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RESEARCH

Effectiveness and Complications of Anthracycline and Taxane in the Therapy of Breast Cancer: A Meta-analysis

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Abstract
Objective To compare the efficacy and safety between anthracycline & taxane and anthracycline in the treatment of breast cancer.
Methods Computer-assisted literature search was performed with PubMed, MEDLINE, EMBASE and Cochrane Controlled Trials Register (CCTR) to identify pertinent literatures. Software RevMan 5.0 was used for statistical analysis. The measurement of interest outcomes included severe neurotoxicity, death without breast cancer recurrences, leukemia, venous thrombus and severe cardiotoxicity.
Results A total of 10 randomized controlled trial studies (RCTs) containing 18,198 cases were selected in this meta-analysis. Of which, 9,902 cases were treated with anthracycline & taxane and 8,296 cases treated with anthracycline alone as control. Anthracycline & taxane showed lower risks of incident leukemia (RR=0.40; 95 % CI: 0.18, 0.90), venous thrombus (RR=0.49; 95 % CI: 0.29, 0.84) and severe cardiotoxicity (RR=0.41, 95%CI: 0.26, 0.66), but higher risks of incident severe neurotoxicity (RR=5.97; 95 % CI: 1.72, 20.65) and non-recurrent death (RR=1.79; 95 % CI: 1.06, 3.04), compared to anthracycline alone.
Conclusion Clinically important differences exist for general safety in favour of the anthracycline & taxane rather than anthracycline alone. However, as a result of tumor recurrent rate, anthracycline might be superior to anthracycline & taxane. A longer duration of follow-up and a larger number of cases are required to better assess the efficacy and safety profile of the treatment of breast cancer.

Keywords Meta-analysis · Breast cancer · Anthracycline · Taxane

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Introduction

Breast cancer is the one of the most common leading death cancer in women, accounting for more than 40,000 deaths each year worldwide [1, 2]. Adjuvant chemotherapy can diminish the risk of recurrence of radically resected early breast cancer (EBC), especially when using the anthracycline-based combinations that are generally more effective than earlier combinations like cyclophosphamide-methotrexate-fluorouracil and have become the standard adjuvant chemotherapy for most patients with breast cancer [3].

Anthracycline, as the most commonly chemotherapy drug used for breast cancer, plays an extremely important role in preoperative adjuvant therapy, rescue treatment after recurrence and metastasis as well as postoperative adjuvant therapy [4, 5]. Two action mechanisms of anthracycline have been discovered. On the one hand, it induces the mutation of the TOP2A gene and leads to high expression of Topo II α, which consequently provides more targets for anthracycline. Thus, the anthracycline can effectively inhibit tumor cells with TOP2A expansion [6, 7]. On the other hand, the amplification of HER2 gene also results in genetic abnormalities including TOP2A gene. However, the anthracycline usually brings some side effects, such as cardiac toxicity and leukemia [8].

Taxane has broad-spectrum antitumor effect and was used for the primary and metastatic breast cancer as well as ovarian cancer [9]. Taxane stimulates the aggregation of tubulin and

promotes the assembly of microtubule dimer into microtubules, resulting in super-stable microtubules and inhibition of the dynamic reorganization of the microtubule network, and ultimately traps cell proliferation at mitosis (G2/M) stage [10]. Taxane therapy usually can reduce acute hypersensitivity syndrome, neurotoxicity, muscle pain and joint pain [11].

Combination therapy of anthracycline and taxane is superior to any previous chemotherapy in treatment of early breast cancer, and thus it has become a standard adjuvant therapy [12–14]. However, most of these studies are either retrospective case series or single-center clinical trials. To date, there have been no large, prospective, randomized multi-center clinical trials performed that compare the relative safety and efficacy of anthracycline & taxane versus anthracycline alone in the treatment of breast cancer. Therefore, we adopted Cochrane systematic method to quantitatively evaluate published clinical trials to provide a reference for the clinical application of anthracycline and anthracycline & taxane.

