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Comparison of cardiac events associated with liposomal doxorubicin, epirubicin and doxorubicin in breast cancer: a Bayesian network meta-analysis

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Abstract ***Background:*** Anthracyclines play a broad and important role in the care of patients with either operable or metastatic breast cancer. However cardiotoxicity narrows the therapeutic index of this drug class leading to potentially clinically meaningful treatment delays or discontinuations. We conducted a Bayesian network meta-analysis, a validated statistical methodology, allowing direct and indirect comparison of cardiotoxicity of different anthracycline and non-anthracycline regimens.

Methods: We conducted a systematic review of prospective randomised controlled trials through MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Google Scholar comparing non-anthracycline based regimens (NON), doxorubicin (DOX), epirubicin (EPI) and liposomal doxorubicin (LD). We included studies published up to 1st January 2014 in both adjuvant and metastatic contexts. Notably, HER2/neu-targeted regimens were excluded. We assessed the studies' eligibility criteria and data collection with consensus of two independent authors. Our primary outcome measure was cardiac events grade 3 or greater (CE3) in accordance with Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. A Bayesian pairwise and network meta-analysis was conducted to estimate pooled Odds Ratio (OR).

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Findings: Nineteen randomised controlled trials met eligibility criteria and were included in this analysis. We found a trend showing that LD is less cardiotoxic than DOX with an OR of 0.60 (95% confidence interval (CI) 0.34–1.07) There was no difference between Epi and LD with an OR of 0.95 (95%CI 0.39–2.33). DOX is more cardiotoxic than Non with an OR of 1.57 (95%CI 0.90–2.72).
Interpretation: DOX has higher CE3 rates than NON does. LD statistically trended to lower cardiac event rates than DOX. Non-statistical significance among EPI, LD and DOX with regard to cardiac toxicity indicates that avoidance of CE3 should not motivate selection of a particular anthracycline in otherwise healthy women in whom total lifetime anthracycline exposure will likely be limited. Overall low incidence of CE3 with any type of anthracycline indicates that we can safely use any anthracycline if cumulative dose limits are not exceeded. While CE3 does not limit our choice of anthracycline LD appears to be the least cardiotoxic.
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1. Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide and anthracyclines are key therapeutic agents associated with improved survival [1,2]. Despite being a significant part of standard treatments in adjuvant, neoadjuvant and metastatic contexts anthracycline associated cardiac toxicity is a significant concern and may offset anti-neoplastic benefit [3]. Compared with non-anthracycline regimens, anthracyclines have been shown to cause five times more compromised left ventricle ejection fraction (LVEF) and chronic heart failure. The risk of cardiotoxicity correlates with lifetime cumulative anthracycline exposure [4,5]. Cumulative ceiling doses were defined since CE3 rates dramatically increase when doxorubicin is given at 400–450 mg/m^2 and higher and epirubicin at 900–1000 mg/m^2 and higher [6,7]. Molecular pathogenesis of anthracycline-induced cardiotoxicity is yet unclear, though, the most promising hypothesis is the interaction with topoisomerase II (Top2) [8]. Top2 has two isozymes which are Top2alpha and Top2beta [9]. Among the isozymes, anthracycline and Top2alpha complex lead to cell death. Mammalian cardiomyocyte only has Top2beta and successful prevention of cardiac toxicity with cardiomyocyte specific deletion of Top2beta in a mice study identified Top2beta/anthracycline complex role in the development of cardiotoxicity [10]. The search for anthracycline analogues with less cardiotoxicity led to the development of agents such as epirubicin and liposomal doxorubicin [11]. A comparative study has shown that epirubicin appears to be equally effective and less cardiotoxic compared to doxorubicin for metastatic breast cancer [12]. Liposomal doxorubicin, developed by encapsulating nanotechnology which allows targeting tumour cells without excess exposure of normal cells, has also been shown to have comparable efficacy with significantly reduced cardiac toxicity [13,14].

There are numerous trials comparing the cardiac toxicity of chemotherapeutic agents, however, there is no level 1 evidence showing their relative cardiac toxicity with quantitative analysis. Network meta-analysis (NMA) is a useful methodology that offers direct and indirect comparisons in order to estimate the relative efficacy between all interventions even though some have not been compared head to head [15–17]. To investigate the cardiac toxicity among anthracyclines, we conducted a Bayesian NMA.

2. Methods

2.1. Study search and selection criteria

We conducted a systematic review of prospective randomised controlled trials through MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Google Scholar comparing non-anthracycline based regimens, doxorubicin, epirubicin and liposomal doxorubicin according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [18]. We included randomised controlled trials evaluating either regimens in the metastatic or adjuvant setting published up to 1st January 2014. Trials of HER2/neu-inhibitor containing regimens were excluded as were studies comparing various doses of the same cytotoxic agents and trials which didn't provide cardiac adverse event data.

2.2. Study selection and data collection

Two independent investigators (NY and TF) selected the articles and extracted information. Collected data presented in Table 1 included the total number of patients in each trial, the number of CEs, treatment setting (metastatic or adjuvant), the name of regimens, median patient age, history of prior anthracycline treatment, cumulative dose of anthracycline and observation

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