Research Article

Efficacy and Safety of Albumin-bound Paclitaxel Versus Solvent-based Paclitaxel in Breast Cancer: A Meta-analysis

Fengchang Zhu¹, Chengyin Liu²#, Huaji Zhang³, Liping Bai⁴*

¹Division of International Exchange, Chinese Pharmaceutical Association, Beijing, China
²Research Editorial Office, Science and Technology Review Publishing House, Beijing, China
³Chinese Pharmaceutical Journal Co., Ltd, Beijing, China
⁴Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

#Both authors contributed equally to this manuscript.

*Correspondence to: Liping Bai, PhD, Professor, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences & Peking Union Medical College, Tian Tan Xi Li No.1, Beijing 100050, China; Email: lipingbai1973@163.com

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Abstract
Objective: A meta-analysis was performed to evaluate the safety and efficacy of albumin-bound paclitaxel (Nab-PTX) versus solvent-based paclitaxel (Sb-PTX) for breast cancer.

Methods: In this systematic review and network meta-analysis, we searched databases including PubMed, Embase, and Cochrane-Library, for randomized controlled trials on the safety and efficacy of Nab-PTX and Sb-PTX for breast cancer. Pathologic complete response (pCR), objective response rate (ORR), and adverse events (AEs) were collated and analyzed using the meta-package in the R language.

Results: A total of 13 studies (comprising 4252 patients) met the inclusion criteria, in which 9 studies adopted neoadjuvant chemotherapy and 4 adopted conventional chemotherapy for breast cancer. Trails with neoadjuvant chemotherapy revealed that Nab-PTX resulted in a significantly higher pCR (0.280 [95% confidence interval (CI): 0.218-0.341]) and a higher ORR (0.822 [95% CI: 0.719-0.924]) versus Sb-PTX (0.163 [95% CI: 0.098-0.227], 0.770 [95% CI: 0.681-0.859]). In conventional chemotherapy, Sb-PTX and Nab-PTX showed a similar ORR (0.343 [95% CI: 0.204-0.483] vs. 0.438 [95% CI: 0.317-0.559] [odds ratio=1.53, 95% CI: 0.88-2.67]. In terms of AEs, the incidence of all grade-peripheral sensory neuropathy (PSN) and grade≥3 PSN for Sb-PTX was 0.392 (95% CI: 0.243-0.541) and 0.020 (95% CI: 0.009-0.031), and for Nab-PTX was 0.591 (95% CI: 0.452-0.729) and 0.087 (95% CI: 0.046-0.031).

Conclusion: Neoadjuvant chemotherapy using Nab-PTX significantly enhanced the pCR and ORR of breast cancer patients, while conventional chemotherapy showed no significant pCR and ORR benefits. Given the significantly increased incidence of PSN, neoadjuvant chemotherapy using Nab-PTX requires caution in its clinical application.
Keywords: nanocarriers, paclitaxel, breast cancer, neoadjuvant chemotherapy, meta-analysis


1 INTRODUCTION

Breast cancer originates from the uncontrolled proliferation of breast epithelial cells under the action of multiple oncogenic factors. Multiple organ lesions may develop in advanced stages due to distant metastases, which poses a great threat to the life safety of patients[12]. Breast cancer is the most prevalent malignancy among women[3], and its early symptoms are insidious, such as breast lumps, abnormal skin, nipple overflow, and abnormal nipples or areolas[5,6]. Advanced manifestations include loss of appetite, anorexia, wasting, fatigue, anemia, and fever[5,6]. Thus, breast cancer treatment requires both local and systemic therapies according to the biological behavior of the tumor and the patient condition to enhance treatment efficacy and the quality of life of patients[7].

