ROSEMAN UNIVERSITY OF HEALTH SCIENCES

COLLEGE OF PHARMACY

ANALYZING THE CARDIOTOXIC EFFECTS OF CONVENTIONAL AND LIPOSOMAL DOXORUBICIN IN BREAST CANCER PATIENTS

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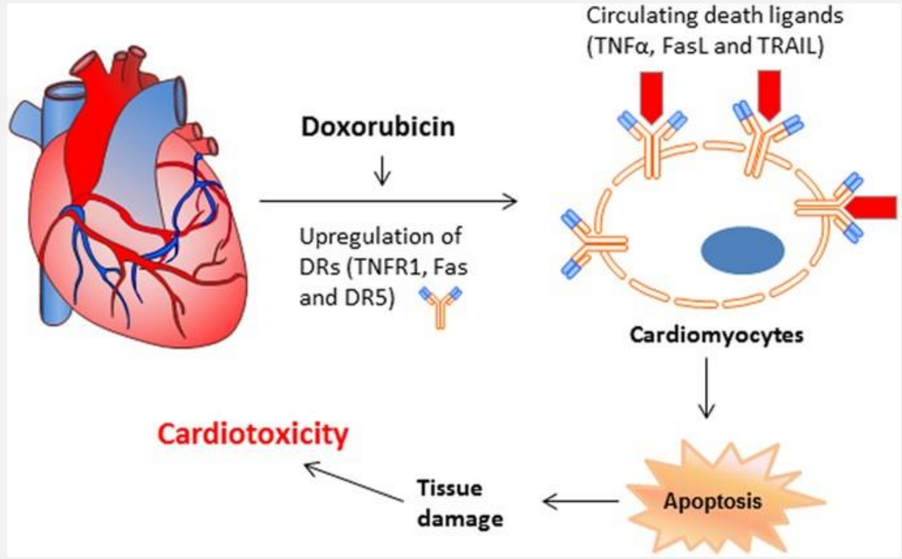
CARDIOTOXICITY

What is it?

- Cardiotoxicity is a long-term adverse effect that comes from chemotherapy agents, which damages the heart muscles
- A broad spectrum of cardiovascular complications include hypertension, heart failure, left ventricular dysfunction, reduced left ejection fraction, and QT prolongation

Why is it important?

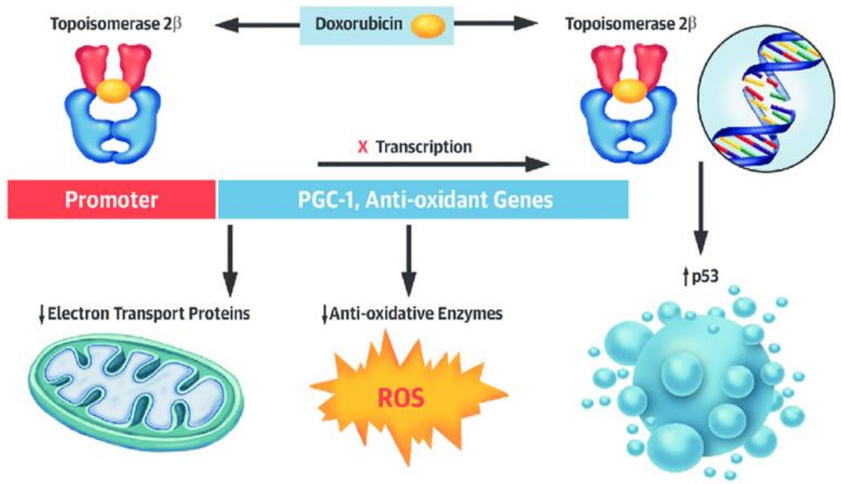
- Cardiotoxicity complications can alter and delay the treatment plan for cancer patients
- By having treatment plans delayed, there will be a potential increase in morbidity and mortality
- Chemotherapeutic agents, such as anthracyclines are common in proliferating cancer cells in the myocardium



Source from scientific reports: L. Zhao, B. Zhang

DOXORUBICIN

- Doxorubicin is an antineoplastic agent in the anthracycline class with an activity against numerous of cancers
- The mechanism of action of doxorubicin is inhibits topoisomerase II and intercalates between base pairs in DNA/RNA to prevent cellular replication
- The major adverse of effect is cardiotoxicity due to mechanisms involving generating large free oxygen radicals that damages DNA
- A cumulative total lifetime dose of doxorubicin of 450-500 mg/mg^2 puts a patient at higher risk for cardiotoxicity



Source from Journal of the American College of Cardiology: Chang, et al.

