Adjuvant Chemotherapy, with or without Taxanes, in Early or Operable Breast Cancer: A Meta-Analysis of 19 Randomized Trials with 30698 Patients

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Abstract

Background: Taxanes have been extensively used as adjuvant chemotherapy for the treatment of early or operable breast cancer, particularly in high risk, node-negative breast cancer. Previous studies, however, have reported inconsistent findings regarding their clinical efficacy and safety. We investigated disease-free survival (DFS), overall survival (OS), and drug-related toxicities of taxanes by a systematic review and meta-analysis.

Methodology and Principal Findings: We systematically searched PubMed, EMBASE, the Cochrane Center Register of Controlled Trials, proceedings of major meetings, and reference lists of articles for studies conducted between January 1980 and April 2011. Randomized controlled trials (RCTs) comparing chemotherapy with and without taxanes in the treatment of patients with early-stage or operable breast cancer were eligible for inclusion in our analysis. The primary endpoint was DFS. Nineteen RCTs including 30698 patients were identified, including 8426 recurrence events and 3803 deaths. Taxanes administration yielded a 17% reduction of hazard ratio (HR) for DFS (HR = 0.83, 95% CI 0.79–0.88, p < 0.001) and a 17% reduction of HR for OS (HR = 0.83, 95% CI 0.77–0.90, p < 0.001). For high risk, node-negative breast cancer, the pooled HR also favored the taxane-based treatment arm over the taxane-free treatment arm (HR = 0.82, 95% CI 0.77–0.87, p = 0.022). A significantly increased rate of neutropenia, febrile neutropenia, fatigue, diarrhea, stomatitis, and oedema was observed in the taxane-based treatment arm.

Conclusions/Significance: Adjuvant chemotherapy with taxanes could reduce the risk of cancer recurrence and death in patients with early or operable breast cancer, although the drug-related toxicities should be balanced. Furthermore, we also demonstrated that patients with high risk, node-negative breast cancer also benefited from taxanes therapy, a result that was not observed in previous studies.

Introduction

Breast cancer (BC) is a leading cause of morbidity and mortality among women worldwide [1–2]. Most BCs (>75%) are diagnosed at an early stage or are operable [3]. For these patients, it is essential to administer adjuvant chemotherapy to reduce the risk of recurrence [4–5]. Taxanes (paclitaxel or docetaxel) are active cytotoxic agents that promote polymerization of tubulin and stabilization of microtubules by preventing their disassembly. Recently, several randomized trials have been conducted to identify the efficacy and safety of taxane-based adjuvant chemotherapy for early or operable BC, often with conflicting results. Additionally, the efficacy of taxanes for patients with high risk, node-negative BC remains uncertain. Two previous meta-analyses [6–7] have been conducted to determine the efficacy and safety of this agent in patients with BC although investigators did not present the efficacy of taxanes in node-negative BC. We undertook a meta-analysis to update the results and resolve the uncertain efficacy of taxanes in women with node-negative BC. Furthermore, we also reported the efficacy of taxanes treatment in some specific subgroups.

Methods

Search strategy and selection criteria

Randomized controlled trials (RCTs) and literatures trials resulted of taxane therapy were eligible for inclusion in our meta-analysis, with no restriction on language or publication status.
investigators (Y-YQ and X-JG).and selection of studies was conducted independently by 2
either disease-free survival (DFS) or overall survival (OS). Search
adjuvant chemotherapy arm; and (c) the primary outcome was
Meta-Analysis) Statement issued in 2009 (Checklist S1) [8].
PRISMA (Preferred Reporting Items for Systematic Reviews and
process was initiated as follows:
(1) Electronic databases (from January 1990 to April 2011): We
retrieved literatures from PubMed, Embase and the Co-
chrane Center Register of Controlled Trials, using the search
terms of “early breast cancer,” “operable breast cancer,”
“node-negative breast cancer,” “stage I or stage II breast
cancer,” and “docetaxel or taxane or paclitaxel”.
(2) Additional resources: Two important annual meetings
including American Society of Clinical Oncology Annual
Scientific Meeting (ASCO) and the San Antonio Breast
Cancer Symposium (from 1995 to 2011), were manually
searched. In addition, information about registered random-
ized controlled trials was obtained from the website http://
clinicaltrials.gov/ (US NIH). Relevant reviews and meta-
analyses regarding the role of taxane-based adjuvant chemo-
therapy in patients with early or operable BC were examined
for potential trials.

This review was conducted and reported according to the
PRISMA (Preferred Reporting Items for Systematic Reviews and
Meta-Analysis) Statement issued in 2009 (Checklist S1) [8].
The eligible RCTs should meet the following inclusion criteria:
(a) early or operable BC; (b) high quality RCT comparing a
taxane-based adjuvant chemotherapy arm with a taxane-free
adjuvant chemotherapy arm; and (c) the primary outcome was
either disease-free survival (DFS) or overall survival (OS). Search
and selection of studies was conducted independently by 2
investigators (Y-YQ and X-JG).