Chemotherapy is a systemic treatment using cytotoxic drugs to scavenge small lesions unresectable by surgery, reduce the recurrence of cancer metastases, and improve patient survival[8]. Paclitaxel is a diterpene alkaloid with anticancer activity. It destabilizes microtubulins and the microtubulin dimers that constitute microtubules, promotes microtubulin polymerization and microtubule assembly, and prevents depolymerization, thereby stabilizing microtubules, inhibiting mitosis of cancer cells, triggering apoptosis, and effectively preventing the proliferation of cancer cells[9,10]. Paclitaxel is the current drug of choice for breast cancer but is associated with adverse events such as bone marrow suppression, allergic reactions, skin reactions (erythema), and gastrointestinal reactions[11]. Nano drug carriers are made of natural or synthetic polymeric materials, with a particle size of 10 to 1000nm and are widely used in the pharmaceutical field as they feature a small particle size, lower drug toxicity to the body, improve drug stability, and maintain a proper release rate of drugs[12,13]. Albumin-bound paclitaxel (Nab-PTX) is a commonly used clinical nanof ormulation of paclitaxel, but its efficacy is debated[14,15]. Previous studies have compared the pathological remission rate and safety of paclitaxel (albumin-binding type) single drug weekly regimen in neoadjuvant chemotherapy for locally advanced breast cancer and paclitaxel (albumin-binding type) single drug weekly regimen of 5-fluorouracil + epirubicin + cyclophosphamide every 3 weeks regimen. The results showed that the weekly regimen of Nab-PTX had the mildest toxicity and obvious efficacy in patients with locally advanced breast cancer, with a CCR rate of 32%. The sequential protocol was better tolerated, and surgery was performed on all patients.

In the current study, a meta-analysis was used to evaluate the efficacy of Nab-PTX versus solvent-based paclitaxel (SB-PTX) for breast cancer to provide an evidence-based medical rationale for treatment selection.

2 MATERIALS AND METHODS

2.1 Literature Search

A literature search was conducted on Pubmed, Embase, and Cochrane-Library from database inception to December 30, 2021, using the search terms (“Paclitaxel” or “PTX” or “Taxol” or “Taxotere”) and (“breast cancer” or “mammary cancer” or “Breast Carcinoma” or “Breast Tumor” or “TNBC”) and the corresponding Chinese search terms. Languages were set to English and Chinese, and references of the included literature were searched and retrospectively added to potentially missing studies whenever possible.

2.2 Inclusion and Exclusion Criteria

2.2.1 Inclusion Criteria

(1) Randomized clinical trials (RCT).
(2) Study subjects were pathologically diagnosed with breast cancer.
(3) Randomization followed by division into at least two groups, one receiving paclitaxel chemotherapy and the other receiving albumin paclitaxel or paclitaxel liposome chemotherapy.
(4) Study endpoints included one of the following items: pathologic complete response (pCR), ORR, overall survival (OS), progression-free survival (PFS), and AEs.
(5) Study design was scientific and standardized, with clear grouping and interventions and complete documentation such as follow-up data.

2.2.2 Exclusion Criteria

(1) Non-RCT studies or non-primary studies.
(2) With no extractable outcome indicators of interest such as OS, PFS, and AEs.
(3) Studies with less than 40 participants included in a single group.
(4) Duplicate publications or overlapping data studies.

2.2.3 Literature Screening

Data were retrieved by two investigators and literature management was performed using Endnote. Duplicates were excluded and the remaining literature was screened separately at the three levels of the article title, abstract, and full text, and was decided whether to be included against the above criteria.

2.3 Data Extraction

Data were extracted and collated by two investigators independently, including authors, time of publication, subject type, intervention method, whether blinded, and whether randomized. ORR, pCR, OS, PFS, and AEs were used as the
main effect measures for the meta-analysis.

2.4 Quality Assessment

The risk of bias in the included studies was assessed using the RCT risk of bias assessment tool recommended in the Cochrane Systematic Evaluators’ Handbook 5.1, and two systematic evaluators performed the evaluation separately. Any discrepancies were resolved by consensus with a third evaluator.