FORMULATIONS OF DOXORUBICIN AND BREAST CANCER

Conventional Doxorubicin

Vs.

Liposomal Doxorubicin "Safer?"

Pegylated Liposomal (Doxil)

Non-Pegylated Liposomal (Myocet)

Question: Does this apply to patients with breast cancer?

METHODOLOGY

Objective

To determine the risk of cardiotoxicity of different formulations of doxorubicin in breast cancer

Strategy

Assessing papers searches on drugs regimens involving doxorubicin on breast cancer

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Explore cardiotoxicity content of doxorubicin with different formulations in clinical trials

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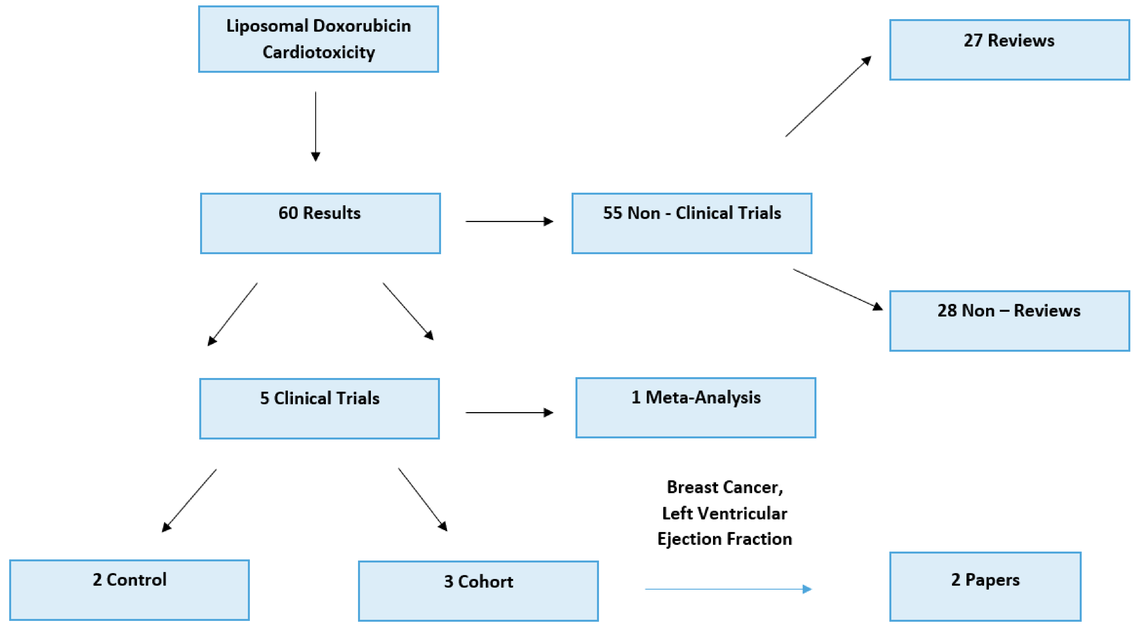
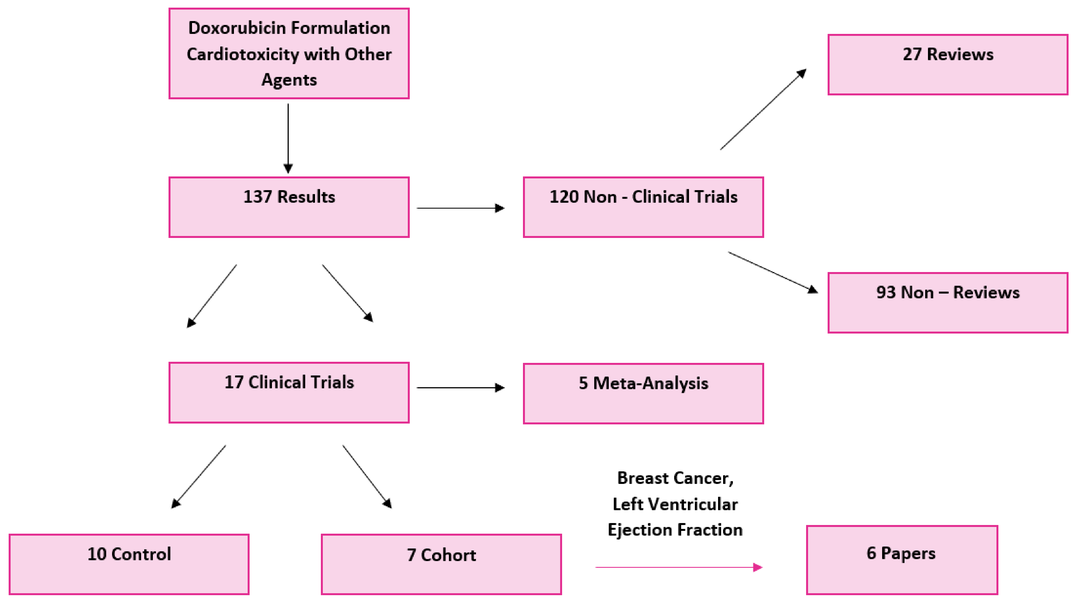
Identify the likelihood of cardiotoxicity