Data extraction and quality assessment
Data extraction and quality assessment were conducted
independently by 2 investigators (Y-YQ and HL) using a
standardized data recording form and Jadad scale [9]. Information
was examined and adjudicated independently by 2 additional
investigators (X-FY and Y-HZ) referring to the original articles
after data extraction and assessment.
The following information was extracted from each eligible
study: study design, year of publication, number of patients,
regimen details, median follow-up, median age, node status, main
endpoint, the hazard ratios (HRs) and corresponding 95%
confidence interval (CI), and the drug-related toxicities (WHO
grades ≥3). For studies which reported HRs for the taxane-free
treatment arm rather than the taxane-based treatment arm, HRs
were recalculated by the exponential of negative ln(HR). If HRs
and 95% CIs were not directly obtained from the original articles,
they were estimated indirectly using reported events in each arm
and the corresponding P value as suggested by Tierney et al [10].
If information could not be obtained from the original literature,
direct communication with the authors was initiated. The
quantitative 5-point Jadad scale was used as a gauge to assess
the quality of the inclusive trials in our study.

Statistical analysis
The primary efficacy outcome of our meta-analysis was disease-
free survival (DFS). DFS was defined as time from randomization
to any recurrence of BC (local or distant), new primary BC, a
second cancer, or death. The subgroup analyses were prospectively
planned according to node status, drug usage, schedule,
observation period, menopausal status, hormone receptor status,
and tumor size. Interaction tests were performed to compare
differences between the 2 estimates [11]. The adverse events (AEs)
of taxane-based treatment were analyzed as drug-related toxicities
(WHO grades ≥3). The pooled estimation plotted as odd ratios
(ORs) was obtained [12]. A pooled OR and 95% CI greater than
1 indicated a statistically significant result.

Heterogeneity between trials was evaluated by chi-square (χ^2
) test and I-squared (I^2) statistic [13]. These indices assess the
percentage of variability across studies attributable to heterogene-
ity rather than chance. Statistical heterogeneity was considered
significant when p<0.10 for the χ^2 test or I^2>50%. Although
fixed-effects model and random-effects model yielded similar
conclusions, we chose to use the random-effects model, which
assumed that the true underlying effect varied among included
trials. Moreover, many investigators consider that the random-
effects model to be a more natural choice than fixed effects model
in medical decision-making contexts [14–15]. The probability of
publication bias was assessed with the funnel plots and the Begg-
Mazumdar test [16]. Additionally, the pooled HR estimates were
recalculated after excluding low-scoring trials to test their
sensitivity. All reported P values were two-sided and P values less
than 0.05 were regarded as statistically significant. Statistical
analyses were carried out using STATA 11.0 (Stata Corporation,
Lakeway, Texas, USA).

Results

Trial characteristic
Twenty-two potential trials were identified and 3 trials [17–19]
of them were excluded for specific reasons listed in flow chart
(Figure 1 and Protocol S1 [8]). The remaining 19 trials [20–42]
included 30698 women with early or operable BC. Two trials
[30–31,33] were published in abstracts and the remaining 17
trials [20–27,29,32,34–37,39–42] were published in full articles.
All of the trials included were open-label, phase III, randomized
trials. Concurrent regimens were conducted in 5 trials
[20,22,25,27,37], while sequential regimens were tested in the
remaining 14 trials [21,23–24,29–30,32–36,38,40–42]. The
GEICAM 9805 [20] recruited patients with node-negative breast
cancer, and the ECTO trial [38] only recruited patients with
tumor size >2 cm. Recurrence/relapse-free survival (RFS) was
the main endpoint of FinHer and Boccardo et al [23,34],
and freedom from progression (FFP) was the main endpoint of
the ECTO trial [38]. However, the definition of RFS and FFP of
these 3 trials was similar to DFS, so we included them. Fourteen
[20–21,23–24,27,29–30,32,34,37–38,40–42] of the 19 trials had
Jadad scores of 3, and 5 trials [22,26,33,35–36] were assessed
with scores of 2. Other detailed information from each trial was
also listed in Table S1.

Total effect of efficacy
Data for DFS were available from all 19 trials [20–25,27,29–
30,32–38,40–42] with 8426 events reported. The taxane-based
treatment arm was associated with a clinically and statistically
significant 17% improvement in DFS when compared with the
taxane-free treatment arm (HR = 0.83, 95% CI 0.79–0.88;
p<0.001; Figure 2) under a random-effect model, and there was
no evidence of significant heterogeneity among individual trials
(p = 0.194, I^2 = 21.4%). The taxane-based treatment arm had
lower risk of recurrence in both concurrent and sequential
regimens than the taxane-free treatment arm (p value 0.002 and
0.000, respectively; test for interaction, p = 0.046).

