Efficacy and safety of nanoparticle albumin-bound paclitaxel as neoadjuvant chemotherapy in HER2-negative breast cancer

ABSTRACT

Context: Nanoparticle albumin-bound paclitaxel (Nab-PTX) is a form of paclitaxel bound to albumin nanoparticles and is used widely in a neoadjuvant setting for patients with breast cancer.

Aims: We conducted a retrospective study to compare the efficacy and safety of Nab-PTX to PTX as neoadjuvant chemotherapy for patients with operable HER2-negative breast cancer.

Settings and Design: In total, 50 patients were enrolled. Nab-PTX was administered in the study group, and PTX was administered in the control group.

Subjects and Methods: The clinical response and safety profile were recorded. The expression of secreted protein acidic rich in cysteine (SPARC) in tumor tissue was examined.

Statistical Analysis: The efficacy and safety analyses were computed using SPSS statistical software. Multiple logistic regression analysis was performed to evaluate the exploratory variables (age, stage, estrogen receptor, partial response, and SPARC expression) for the pathological complete response (pCR), and Fisher’s exact test was performed to evaluate the relationship between SPARC and pCR.

Results: Both groups of patients achieved a good clinical response. The pCR rate for the Nab-PTX regimen was significantly higher than that for the PTX regimen. The most common adverse events were neutropenia, peripheral sensory neuropathy, arthralgia, and myalgia. In 68% of cases in the Nab-PTX group, high SPARC expression was observed.

Conclusions: As neoadjuvant therapy, the Nab-PTX regimen has advantages over conventional taxane regimen in patients with HER2-negative breast cancer. With this regimen, a high pCR rate was achieved with a good safety profile.

KEY WORDS: Adverse events, HER2-negative breast cancer, nanoparticle albumin-bound paclitaxel, neoadjuvant chemotherapy, pathological complete response, secreted protein acidic rich in cysteine

INTRODUCTION

Breast cancer is the primary cause of death in adult women.[1] Neoadjuvant chemotherapy (NAC) has become a standard treatment option in patients with operable and locally advanced breast cancer.[2] After receiving NAC, patients attain superior pathological complete response (pCR), and survival outcome improves considerably.[3,4]

Nanoparticle albumin-bound paclitaxel (Nab-PTX) is composed of albumin-bound to a nanoparticle of 130 nm and is a solvent-free drug. As Nab-PTX does not contain surfactants or alcohol, premedication with steroids or antihistamines is not needed, removing any possibility of Cremophor EL or ethanol-associated toxicities. Several studies using Nab-PTX in neoadjuvant therapy have reported promising therapeutic effects.[5-8] However, until now, there have been no clear recommendations for its use. The response and adverse events (AEs) assessments vary in different studies.

Cite this article as: Yang M, Qu H, Liu A, Liu J, Sun P, Li H. Efficacy and safety of nanoparticle albumin-bound paclitaxel as neoadjuvant chemotherapy in HER2-negative breast cancer. J Can Res Ther 2019;15:1561-6.
Therefore, to assess the clinical utility of Nab-PTX in preoperative NAC, we conducted a retrospective study to compare the efficacy and toxicity of Nab-PTX with the conventional taxane used in patients with operable breast cancer.

SUBJECTS AND METHODS

Study design
The study was designed to evaluate the efficacy and safety of preoperative treatment with Nab-PTX. We performed a retrospective review of cases of patients with operable breast cancer. Patients were classified into two groups according to the drug they received for treatment. We assigned patients that received Nab-PTX to the first group and patients that received PTX to the second group.

Patient eligibility criteria
Women who met the following criteria between July 1, 2014, and October 1, 2015, at the Yuhuangding Hospital Affiliated to Qingdao University were eligible for inclusion: between 30 and 80 years of age, inclusive, with histologically confirmed operable breast cancer (T2-4bN0-2M0, Stage IIA-IIIB) and HER2-negative cancer; at least one measurable lesion according to the RECIST criteria; Eastern Cooperative Oncology Group performance status was 0 or 1; no previous therapy for breast cancer, including chemotherapy, radiotherapy, endocrine therapy, immunotherapy, and surgery, and normal electrocardiograms. Cut-off values for laboratory values were as follows: aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤2 times the upper limit of normal; total bilirubin, indirect bilirubin, and creatinine clearance (cCR) ≤1.5 times the upper limit of normal; hemoglobin ≥100 g/L; leukocyte count ≥4 × 10⁹/L; neutrophil count ≥1.5 × 10⁹/L; thrombocyte count ≥100 × 10⁹/L. Patients with active concomitant malignancy, active infection, and serious concomitant diseases, such as heart failure, uncontrolled diabetes, liver failure, uncontrollable peripheral neuropathy, or severe drug allergy, were excluded. Pregnant or lactating women were also excluded.