SEARCH RESULTS





KEY PAPERS AND DETAILS

Authors	Combine with	Dosing Schedule	Sample Size	Cardiotoxicity Assessment	CONSORT (Out of 30)	Newcastle Ottawa (Out of 8)
Conventional Doxorubicin and Liposomal Doxorubicin						
Batist et. al, 2001	Cyclophosphamide	Myocet 60 mg/m^2 or Doxorubicin 60 mg/m2 as a 1-hour IV infusion Cyclophosphamide 600 mg/m^2 IV infusion over 15 mins	297	MUGA scan	24	8
Harris et. al, 2001	N/A	Myocet 75 mg/m^2 or Doxorubicin 75 mg/m2 as a 1-hour IV infusion	224	MUGA scan	29	8
Liposomal Doxorubicin and Other Agents						
Rayson et. al, 2001	Cyclophosphamide & Trastuzumab	Liposomal Doxorubicin 60 mg/m^2 or Doxorubicin 60 mg/m^2 every 21 days for four cycles Cyclophosphamide 600 mg/m^2 every 21 days Trastuzumab 2 mg/kg weekly for 12 weeks	181	ECHO, MUGA scan	27	8
Schmid et. al, 2009	Docetaxel	Liposomal Doxorubicin 60 mg/m^2 as a 1-hour IV infusion in 3-weeks cycle Docetaxel 75 mg/m^2 as an 1-hour IV infusion in 3 weeks cycle	51	ECHO	23	8
Gil-Gil et. al, 2015	Cyclophosphamide & Paclitaxel	Liposomal Doxorubicin 35 mg/m^2 on day 1 every 4 weeks Cyclophosphamide 600 mg/m^2 on day 1 every 4 weeks Paclitaxel 80 mg/m2 weekly for 12 weeks	50	ECHO	23	7
Curtit et. al, 2011	Docetaxel	Liposomal Doxorubicin 60 mg/m^2 as a 90 min IV infusion on day 1 of a 21-day cycle Docetaxel 75 mg/m^2 as a 1-hour IV infusion on day 1 of a 21-day cycle	34	ECHO	17	8
Cheng et. al, 2019	Cyclophosphamide & Docetaxel	Liposomal Doxorubicin 35, 40, 45, or 50 mg/m^2 on day 1 of a 21-day cycle Cyclophosphamide 600 mg/m^2 on day 1 of a 21-day cycle Docetaxel 75 mg/m^2 on day 1 of a 21-day cycle	19	ECHO	23	7
Stickeler et. al, 2009	Trastuzumab	Liposomal Doxorubicin 40 mg/m^2 IV bolus on day 1 every 4 weeks up to 9 cycles Trastuzumab 4 mg/kg on day 2, followed by weekly 2 mg/kg	16	ECHO	24	7