2.5 Statistical Analysis

The R software meta-package was used to collate and meta-analyze the data. Dichotomous variables were expressed using odds ratio (OR) or risk ratio and 95% confidence interval (CI). The heterogeneity of the included studies was evaluated by the $I^2$ test. $I^2=0$ and $P>0.1$ in both subgroups indicated no heterogeneity in the included studies and a fixed-effects model was used for analysis. $I^2>0$ and $P<0.1$ in both subgroups indicated the presence of heterogeneity, which required analysis of the source of heterogeneity for its removal. A meta-analysis was performed using a random-effects model if heterogeneity could not be removed. Funnel plots were used to describe publication bias, and Egger’s test was used to test for funnel plot asymmetry.

3 RESULTS

3.1 Eligible Literature

Of 304 original papers retrieved by an electronic search, 233 papers were excluded after literature abstracts reading and exclusion of case reports, abstracts, reviews, and single-arm research, and 71 papers were coarsely included. Studies with duplicate reports, unspecified data, subgroup analyses, and post hoc analyses were further ruled out, and the final 13 pieces (comprising 4252 patients) of literature were recruited[16-28], in which 9 studies[16-21,24-28] adopted neoadjuvant chemotherapy and 4 adopted conventional chemotherapy[16,17,22,23] for breast cancer. The basic information of the included literature is shown in Table 1, and the quality evaluation of the included literature is shown in Figure 1.

### Table 1. Basic Information of the Included Literature

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Stage</th>
<th>Patients</th>
<th>Cancer type</th>
<th>Therapy</th>
<th>Sb-PTX</th>
<th>Nab-PTX</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradishar et al.[16]</td>
<td>2005</td>
<td>Phase III</td>
<td>Metastatic BC</td>
<td>Undistinguished</td>
<td>RC</td>
<td>229</td>
<td>225</td>
<td>ORR</td>
</tr>
<tr>
<td>Rugo et al.[17]</td>
<td>2015</td>
<td>Phase III</td>
<td>Stage III C or IV BC</td>
<td>Undistinguished</td>
<td>RC</td>
<td>267</td>
<td>275</td>
<td>ORR</td>
</tr>
<tr>
<td>Untch et al.[18]</td>
<td>2015</td>
<td>Phase III</td>
<td>Invasive BC</td>
<td>Undistinguished</td>
<td>NAC</td>
<td>600</td>
<td>606</td>
<td>pCR, ORR, AEs</td>
</tr>
<tr>
<td>Gianni et al.[19]</td>
<td>2018</td>
<td>Phase III</td>
<td>Stage II to IV a-d BC</td>
<td>ERBB2/ HER2-Negative</td>
<td>NAC</td>
<td>349</td>
<td>346</td>
<td>pCR, ORR, AEs</td>
</tr>
<tr>
<td>Kuwayama et al.[20]</td>
<td>2018</td>
<td>Phase II</td>
<td>Stage I–III BC</td>
<td>HER2-Negative</td>
<td>NAC</td>
<td>77</td>
<td>75</td>
<td>pCR, ORR, AEs</td>
</tr>
<tr>
<td>Guan et al.[22]</td>
<td>2019</td>
<td>Phase II</td>
<td>Metastatic BC</td>
<td>Undistinguished</td>
<td>RC</td>
<td>104</td>
<td>106</td>
<td>ORR</td>
</tr>
<tr>
<td>Tamura et al.[23]</td>
<td>2017</td>
<td>Phase II</td>
<td>Metastatic BC</td>
<td>HER2-Negative</td>
<td>RC</td>
<td>98</td>
<td>99</td>
<td>ORR</td>
</tr>
<tr>
<td>Huang et al.[24]</td>
<td>2015</td>
<td>Phase II</td>
<td>Locally advanced BC</td>
<td>Undistinguished</td>
<td>NAC</td>
<td>90</td>
<td>30</td>
<td>pCR, ORR, AEs</td>
</tr>
<tr>
<td>Chen et al.[25]</td>
<td>2021</td>
<td>Phase II</td>
<td>Stage II–III BC</td>
<td>Undistinguished</td>
<td>NAC</td>
<td>63</td>
<td>41</td>
<td>pCR, ORR, AEs</td>
</tr>
<tr>
<td>Lv et al.[26]</td>
<td>2022</td>
<td>Retrospective</td>
<td>Stage II–III BC</td>
<td>HER2-negative</td>
<td>NAC</td>
<td>80</td>
<td>79</td>
<td>pCR, ORR, AEs</td>
</tr>
<tr>
<td>Li et al.[28]</td>
<td>2021</td>
<td>Retrospective</td>
<td>Metastatic BC</td>
<td>HER2-positive</td>
<td>NAC</td>
<td>97</td>
<td>104</td>
<td>pCR, AEs</td>
</tr>
</tbody>
</table>