OS was reported in 17 trials [20–25,27,29–30,32,34–35,37–
38,40–42] of the 19 trials (BIG 2–78 and NSABP B-27 [33,36] did
not reported OS data), including 25 407 patients who were
recruited in the meta-analysis on the risk of death, resulting in
3803 deaths. The efficacy of taxanes on reducing the risk of death
was presented more both in all trials (HR of overall 0.83, 95% CI 0.77–0.90) and the trials of different therapy regimens (Figure 3). We found no evidence of publication bias on either DFS or OS by the funnel plots and the Begg-Mazumdar test.

In addition, the sensitivity analysis was conducted among 14 trials [20–21,23–24,27,29–30,32,34,37–38,40–42] after excluding 5 trials [22,26,33,35–36] with a low Jadad score (score <3). The estimated pooled HRs for DFS (HR 0.82, 95% CI 0.76–0.87) and OS (HR 0.85, 95% CI 0.78–0.92) all favoured the arm treated with taxanes when compared with arm without, and no evidence of significant heterogeneity was observed among individual trials.

Subgroup analysis of efficacy

**Node status.** Only 4 trials [20,24,26–27] reported HR for DFS of patients with node-negative BC. The pooled HR of DFS for these trials was 0.83 (95% CI 0.71–0.97, p = 0.022; Figure 4), which corresponds to a 17% reduction in the risk of recurrence among patients with node-negative BC who received taxanes (docetaxel). Among the 19 included trials, 10 trials [21,23,29–30,32–33,35,37,41–42] included only patients with node-positive disease, and the pooled HR of these trials for DFS also favoured taxane treatment (HR 0.82, 95% CI 0.77–0.87; Table 1).

Furthermore, 5 trials [21,24,31,35,37] reported HRs for DFS separately in the nodes 1–3 and nodes ≥4 subgroups. The pooled HRs also show greater efficacy in the taxane-based treatment arm of the subgroups with nodes 1–3 and nodes ≥4 (HR 0.73, 95% CI 0.59–0.90, and HR 0.89, 95% CI 0.80–0.98, respectively; Figure 4).

**Drug dosage, schedule, and observation period.** The subgroup analysis of DFS was stratified to trials of different
taxane agents (paclitaxel or docetaxel) with different dosage and schedule (docetaxel ≤ 75 mg/m² or = 100 mg/m² and paclitaxel weekly, every 2 weeks, or every 3 weeks) and different observation periods (median follow-up ≤ 5 years or >5 years). Most of the results showed that the taxane-based treatment arm provided greater efficacy on improving DFS among patients with early or operable BC (Table 1). An 18% HR reduction (95% CI 0.76–0.88) was observed for paclitaxel therapy, a 17% HR reduction (95% CI 0.77–0.90) was observed for docetaxel therapy, and a 14% HR reduction (95% CI 0.82–0.90) was observed in the treatment arm after follow-up of greater than 5 years. Not all taxane schedules might be equal, and table 1 also indicated that there was no significantly statistical difference between the paclitaxel every 2 weeks arm and control arm (HR 0.84, 95% CI 0.67 to 1.04), although analyses of remaining 2 paclitaxel schedules (weekly and every 3 weeks) favoured the taxane-based treatment arm.

Others. Subgroup analysis of patients according to their menopausal status, ER (oestrogen receptor) status, and tumor size was shown in table 1 and figure 5. Superior efficacy of taxanes was found in both premenopausal (HR 0.78, 95% CI 0.65–0.94) and postmenopausal patients (HR 0.78, 95% CI 0.68–0.90) after pooling data from 6 trials [20–21,23–25,27,29,35,37]. Efficacy data of adjuvant chemotherapy according to tumor size (<2 cm and ≥2 cm) was available in 4 trials [20,24,27,35] and 5 trials [20,24,27,35,38], respectively. The pooled HRs for DFS favoured the taxane-based treatment arm when compared with the taxane-free treatment arm both in the tumor size <2 cm subgroup (HR 0.84, 95% CI 0.72–0.99) and in the tumor size ≥2 cm subgroup (HR 0.87, 95% CI 0.75–0.99) (Figure 5). Eleven trials [20–21,23–24,27,29,35,37,40–41] reported subgroup results of ER status. For ER-positive subgroup the pooled HR of 0.83 (95% CI 0.76–0.90) for DFS indicated a 17% reduction in the risk of recurrence presented in the taxanes-based treatment arm, and for the ER-negative subgroup the pooled HR of 0.80 (95% CI 0.73–0.88) for DFS indicated a 20% reduction in the risk of recurrence among patients received taxanes. However, subgroup analysis of HER-2 (human epidermal growth factor receptor-2) status (5 trials [23–25,29,37] included) showed no significantly statistical difference in efficacy of taxanes when comparing the taxane-based treatment arm with the taxane-free treatment arm in either HER-2-positive group (HR 0.84, 95% CI 0.68–1.03) or HER-2-negative group (HR 0.87, 95% CI 0.73–1.03; Figure 6). Although statistical significance was not attained, when examining the data by HER-2 status, there were similar trends favouring taxanes.