Methods

Literature Search

Database search was performed using PubMed, MEDLINE, EMBASE and CCTR until December 2011 to identify literatures about anthracycline & taxane and anthracycline alone in treatment of breast cancer. Additional information from the internet search engine Google scholar was also incorporated. The following search terms were used as key terms or keywords: “randomized controlled trial” OR “clinical trial” AND “anthracycline” AND “taxane” AND “breast cancer”.

Literature Screening

Inclusion Criteria

To be included in the meta-analysis, retrieved studies had to fulfill the following inclusion criteria: (1) early breast cancer; (2) randomized trial comparing anthracycline-taxane with anthracycline alone; (3) clearly defined sample size and publish date; (4) comparative results on mortality, leukemia and cardiovascular toxicity; (8) scientific data collection method; (9) correct data analysis methods.

Exclusion Criteria

The exclusion criteria in the meta-analysis included: (1) not providing the source of cases and controls, non-therapeutic clinical research, animal experiments and non-original documents, no clear number of case for each group; (2) the diagnostic criteria is not clear; (3) data collection method is not scientific; (4) other treatment means were applied for breast cancer; (5) data analysis method is incorrect or not provided; (6) review literatures; (7) repeated literatures; (8) retrospective analysis.

Literature Evaluation & Data Extraction

Literature evaluation and data extraction were carried out by two researcher separately from the following aspects: (1) general information: first author, source and publication date; (2) research design; (3) number of cases, characteristics and treatment outcomes; (4) result of study.

Statistical Analysis

Software RevMan 5.0 was used for meta-analysis. Standardized mean difference (SMD) and relative risk (RR) were calculated along with 95 % confidence interval (CI) to evaluate continuous data and binary data, respectively. A random-effects model was adopted if there is heterogeneity between studies. Otherwise, a fixed effects model was applied instead. Significance level was set as $P<0.05$.

Results

Basic Information

After preliminary screening of the retrieved literatures, a total of 36 papers that comparing the adjvant therapy of anthracycline-taxane with anthracycline alone in the treatment of early breast cancer were identified. After screening, 10 papers met the inclusion criteria [15–24].

Author, publication year, journals, the number of test group, the number of control group and the Jadad score were listed in Table 1. All of the 10 researches were clinical randomized case-controlled study including 9,902 cases in anthracycline and taxane group and 8,296 in anthracycline group. The publication year is from 2006 to 2010.

Comparison Results between Anthracycline & Taxane Group and Taxane Group

Severe Neurotoxicity

Nine studies [15–23] that reported information about severe neurotoxicity were included in this analysis. There were 8,571 cases in anthracycline & taxane group and 6,495 cases in taxane group. The RR was calculated as 5.97 with 95 % CI (1.72, 20.65) and it was significant ($P=0.005$) (see Figure Legends Fig. 1). A random effects model was adopted since there was heterogeneity between studies ($P<0.00001$). Risks of incident severe neurotoxicity favour the use of anthracycline alone rather than anthracycline & taxane.

Table 1 Basic information and research quality for the 10 included studies

Publication	Journal	Number of test group	Number of control group	Jadad score
Boccardo 2010 [15]	Oncology	122	122	3
Burnell 2010 [16]	J Clin Oncol	1362	680	1
Ellis 2009 [17]	Lancet	2073	2089	3
Francis 2008 [18]	J Natl Cancer Inst	1919	968	2
Gianni 2009 [19]	J Clin Oncol	432	444	3
Goldstein 2008 [20]	J Clin Oncol	1469	1469	3
Martin 2008 [21]	J Natl Cancer Inst	614	632	3
Martin 2010 [22]	N Engl J Med	532	519	3
Polyzos 2010 [23]	Breast Cancer Res Treat	378	378	3
Roche 2006 [24]	J Clin Oncol	1001	995	3

