- difficult or labored breathing
- fever
- hoarseness
- lower back or side pain
- pain, redness, or swelling in the arm or leg
- painful or difficult urination
- swelling of the hands, ankles, feet, or lower legs
- tenderness
- unusual bleeding or bruising
- unusual tiredness or weakness)

All unanticipated problems or deviations should be reported immediately to principal investigator/sponsor. The immediate reports should be followed promptly by details written reports to investigator/sponsor. All reports will identify subjects by unique code numbers assigned rather than other identifiers. Unanticipated problems will be reported to IRB within 5 days of becoming aware of an event.

A risk to study participants is the potential for loss of confidentiality of study data.

Measures to protect the confidentiality of study data will be implemented as described in the Data and Safety Monitoring Plan section below.

There will be no direct benefits to the study participants; however, knowledge gained from the study could potentially benefit patients in the future.

Subject Compensation

Subjects completing all study visits will receive $400 compensation for their time. Subjects will be issued a Greenphire, Inc. ClinCard, which is a debit card that the stipends are loaded onto and can be used at their discretion. When a visit is completed, funds will be approved and loaded onto the card. Once approved to be released to the cards, the funds will be available for use.

Subjects who partially complete the study will receive prorated compensation as described below.

Screening - $50
Infusion – $80
12-hr blood draws – $10 per blood draw (maximum of $120)
24-hr blood draw – $50
48-hr blood draw – $50
1-week post infusion lab draw - $50

A parking voucher will be provided for each visit. Meals vouchers will also be provided to the subjects during the 12 hour infusion visit at visit 2.

DATA AND SAFETY MONITORING PLAN
Overall framework for safety monitoring and what information will be monitored.

Plan for data management: A password-protected database will be used to manage all study data. To ensure confidentiality only subject ID numbers will be entered into the database.

Paper records will be stored in the the PHOENIX 1 Clinical Trial office. The records are stored in a double locked file cabinet, in the locked office. Only study staff will have access. Consent and HIPAA will have direct identifiers. Other paper source documents will be coded and the key to the code will be stored separately. Data from the de-identified source documents will also be stored on a password locked Microsoft Excel Spreadsheet located in a secure Box folder. Only study staff will have access to this document. Records may be retained indefinitely, and at minimum, will be retained in accordance with institutional policy and applicable regulatory requirements. A UAMS approved vendor will be used to destroy documents. The key to the code will be destroyed at this time and thereby creating a de-identifiable data with the exception of the consent.

Participants will not be individually identified in any publication. Participants' right to privacy will be protected.

Plan for safety monitoring*:* The data and safety monitoring plan (DSMP) for this trial focuses on close monitoring by the PIs and the safety officer. QA monitoring will also be performed by independent Winthrop P. Rockefeller Cancer Institute staff.

Frequency of monitoring: Monitoring will include enrollment, attrition, efficacy end-points, and adverse events. In addition to monitoring by the PIs, study coordinator, and safety officer monitoring, the University of Arkansas for Medical Sciences IRB monitors all aspects of the project on an annual basis. The frequency of the structured data review for this study can be summarized below.

Data type Frequency of review
Subject accrual (adherence to protocol regarding demographics, inclusion/exclusion): At the end of each recruitment
Adverse event rates (injuries): semi-annually
Compliance to treatment: semi-annually
Out of range laboratory data: semi-annually
Stopping rules report regarding statistical power implications of dropouts and missing data: semi- annually
IRB review: annually

Process for Managing and Reporting Adverse Events, Serious Adverse Events and Unanticipated Problems:
Unanticipated events will be reported to UAMS IRB, and both serious and non-serious adverse events will be reported to the Safety Officer. Adverse events will be categorized and classified according to Common Terminology Criteria for Adverse Events Scale (CTCAE v5.0). Safety reports will be sent to the safety officer. Serious adverse events will be reported to the NIH Office of Biotechnology Activities, the funding IC, and the FDA, in addition to UAMS IRB. The PI will be responsible for assembling the data and producing these reports, as well as assuring that all parties obtain copies of these reports.

Qualifications and responsibilities of the Safety Officer:
The safety officer for this trial will be **Jawahar (Jay) Mehta, MD., PhD**. **Dr. Mehta is a Distinguished Professor of Medicine, and Physiology and Biophysics, and the Stebbins Chair in Cardiology at UAMS.** Dr. Mehta serves or has served on the editorial board of numerous journals including the American Journal of Cardiology; Circulation; Hypertension; Journal of the American College of Cardiology. Dr. Mehta has been funded numerous times by the Department of Veterans Affairs, the American Heart Association, and the National Institutes of Health. In 2017, he was ranked among the top 27 cardiologists in the nation. As Safety Officer, Dr. Mehta will review eligibility criteria with Dr. Chang. He will review all reports sent by the study coordinator to determine whether there is any corrective action, trigger of an ad hoc review, or stopping rule violation that should be communicated to the UAMS IRB. In addition, the safety officer

may comment on whether the study PI needs to report any specific out- of-range laboratory data.

Specimen Handling and Storage

Specimens will be collected in the Winthrop P. Rockefeller Cancer Institute. Study staff will obtain the blood samples at the prescribed time intervals. Staff will label the tubes with only the unique code and take them directly to the lab. Identifiers will not be included on the tubes. CTO staff will call Dr. Jinn-Yuan Hsu or the assigned study staff to pick up the specimens. The specimens will be retrieved immediately and taken to the laboratory of the principal investigator to be processed and analyzed. Only the PI and study team will have access to the samples. After all the samples have been tested, the samples will be discarded.

Data Analysis

The goal of this protocol is to find the effective dose of dexrazoxane in degrading Top2b for the subsequent randomized clinical trial. We will select a dose of dexrazoxane, which reduces Top2b to less than 5% of baseline level in 8 hours in 5 volunteers. FDA recommended dose of dexrazoxane is 10 times the dose of doxorubicin. In the attached FDA approval documentation of dexrazoxane, 500mg/m2 is cited as a recommended dose. We will study dose levels 500mg/m2 or below. Healthy volunteers will be administered a dose of dexrazoxane. Blood will be drawn to purify peripheral blood leukocytes for Top2b and Top2a assessment using Western blot analysis. The following time points will be assessed: Pre-infusion,1,2,3,4,5,6,7,8,9,10,11,12,24, and 48 hours after start of dexrazoxane infusion. Each dose level will be administered to up to five subjects, starting with an initial dose of 100 mg/m2, and escalating in 100 mg increments.

Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient

information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participant's privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject and the person obtaining the consent. A copy of the signed consent will be given to the participant, and the informed consent process will be documented in the research record.

Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant. The study will be listed on clinicaltrials.gov in accordance with (journal or FDA) requirements.

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