Toxicities

Data concerning AEs were extracted from 15 trials [20–21,23–25,27,29,32,34–35,37,39–42]. A summary of drug-related toxi-
ties (≥ grade 3) was shown in figure 7. The pooled ORs of each
group, stratified according to grade 3 or greater toxicities,
indicated that a significant increase in toxicity associated with
taxane treatment was observed for neutropenia (OR = 1.54,
95% CI 1.10–2.15), febrile neutropenia (OR = 2.28, 95% CI
1.25–4.16), fatigue (OR = 2.10, 95% CI 1.37–3.22), diarrhea
(OR = 2.16, 95% CI 1.32–3.53), stomatitis (OR = 1.68, 95% CI
1.04–2.71), and oedema (OR = 6.61, 95% CI 2.14–20.49). How-
ever, heterogeneity among trials was found in these analyses,
possibly due to the use of different agents at various dosage and
the use of different control arms. Moreover, subgroup analyses
were performed based on stratification with the 2 types of taxanes. The
results suggested that paclitaxel was associated with statistically
fewer toxicity events when compared with taxane-free therapy in
some toxicities, such as neutropenia (OR = 0.72, 95% CI 0.53–
0.98), and febrile neutropenia (OR = 0.51, 95% CI 0.32–0.79) but
not in other toxicities. However, figure 7 showed that docetaxel
was associated with a significant increase in neutropenia, febrile
neutropenia, leukopenia, stomatitis, oedema, fatigue and/or
asthenia, and diarrhea (Figure 7).

**Discussion**

Nineteen randomized, open-label, phase III trials of 30698
women (with 8426 recurrence events and 3803 deaths) were
included to examine the role of taxanes added in adjuvant
chemotherapy for patients with early or operable breast cancer. The pooled HRs for DFS and OS for all available trials showed
that taxane-based therapy was associated with significant
reduction in the risk of recurrence and death, and the similar
results were observed in the sensitivity analysis. There was no
significant evidence of statistical heterogeneity among individual trials. This meta-analysis also indicated that taxane-based
adjuvant chemotherapy was more efficacious in improving DFS and OS when compared with taxane-free therapy. This
result was consistent with results reported in 2 previous reviews
[6–7].

The study conducted by Sparano et al reported that there were
no significant differences in DFS between the paclitaxel-treated
groups and docetaxel-treated groups [43]. This finding was
similar to the results of our study (test for interaction between
docetaxel and paclitaxel, p = 0.824) as well as the meta-analysis
conducted by De Laurentiis et al (test for interaction between
docetaxel and paclitaxel, p = 0.16) [6]. However, Sparano et al
also reported that greater benefits in improving DFS were
observed in the group receiving paclitaxel weekly and the group
receiving docetaxel every 3 weeks when compared with the group
receiving paclitaxel every 3 weeks. The results of our subgroup
analysis according to the paclitaxel schedule showed that patients
receiving paclitaxel weekly and every 3 weeks, but not those
receiving paclitaxel every 2 weeks, demonstrated superior efficacy
to patients in the control arm of the study. We recognize that
comparisons between 2 types of taxanes can be confounded by
drug schedule, as shown in the Sparano trial [43]. Because of
insufficient data, we were unable to make firm conclusion about
the efficacy of various drug schedule (only 4 trials [23,38,41–42]...
The results of subgroup analysis also indicated that there were significantly gains in DFS in the taxane-based treatment arm, except for patients with HER-2 status. The pooled HRs of analysis of among women with either HER-2 positive or HER-2 negative status showed a favorable trend but no statistical difference between the 2 treatment arms. However, De Laurentiis et al reported that the HR for DFS in the HER-2 positive subgroup was 0.51 (95% CI 0.29–0.87) and in the HER-2 negative subgroup was 0.70 (95% CI 0.55–0.91) [6]. Only 2 trials [29,37] were included in their research and the estimated HR may be less reliable.

Nowadays, the predictive value of hormone receptor (particularly HER-2) in determining taxane responsiveness remains controversial [44–45]. Additional 3 trials [23–25] were included in our analysis, and the pooled HR did not confirm the predictive value of HER-2, however, the point estimate of HRs of most trials favoured taxanes. Therefore, the presence of HER-2 as a predictor of taxane responsiveness needs to be further investigated.