Figure 1. Quality evaluation of included literature.
3.2 Meta-analysis

3.2.1 Clinical Efficacy of Sb-PTX and Nab-PTX in NAC

The use of Sb-PTX and Nab-PTX in neoadjuvant chemotherapy was compared in nine papers, all of which reported pCR [18-21,24-28], and six papers reported ORR [18-20,24-26]. The pCR was 0.163 (95% CI: 0.098-0.227) after Sb-PTX treatment and 0.280 (95% CI: 0.218-0.341) after Nab-PTX treatment ($I^2=31\%$, $P=0.17$). The results of meta-analysis showed a significantly higher pCR after Nab-PTX treatment versus Sb-PTX (OR = 0.64, 95% CI: 0.54-0.76) (Figure 2A). The ORR was 0.770 (95% CI: 0.681-0.859) after Sb-PTX treatment and 0.822 (95% CI: 0.719-0.924) after Nab-PTX treatment ($I^2=0\%$, $P=0.80$). The results of the meta-analysis also showed a significantly higher ORR after Nab-PTX treatment versus Sb-PTX (OR = 0.82, 95% CI: 0.67-1.00) (Figure 2B).

3.2.2 Clinical Efficacy of Sb-PTX and Nab-PTX in Conventional Chemotherapy

There were four studies comparing Sb-PTX and Nab-PTX in conventional chemotherapy, and all reported ORR [18,20,24-26]. The ORR was 0.343 (95% CI: 0.204-0.483) for Sb-PTX and 0.438 (95% CI: 0.317-0.559) for Nab-PTX ($I^2=84\%$, $P<0.01$). The results of the meta-analysis showed no significant difference in ORR after treatment with Sb-PTX and Nab-PTX (OR = 1.53, 95% CI: 0.88-2.67) (Figure 3).

3.2.3 Safety of Sb-PTX and Nab-PTX in NAC

Peripheral sensory neuropathy (PSN) is a common adverse effect of paclitaxel, which is associated with discontinuation of therapy, impaired treatment outcome, and compromised quality of life of patients. In the present study, eight papers investigated the incidence of PSN in Sb-PTX and Nab-PTX, of which seven reported the incidence of all grade-PSN [18,20,24-27] and six reported the incidence of grade≥3 PSN [18,20,24-27]. The incidence of all grade-PSN was 0.392 (95% CI: 0.243-0.541) for Sb-PTX therapy and 0.591 (95% CI: 0.452-0.729) for Nab-PTX therapy ($I^2=60\%$, $P=0.02$). The results of the meta-analysis showed that the incidence of all grade-PSN was significantly lower with Sb-PTX than with Nab-PTX (OR = 0.44, 95% CI: 0.37-0.53) (Figure 4A). The incidence of grade≥3 PSN was 0.020 (95% CI: 0.009-0.031) for Sb-PTX therapy and 0.087 (95% CI: 0.046-0.129) for Nab-PTX therapy ($I^2=0\%$, $P=0.79$). The results of the meta-analysis showed a significantly lower incidence of grade≥3 PSN with Sb-PTX therapy versus Nab-PTX (OR = 0.27, 95% CI: 0.18-0.40) (Figure 4B).