ASSESSMENT ON THE EXTENT OF CARDIOTOXICITY

Authors	Numbers of Cardiotoxicity	Grade of Cardiotoxicity
Conventional Doxorubicin and Liposomal Doxorubicin		
Batist et. al, 2001	42 patients out of 297 patients	NCI Common Toxicity Criteria Grade 3 and 4, CHF (5 patients)
Harris et. al, 2001	11 patients out of 224 patients	NCI Common Toxicity Criteria Grade 3 and 4, CHF (9 patients)
Liposomal Doxorubicin and Others		
Rayson et. al, 2001	16 patients out of 181 patients	NCI Common Toxicity Criteria Grade 1 and 2, LVEF
Schmid et. al, 2009	11 patients out of 51 patients	NCI Common Toxicity Criteria Grade 3 LVEF (6 patients) LV Diastolic dysfunction (5 patients)
Gil-Gil et. al, 2015	5 patients out of 50 patients	NCI Common Toxicity Criteria Grade 1, LVEF (5 patients)
Curtit et. al, 2019	5 patients out of 34 patients	NCI Common Toxicity Criteria Grade 3, CHF
Cheng et. al, 2019	1 patient out of 19 patients	NCI Common Toxicity Criteria Grade 1, SVT premature contraction
Stickeler et. al, 2009	3 patients out of 16 patients	NCI Common Toxicity Criteria Grade 3, LV dysfunction

% CARDIOTOXICITY AND RELATIVE RISK

Authors	Drug Regimen	Cardiotoxicity	% Cardiotoxicity	Relative Risk
Conventional Doxorubicin and Liposomal Doxorubicin				
Batist et. al, 2001	Liposomal Doxorubicin + Cyclophosphamide	9	6%	**35%**
	Conventional Doxorubicin + Cyclophosphamide	33	21%	
Harris et. al, 2001	Liposomal Doxorubicin	2	2%	**29%**
	Conventional Doxorubicin	9	8%	
	Conventional Only	42/271	15%	**31%**
	Liposomal Only	11/250	4%	
	Total Effects	53/521	10%	
Liposomal Doxorubicin and Other Agents				
Rayson et. al, 2001	Liposomal Doxorubicin + Cyclophosphamide + Trastuzumab	5	4%	**25%**
	Conventional Doxorubicin + Cyclophosphamide + Trastuzumab	11	19%	
Schmid et. al, 2009	Liposomal Doxorubicin + Docetaxel	11	21%	N/A
Gil-Gil et. al, 2015	Liposomal Doxorubicin + Cyclophosphamide + Paclitaxel	5	8%	N/A
Curtit et. al, 2019	Liposomal Doxorubicin + Docetaxel	5	14%	N/A
Cheng et. al, 2019	Liposomal Doxorubicin + Cyclophosphamide + Docetaxel	1	5%	N/A
Strickeler et. al, 2009	Liposomal Doxorubicin + Trastuzumab	3	19%	N/A
	Conventional Only	11/59	19%	**52%**
	Liposomal Only	30/290	10%	
	Liposomal + Trastuzumab	8/136	6%	
	Liposomal + Docetaxel	17/104	16%	
	Liposomal + Paclitaxel	5/50	10%	
	Total Effects	41/351	12%	

N/A = Not calculable due to inappropriate control match

CONCLUSIONS

Conclusions

- Risk of cardiotoxicity of liposomal formulation is still lower when compared to the conventional formulation outside of the original trials
- Papers found lacked appropriate controls which may limit the overall interpretation of results

Future Directions

- Assess the risk of cardiotoxicity of conventional doxorubicin combined with other agents in comparison to that of liposomal doxorubicin for the treatment of other types of cancers
- Analyze the risk of other toxicities related to different formulations of doxorubicin

THANK YOU!