A different toxicity profile was confirmed between taxane-based and taxane-free treatment arms. Drug-related toxicities, such as neutropenia, febrile neutropenia, and oedema, were reported in both this study and previous meta-analyses [7]. In our study, the subgroup analyses of toxicity showed paclitaxel may be associated with fewer toxicities than docetaxel. However, this conclusion could not be definitively confirmed because of less available data on paclitaxel. We need more data to support our result in the future. Unfortunately, only 3 of these trials provided information about quality of life (QoL) [20,37,40]. These trials showed no significant difference in QoL scores between the 2 treatment arms. Although GEICAM 9805 trial and BCIRG 001 trial [20,37] found that taxane was associated with a transient reduction in QoL scores, these scores returned to baseline values afterwards.

The efficacy of taxanes for patients with node-negative breast cancer, longer observation periods, and varying tumor size was not reported in the 2 previous meta-analyses. To resolve these uncertainties, we investigated the efficacy by subgroup analysis of available trials.

There was insufficient evidence to define the efficacy of taxanes among the patients with high-risk, node-negative BC, although the efficacy for node-positive, early-stage breast cancer had been confirmed. The benefits of adjuvant chemotherapy (cyclophosphamide combined with methotrexate and 5-fluorouracil) for node-negative disease was confirmed in 3 trials (NSABP B-13, B-19, B-23) [46]. The GEICAM 9805 trial [20] randomly assigned 1060 patients with high-risk, axillary-nod-negative BC to TAC(-docetaxel, doxorubicin, and cyclophosphamide) arm or FAC (fluorouracil, doxorubicin, and cyclophosphamide) arm, and the trial reported that the hazard ratio for DFS significantly favoured the TAC arm (HR 0.68, 95% CI 0.49–0.93, p = 0.01). However, 4

![Figure 4. Efficacy of taxanes in subgroup of node-negative, node = 1–3, node ≥4: meta-analysis of DFS. NR: not report. doi:10.1371/journal.pone.0026946.g004](image-url)
Table 1. Taxane-based therapy versus non-taxane-based therapy in subgroups: meta-analysis of disease-free survival (DFS).

| Trials | DFS | p value | Test of Heterogeneity |
|--------|-----|---------|----------------------|
|        | HR  | 95% CI  | z² | I² | p  |
| Docetaxel | 20,21,22,24,25,27,30,33–37 | 0.83 | 0.77 to 0.90 | 0.000 | 22.85 | 43.1% | 0.044 |
| < 75 mg/m² | 20,22,25,27,33,37 | 0.81 | 0.73 to 0.91 | 0.000 | 7.63 | 34.5% | 0.178 |
| 100 mg/m² | 21,24,30,34–36 | 0.84 | 0.76 to 0.94 | 0.000 | 14.98 | 53.3% | 0.036 |
| Paclitaxel | 23,29,32,38,40–42 | 0.82 | 0.76 to 0.88 | 0.000 | 5.42 | 0.0% | 0.770 |
| Weekly sequential | 29 | 0.77 | 0.62 to 0.95 | 0.016 | . | . | . |
| Every 2 weeks | 32,40 | 0.84 | 0.67 to 1.04 | 0.109 | 0.10 | 0.0% | 0.752 |
| Every 3 weeks | 23,38,41,42 | 0.82 | 0.73 to 0.93 | 0.003 | 4.96 | 39.5% | 0.175 |
| Trials with N+ only | 21,23,29,30,32,33,35,37,41,42 | 0.82 | 0.77 to 0.87 | 0.000 | 5.69 | 23.8% | 0.080 |
| Observation Period | | | | | | | |
| Median Follow-up ≤ 5 years | 34,35,37,38 | 0.73 | 0.64 to 0.83 | 0.000 | 5.36 | 25.3% | 0.253 |
| Median Follow-up > 5 years | 20–25,27,29,30,32,33,36,40-42 | 0.86 | 0.82 to 0.90 | 0.000 | 19.78 | 24.1% | 0.181 |
| Menopausal Status | | | | | | | |
| Premenopausal | 20,21,23,30,35,37 | 0.78 | 0.65 to 0.94 | 0.010 | 9.63 | 48.1% | 0.086 |
| Postmenopausal | 20,21,23,30,35,37 | 0.78 | 0.68 to 0.90 | 0.001 | 5.47 | 8.5% | 0.362 |
| ER Status | | | | | | | |
| ER+ | 20,21,22,24,27,29,30,35,37,40,41 | 0.83 | 0.76 to 0.90 | 0.000 | 13.74 | 27.2% | 0.185 |
| ER− | 20,21,22,24,27,29,30,35,37,40,41 | 0.80 | 0.73 to 0.88 | 0.000 | 5.88 | 0.0% | 0.826 |