3.3 Publication Bias Analysis

The results of the publication bias funnel plots and sensitivity analysis forest plots by the one-by-one exclusion method for each study are shown in Figure 5A-5E. The funnel plots of each study were symmetrical and the results of sensitivity analysis using study-by-study exclusion showed no significant change, confirming the absence of significant publication bias in the included literature.

4 DISCUSSION

The results of the present study showed that Nab-PTX treatment resulted in significantly higher pCR and ORR.
but also a significantly higher incidence of PSN than Sb-PTX treatment in neoadjuvant chemotherapy. Neoadjuvant chemotherapy is systemic chemotherapy administered prior to local therapeutic approaches (e.g., surgery or radiotherapy) to reduce the mass size and scavenge invisible metastatic cells[29]. The pCR is an intermediate endpoint associated with the final endpoint (e.g., event-free survival and OS) and is an important indicator in adjuvant chemotherapy[30]. Albumin is an endogenous substance and a non-modulating protein, and the use of albumin as a nanocarrier for paclitaxel enables rapid drug delivery to cancerous tissues with a long duration of action. The use of Nab-PTX in neoadjuvant chemotherapy for breast cancer further reduces drug toxicity[31]. The GBG69 study suggested that compared with Sb-PTX, Nab-PTX in preoperative neoadjuvant therapy significantly improved pCR in breast cancer patients at the early stage, especially in triple-negative breast cancer, and showed disease-free survival benefits. The response rate of Nab-PTX was significantly higher than that of paclitaxel (21.5% vs. 11.1%) for advanced breast cancer and was also nearly doubled that of Sb-PTX for patients with failed first-line standard therapy (15.5% vs. 8.4%), but there was no difference between the two in terms of OS[32]. The present study showed that the pCR and ORR after Nab-PTX treatment were 28.0% and 82.2%, respectively, both of which were significantly higher than that of 16.3% and 77.0% for Sb-PTX treatment. In addition, several studies have confirmed that albumin taxol has stronger anti-tumor activity compared with traditional taxol and is considered one of the preferred chemotherapy drugs for advanced breast cancer with significant efficacy.

The results of the present study showed no significant difference in the ORR between Sb-PTX and Nab-PTX in conventional chemotherapy, and inconsistency of results was also found in the 4 papers using conventional chemotherapy. The ORR of Nab-PTX treatment was
significantly higher than that of Sb-PTX in the study by Gradishar et al.\cite{6} and Guan et al.\cite{22}, but no significant difference was observed in the other 2 studies. Previous studies have shown an ORR of 19% for the treatment of breast cancer after Sb-PTX and 33% after Nab-PTX, suggesting that Nab-PTX could significantly improve the overall remission rate of breast cancer patients versus Sb-PTX. However, no significant enhancement of ORR was observed in the present study\cite{33}. In addition, Nab-PTX increases the incidence of PSN, which requires caution in dosing selection.

5 CONCLUSION
Neoadjuvant chemotherapy using Nab-PTX significantly enhanced the pCR and ORR of breast cancer patients, while conventional chemotherapy showed no significant pCR and ORR benefits. Given the significantly increased incidence of PSN, neoadjuvant chemotherapy with Nab-PTX requires caution in its clinical application.

Acknowledgments
Not applicable.

Conflicts of Interest
These authors had no conflict of interest.

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Author Contribution
Zhu F and Liu C designed this study and wrote the article; Zhang H collected the data and performed the statistical analysis; Bai L revised the papers for important intellectual content; all authors approved the final version.

Abbreviation List
AEs, Adverse events
BC, Breast cancer
CI, Confidence interval
Nab-PTX, Albumin-bound paclitaxel
NAC, Neoadjuvant chemotherapy
OR, Odds ratio
ORR, Objective response rate
OS, Overall survival
pCR, Pathologic complete response
PFS, Progression-free survival
PSN, Peripheral sensory neuropathy
RC, Routine chemotherapy
RCT, Randomized clinical trial
Sb-PTX, Solvent-based paclitaxel

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