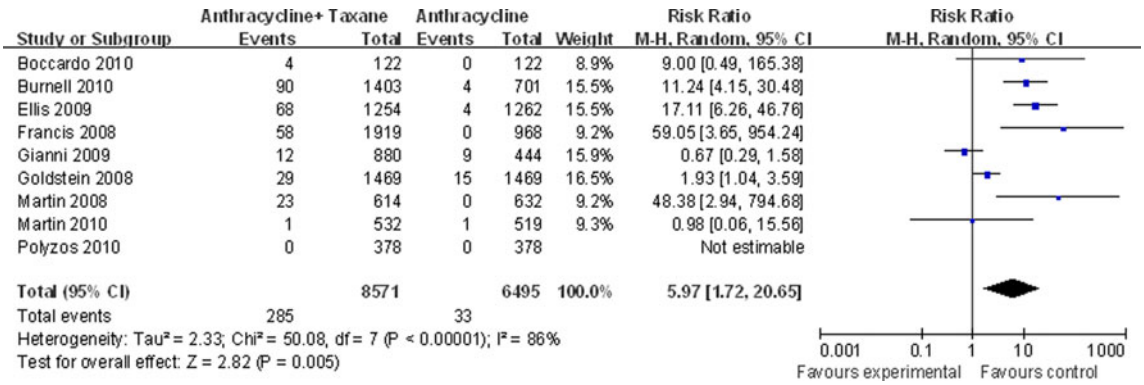

Fig. 1 Comparison Results of severe neurotoxicity between anthracycline & taxane group and taxane group

Non-recurrent Death

The assessment of non-recurrent death was available in six studies [17–19, 21, 23, 24], including 6,417 cases in anthracycline & taxane group and 5,506 cases in taxane group. A fixed effects model was adopted since there was no heterogeneity between studies (P=0.64). The RR was calculated as 1.79 with 95 % CI (1.06, 3.04) with a statistical significant (P=0.03), which indicates that anthracycline alone may be superior to anthracycline & taxane in the effect size of non-recurrent death (see Fig. 2).

Leukemia

Six studies [16–19, 23, 24] were included in this meta-analysis containing 7,165 cases in anthracycline & taxane

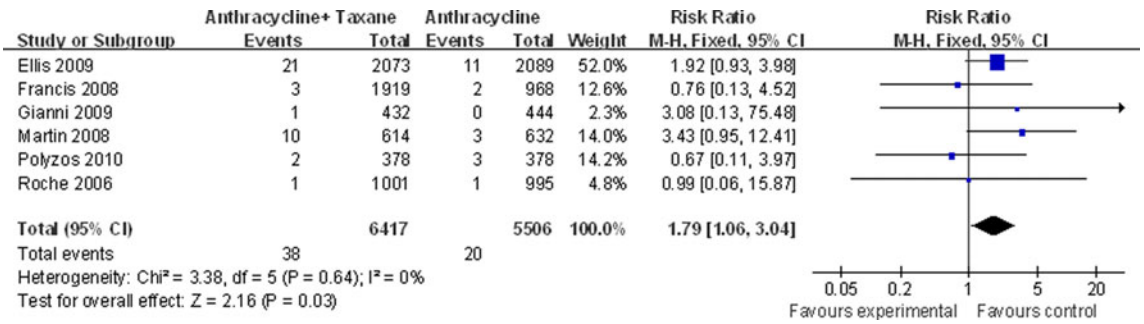

Fig. 2 Comparison Results of Mortality rate (non-recurrent) between anthracycline & taxane group and taxane group