Study | N of patients | HR (95% CI) |
|-------|---------------|-------------|
| Tumor size < 2 cm | | |
| GEICAM 9805 | 535 | 0.69 (0.43, 1.10) |
| UK TACT | 1435 | 0.87 (0.68, 1.11) |
| E2197 | 1245 | 0.96 (0.71, 1.30) |
| PACS 01 | 673 | 0.72 (0.48, 1.07) |
| Subtotal | 3888 | 0.84 (0.72, 0.99); p= 0.040 (x²=2.07, i²=0.0%, p=0.559) |
| Tumor size ≥ 2 cm | | |
| GEICAM 9805 | 525 | 0.68 (0.45, 1.04) |
| UK TACT | 2722 | 0.96 (0.84, 1.10) |
| E2197 | 1632 | 0.96 (0.78, 1.19) |
| PACS 01 | 1155 | 0.88 (0.71, 1.09) |
| ECTO | 904 | 0.65 (0.48, 0.90) |
| Subtotal | 6938 | 0.87 (0.75, 0.99); p= 0.040 (x²=7.11, i²=43.8%, p=0.130) |

Figure 5. Efficacy of taxanes in subgroups of tumor size <2 cm, tumor size ≥ 2 cm: meta-analysis of DFS.

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trials [24,26–27,36] reported the efficacy of taxane (docetaxel) for patients with node-negative BC in subgroup analysis. The results of these 4 trials did not show a significant difference between the docetaxel and control arms (the NSABP B-27 trial [36] did not report exact data of HR for DFS in subgroup analysis). Patients in the GEICAM 9805 trial received docetaxel with 6 cycles, and patients in the other 4 trials received docetaxel with 4 cycles. More therapy cycles of docetaxel may be much more beneficial for node-negative BC. Nevertheless, our study did not compare different therapy cycles because of the limited availability of trials. Data concerning DFS from 4 available trials [20,24,26–27] were pooled (excluded NSABP B-27), and the result (HR 0.83 95% CI 0.71–0.97) significant favored the docetaxel regimen. Therefore, this subgroup analysis provided evidence that docetaxel was useful in improving DFS among patients with high-risk, node-negative BC, which was consistent with the result of the GEICAM 9805 trial.

Trials included in this study were observed with various median follow-up periods. Our aim was to determine whether taxane-based therapy could be efficacious against BC during longer observation periods. The results demonstrated that the benefits of taxanes were still observed during longer follow-up period (HR 0.86, 95% CI 0.82–0.90). However, the results in 2 two trials [22–23] (Anglo-Celtic trial and the Boccado et al. trial with median follow-up of 99 and 102 months, respectively) did not show significant efficacy of taxanes in improving DFS (HR 0.79, 95% CI 0.56–1.12; HR 1.16, 95% CI 0.79–1.75; for these two trials respectively). These results differed from results of our meta-analysis, possibly due to the small sample size of these 2 trials (only 363 patients recruited in Anglo-Celtic trial and 244 patients in Boccado et al. trial). Our study provided stronger evidence demonstrating the efficacy of taxanes for early or operable BC under longer observation periods. Moreover, RCTs which recruit larger population with longer follow-up time will be required to confirm the efficacy of the agent.

The patients included in the ECTO trial [38] all had tumor size greater than 2 cm, with efficacy results showing that the paclitaxel produced significant benefit for this group of patients. For the remaining 4 trials [20,24,27,35], the results did not show any significantly statistical difference between 2 arms in subgroup analysis of tumor size (either tumor size <2 cm or ≥2 cm). However, the estimated HRs using the data of these 5 trials showed taxane-based therapy was statistically superior in reducing the risk of cancer recurrence among patients with both tumor size <2 cm and ≥2 cm compared with taxane-free therapy (Figure 5). Consequently, the pooled analysis confirmed the efficacy of taxanes and was consistent with the results of the overall analysis.

Our meta-analysis also has several potential limitations. First, our study was based on abstracted data and not on individual patient data (IPD), which may not provide robust estimation for the association. Second, the characteristics of the included trials were varied in the follow-up observation period, therapy regimen, agents and dosage. Third, there may be several trials with available data that were ongoing or unpublished at the time of the writing of this manuscript that were not included in this meta-analysis, in addition to the 19 trials included in this study. Consequently, publication bias may be unavoidable in this meta-analysis. However, the results form the funnel plots and the Begg-Mazumdar test did not indicate significant publication bias.

Despite the limitations of our research, the results strongly suggest that adjuvant chemotherapy that includes taxanes provides a significant advantage in improving both DFS and OS among patients with early or operable BC compared with therapy without taxanes. Moreover, the subgroup analysis concerning node status also demonstrated that

| Study                  | N of patients | HR (95% CI)               |
|------------------------|---------------|----------------------------|
| HER–2 +                |               |                            |
| Boccado et al.         | 73            | 1.47 (0.69, 3.13)          |
| UK TACT                | 847           | 0.87 (0.69, 1.09)          |
| US Oncology            | 46            | 0.73 (0.32, 1.70)          |
| GEICAM 9906            | 188           | 0.92 (0.69, 1.24)          |
| BCIRG 001              | 319           | 0.60 (0.41, 0.88)          |
| Subtotal               | 1473          | 0.84 (0.68, 1.03); p=0.098 |

| HER–2 –                |               |                            |
| Boccado et al.         | 103           | 1.20 (0.63, 2.27)          |
| UK TACT                | 2724          | 1.02 (0.87, 1.19)          |
| US Oncology            | 124           | 0.56 (0.30, 1.05)          |
| GEICAM 9906            | 738           | 0.82 (0.70, 0.95)          |
| BCIRG 001              | 943           | 0.76 (0.59, 1.00)          |
| Subtotal               | 4632          | 0.87 (0.73, 1.03); p=0.097 |

Figure 6. Efficacy of taxanes in subgroups of HER–2 status: meta-analysis of DFS.
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docetaxel-based therapy is superior to docetaxel-free therapy, for high risk node-negative BC, in reducing the risk of cancer recurrence. Additional well-designed RCTs with varying drug schedules for both operable and node-negative BC are warranted to further evaluate these conclusions. The benefit of taxanes should be balanced against their toxicity, and additional data on QoL should be provided in further analysis. Physicians should take these adverse drug events into consideration and interpret the results carefully and comprehensively in clinical practice.

Figure 7. Summary of drug-related toxicities grade 3 or greater.
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Supporting Information

Checklist S1  PRISMA Checklist. (DOC)
Protocol S1  PRISMA Flowchart. (DOC)
Table S1  Baseline characteristics for included trials. (DOC)
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Author Contributions

Conceived and designed the experiments: JH YYQ HL. Performed the experiments: YYQ XJG HL XFY. Analyzed the data: YYQ YHZ. Contributed reagents/materials/analysis tools: XJZ. Wrote the paper: YYQ XFY XW WQ CW JL.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, et al. (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127: 2893–2917.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69–90.
3. Verma S, Lavasanis S, Mackey J, Pritchard K, Clemons M, et al. (2010) Optimizing the management of her2-positive early breast cancer: the clinical reality. Curr Oncol 17: 20–33.
4. ERCTGTC (2005) Effects of chemotherapy and hormone therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365: 1607–1717.
5. ERCTGTC (1998) Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trials’ Collaborative Group. Lancet 352: 930–942.
6. De Laurentis M, Cancellor G, D’Agostino D, Giuliano M, Giordano A, et al. (2008) Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. J Clin Oncol 26: 44–53.
7. Ferguson T, Wilcken N, Varg R, Gherci D, Nowak AK (2007) Taxanes for adjuvant treatment of early breast cancer. Cochrane Database Syst Rev CD004421.
8. Moher D, Liberati A, Tetzlaff J, Altman DG, GNP P (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine 6.
9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, et al. (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17: 1–12.
10. Tierney J, Stewart LA, Ghersi D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8: 16.
11. Altman DG, Bland JM (2003) Interaction revisited: the difference between two estimates. BMJ 326: 219.
12. Deeks JJ, Higgins JP, Altman DG (2008) Analyzing data and undertaking meta-analyses. In: Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions 5.0.1. Oxford, UK: The Cochrane Collaboration: chap 9.
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557–560.
14. Ades AE, Lu G, Higgins JP (2005) The interpretation of random-effects meta-analysis in decision models. Med Decis Making 25: 646–634.
15. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177–188.
16. Begh CB, Mazundar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088–1101.
17. Bonnoti H, Potri A, Deloreni M, Mauriac L, Campone M, et al. (2007) Validation of gene signatures that predict the response of breast cancer to neoadjuvant chemotherapy: a substudy of the EORTC 10994/BIG 00-01 clinical trial. Lancet Oncology 8: 1071–1078.
18. Buzdar AU, Singletary SE, Valero V, Booser DJ, Ibrahim NK, et al. (2002) Doxorubicin Plus Cyclophosphamide Is Associated With An Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. J Clin Oncol 20: 1177–1183.
19. Jones SE, Savin MA, Holmes FA, O’Shaughnessy JA, Blum JL, et al. (2006) Phase III trial comparing doxorubicin plus cyclophosphamide with doxorubicin plus cyclophosphamide as adjuvant therapy for operable breast cancer. Journal of Clinical Oncology 24: 5301–5307.
20. Goldstein LJ, O’Neill A, Mies AZ, Perez EA, Shulman LN, et al. (2008) Concurrent doxorubicin plus docetaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0 to 3 positive axillary nodes: North American breast cancer intergroup trial E.2197. Journal of Clinical Oncology 26: 4902–4910.
21. Goldstein L, O’Neill A, Sparano JA, Perez EA, Shulman LN, et al. (2005) E2197: Phase III AT (doxorubicin/docetaxel) vs. AC (doxorubicin/cyclophosphamide) in the adjuvant treatment of node positive and high risk node negative breast cancer. Substudy [abstract]. J Clin Oncol ASCO(suppl): abstr 187.