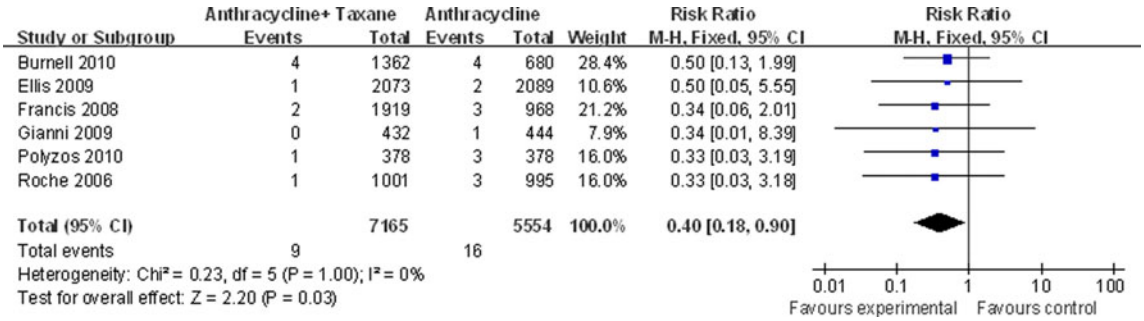

Fig. 3 Comparison results of leukemia between anthracycline & taxane group and taxane group

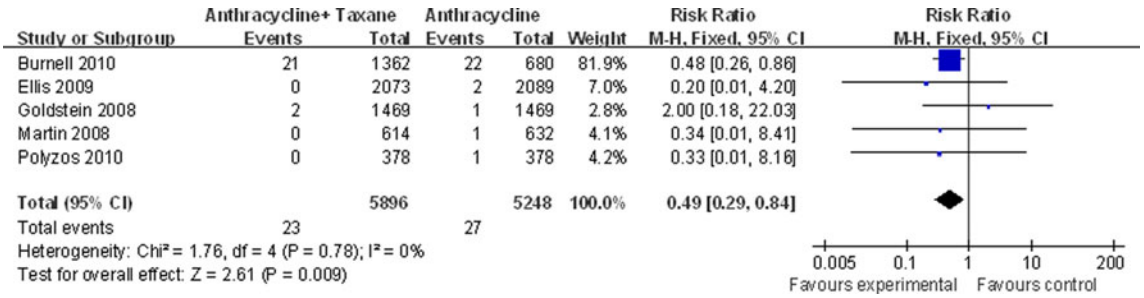

Fig. 4 Comparison results of venous thrombus between anthracycline & taxane group and taxane group

group and 5,554 cases in taxane group. Tere was no evidence of heterogeneity among trials, thus, a fixed effects model was adopted (P=1.00). The estimated pooled RR for all the studies shows a highly significant between anthracycline & taxane and anthracycline group (RR=0.40, 95 % CI [0.18, 0.90], P=0.03), demonstrating that anthracycline & taxane may has a lower risk of incident leukemia compared to anthracycline alone (see Fig. 3).

Venous Thrombus

Data from five studies [16, 17, 20, 21, 23] was available for assessment of venous thrombus. There were 5,896 cases treated with anthracycline & taxane group, while 5,248 patients were treated with anthracycline alone. A fixed effects model was adopted since there was no heterogeneity between studies (P=0.78). The findings showed significant RR favouring anthracycline & taxane group (RR=0.49, 95 % CI [0.29, 0.84], P=0.009) (see Fig. 4)

Severe Cardiotoxicity

Eight studies [15–19, 21, 23, 24] were included in this meta-analysis for the evaluation of incident rate of severe cardiotoxicity, which contained 901 cases in anthracycline & taxane group and 6,308 cases in anthracycline group. A fixed effects model was

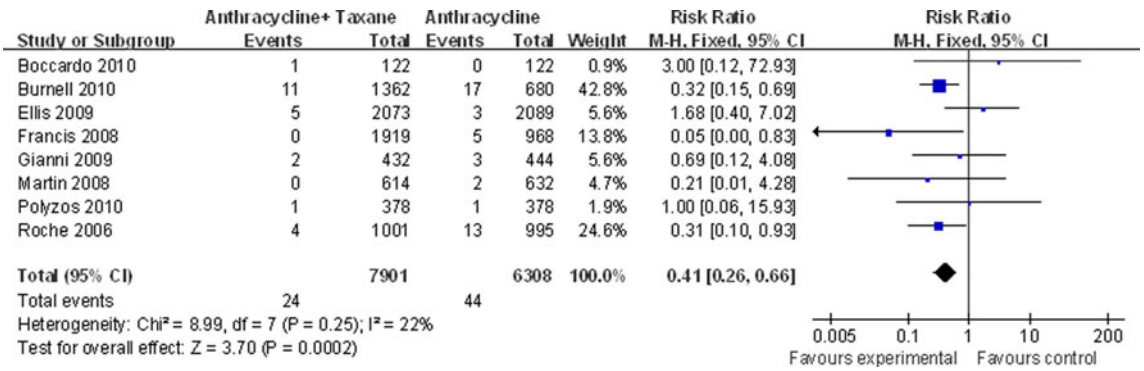

Fig. 5 Comparison results of severe cardiotoxicity between anthracycline & taxane group and taxane group

adopted since there was no heterogeneity between studies (P=0.25). There was a significantly difference in the incidence of severe cardiotoxicity between two interventions (RR=0.41, 95 % CI [0.26, 0.66], P=0.0002) (see Fig. 5), manifesting that anthracycline & taxane may be superior to anthracycline alone in the event of severe cardiotoxicity.

Discussions

Anthracycline and taxanes are now being applied more commonly in the adjuvant setting, the safety of these agents has become an increasingly important issue. Moreover, anthracyclin-based or taxane-based combinations has been also became optimal choice of therapy for early breast cancer [25]. In this study, we identified 10 studies that assessed the addition of a taxane to an anthracycline-based regimen and antracycline alone. These data are sufficient to provide reliable evidence of these drugs as adjuvant treatment for early breast cancer.

Our meta-analysis shows that the addition of a taxane to an anthracycline-based regimen results in a statistically significant reduction of the risk of leukemia, venous thrombus and severe cardiotoxicity for early breast cancer patients compared to anthrcycline alone. Additionally, the effect size of anthrcycline combinations was not superior to anthrcycline alone in the event of non-recurrent death. However, Michele et al. has reported that the addition of a taxane to an anthracycline-based regimen improves the disease-free survival and overall survival of high-risk early breast cancer [3]. Soonmyung et al. has suggested that tumor recurrent rate of breast cancer is highly associated with different characteristics of patients such as node-negative or node- positive and estrogen receptor–positive or estrogen receptor–negative disease [26]. Therefore, a larger number of cases in the future study are still required to evaluate the efficacy of anthrcycline combinations.

Several limitation of this meta-analysis should be acknowledged. First, the studies were carried out in several countries by different researcher under various conditions, so judgment of the type of side effects was inevitably different. Nevertheless, a random effects model was used in order to reduce the error if there was between-study heterogeneity. Second, major organ functions of the subjects included in this analysis are normal, so it cannot reflect the situations of the subjects with organ dysfunction. Therefore, underestimation for incidence of cardiovascular events may exist in both groups. Lastly, this analysis is only at the research level, thus discrepancy is unavoidable.

In the light of the assessment results for publication bias and the purpose to provide a more comprehensive and reliable evidence, we think following aspects need to be further emphasized and paid attention to in future research: (1) subjects should be selected based on strict inclusion and exclusion criteria; a flowchart is needed to describe the situation of exit and loss of follow-up; adopting publicly accepted statistical methods with minimum bias; (2) more researches are required in neurotoxicity, leukemia, venous thrombosis, cardiac toxicity and non-recurrent death to develop a comprehensive assessment, as well as new outcome measures like quality of life [27]; (3) extend the time of follow-up to discover more symptoms and adverse reactions; (4) promoting clinical trial registration system to promote or emphasize the publication of the negative results; (5) RCT report should refer to the international CONSORT standard.

The combination therapy of anthracycline & taxane may possess certain effect in the treatment of early breast cancer and significantly reduce the incidence of leukemia, venous thrombosis and severe cardiac toxicity. In the events of neurotoxicity and tumor recurrent, however, anthracycline & taxane may not be superior to anthracyclin alone. Therefore, the appropriate dosage and contraindications should be paid attention to during its clinical application.

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Conflict of Interest The authors all declare that they have no conflict of interest.

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