22. Roche H, Fumoleau P, Spielmann M, Canon JL, Delozier T, et al. (2006) Improved outcomes from adding sequential paclitaxel but not from doxorubicin plus cyclophosphamide as adjuvant therapy for high-risk, node-negative breast cancer. Journal of the National Cancer Institute 100: 905–914.
23. Cognetti F, De Laurentis M (2008) Sequential epirubicin-docetaxel-CMF as adjuvant therapy for node-positive early stage breast cancer: updated results of the TAXIt216 randomized trial. Ann Oncol 19(suppl): ii1020.
24. Polyzos A, Malamos N, Boukovinas I, Adamou A, Ziras N, et al. (2010) FEC versus sequential epirubicin-docetaxel-CMF as adjuvant therapy for node-positive early-stage breast cancer: Subgroup analysis of the TAXIt216 randomized trial. Breast Cancer Symposia(suppl): abstr 187.
25. Jones S, Holmes FA, O’Shaughnessy JA, Blum JL, et al. (2009) Intensive dose-dense compared with high-dose adjuvant chemotherapy for high-risk operable breast cancer: Southwest Oncology Group/Intergroup study 9623. J Clin Oncol 23: 1677–1682.
26. Crown JP, Francis P, De Leo A, Bayes M, Balil A, et al. (2006) Docetaxel (T) given concurrently with or sequentially to anthracycline-based (A) adjuvant therapy (adjRx) for patients (pts) with node-positive (N+) breast cancer (BrCa), in comparison with non-T adjRx: First results of the BIG 2–98 Trial at 5 years median follow-up (MFU). J Clin Oncol ASCO(suppl): abstr LBAS19.
27. Jornau S, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja J, et al. (2006) Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. New England Journal of Medicine 354: 899–900.
28. Rossin H, Fusenke P, Skalitsky M, Camon I, Jenkinson C, Delozer T, et al. (2006) Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: The FNCLCC PACS 01 trial. Journal of Clinical Oncology 24: 3664–3671.
29. Baur HD, Anderson S, Smith RE, Geyer CE, Jr., Mamounas EP, et al. (2007) Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 25: 2019–2027.
30. Martin M, Pienkowski T, Mackey J, Pavlicki M, Giustalla JP, et al. (2005) Adjuvant docetaxel for node-positive breast cancer. New England Journal of Medicine 353: 2302–2313.
31. Gianni L, Baselga J, Eiermann W, Gullmann Porta V, Semiglav V, et al. (2005) European Cooperative Trial in Operable Breast Cancer (ECTO): Improved freedom from progression (FFP) from adding paclitaxel (T) to doxorubicin (A) following by cyclophosphamide methotrexate and fluorouracil (CMF). J Clin Oncol ASCO(suppl): abstr.343.
32. Gianni L, Baselga J, Eiermann W, Gullmann Porta V, Semiglav V, et al. (2005) Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil and its effects on tumour response as preoperative therapy. Clinic Cancer Res 11: 8715–8721.
33. Fountzilas G, Skarlos D, Fishe J, Gogas H, Briasoulis E, et al. (2005) Five-year outcome for women randomised in a phase III trial comparing docorubicin and cyclophosphamide with doxorubicin and docetaxel as primary medical therapy in early breast cancer: an Anglo-Celtic Cooperative Group Study. Breast Cancer Res Treat 122: 787–794.
34. Roccardo F, Amadori D, Gigulimini P, Simondi P, Farris A, et al. (2010) Epirubicin followed by cyclophosphamide, methotrexate and 5-fluorouracil versus paclitaxel followed by epirubicin and vinorelbine in patients with high-risk operable breast cancer. Oncology 78: 274–281.
35. Ellis P, Barrett-Lee P, Johnson L, Cameron D, Wardley A, et al. (2009) Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACCT): an open-label, phase III, randomised controlled trial. The Lancet 373: 1601–1602.
36. Jones S, Holmes FA, O’Shaughnessy JA, Blum JL, Vukelja SJ, et al. (2009) Docetaxel With Cyclophosphamide Is Associated With An Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. J Clin Oncol 27: 1177–1183.
escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. Journal of Clinical Oncology 21: 976–983.

43. Sparano JA, Wang M, Martino S, Jones V, Perez EA, et al. (2008) Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358: 1663–1671.

44. Andre F, Broglio K, Roche H, Martin M, Mackey JR, et al. (2008) Estrogen receptor expression and efficacy of docetaxel-containing adjuvant chemotherapy in patients with node-positive breast cancer: results from a pooled analysis. J Clin Oncol 26: 2636–2643.

45. Martin M, Mackey J, Vogel C (2007) Benefit from adjuvant taxanes and endocrine responsiveness in breast cancer. Breast 16 Suppl 2: S127–131.

46. Fisher B, Jeong JH, Anderson S, Wolmark N (2004) Treatment of axillary lymph node-negative, estrogen receptor-negative breast cancer: updated findings from National Surgical Adjuvant Breast and Bowel Project clinical trials. J Natl Cancer Inst 96: 1823–1831.