As there were no clear recommendations, the use of the Nab-PTX regimen as neoadjuvant therapy was considered to be an off-label use. The study was approved by the local ethics committee. All patients provided written informed consent for participation.

Treatment
The study design is shown in Figure 1. The enrolled patients were allocated to the Nab-PTX group or the PTX group. Patients in the Nab-PTX group received four cycles of every 3 weeks (q3w) epirubicin/cyclophosphamide (EC) followed by four cycles of Nab-PTX (Abraxane, Abraxis Bioscience, USA) 260 mg/m² q3w. Nab-PTX lyophilized powder was dissolved in 0.9% physiological saline and administered as a 30 min intravenous drip without a pretreatment process.

In the PTX group, the patients received four cycles of q3w epirubicin/cyclophosphamide (EC) followed by four cycles of PTX (Taxol, Bristol-Myers Squibb, US) 175 mg/m² q3w. Before the therapy, patients took dexamethasone 20 mg and diphenhydramine 50 mg orally and received an intravenous injection cimetidine 0.4 g.

Response and toxicity assessments
The primary objective was to evaluate the pathological complete response (pCR) rate, defined as no histological evidence of residual invasive tumor cells in the breast or axillary lymph nodes (ypT0/TisypN0). The secondary objectives were to evaluate the clinical response rate (cRR), histological assessment, and safety profile of Nab-PTX.

The clinical TNM classification (Union of International Cancer Control, version 7) and clinical stage (General Rules for Clinical and Pathological Recording of Breast Cancer, The Japanese Breast Cancer Society, 17th edition) were evaluated and determined before NAC was performed. The clinical tumor size and nodal status were evaluated by ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI). CT scans were used to detect distant metastases. The tumor size was monitored every 2 weeks by palpation and was measured using the same method (CT or MRI) at both baseline and protocol completion.

The clinical tumor response was assessed in accordance with RECIST version 1.1 criteria. Complete response (CR) was defined as the disappearance of all tumor foci after chemotherapy. Partial response (PR) was defined as a decline of at least 30% in tumor maximum diameter, and progressive disease (PD) was defined as an increase of at least 20% from the baseline in the sum of all tumor diameter measurements. The disease was categorized as a stable disease when CR, PR, or PD was not noted. Patients were considered responders if they achieved CR or PR. All patients who received chemotherapy (more than one cycle of each regimen) were evaluated for safety. Toxicities were evaluated according to
All patients were followed up for at least 3 years. The progression-free survival (PFS) was calculated as the period from the date of surgery to the first observation of the tumor recurrence (metastatic recurrence and/or local relapse) or the last follow-up.

Histological assessment of tissue specimens
Breast cancer was diagnosed by core needle or vacuum-assisted biopsy specimen prior to any treatment. After eight cycles of NAC, pathologists evaluated and recorded the histological type and pathological response based on the findings in the surgical specimen.

To investigate the association between the efficacy of Nab-PTX and the expression of SPARC, we performed immunohistochemistry (IHC) on biopsy samples to measure SPARC expression. The slides were scored for SPARC expression on a scale from 0 to 3, where 0 represented no expression, and 3 represented a strong expression. We considered that SPARC expression was negative in patients with a score of 0–1 and positive in patients with a score of 2–3.

All microscopy slides were independently evaluated by two experienced pathologists.

Statistical analysis
Efficacy and safety analyses were performed using SPSS statistical software (version 23; IBM Corp., Armonk, NY, USA). Furthermore, to evaluate exploratory variables (age, stage, ER, PR, and SPARC expression) for pCR, multiple logistic regression analysis was performed. Fisher’s exact test was performed to evaluate the relationship between SPARC and pCR. P < 0.05 was considered statistically significant.

RESULTS

Patient characteristics
Between July 2014 and October 2015, 25 consecutive patients used Nab-PTX regimen as neoadjuvant therapy in our hospital. These patients all met the study criteria. In addition, we matched the other 25 patients through clinical data who were administered the conventional taxane regimen. All patients were diagnosed with invasive ductal carcinoma using core needle or vacuum-assisted biopsy. The patients’ baseline characteristics are summarized in Table 1. The patients’ characteristics were very similar between the Nab-PTX and PTX groups, including median age (P = 0.762), menopausal status (P = 0.754), clinical stage (P = 0.725), ECOG performance (P = 0.667), and ER and/or PR status (P = 0.769).

Clinical and pathological assessments
Both groups had a marked response to the treatment with Nab-PTX or PTX and showed a cRR rate of 100%. The cCR rate for the Nab-PTX regimen was 48% (12/25), which was higher than the rate of 16% (4/25) for the PTX regimen; this difference was statistically significant (P = 0.032). Further analysis revealed that the pCR rates for patients administered the Nab-PTX regimen and PTX regimen were 40% (8/25) and 4% (1/25), respectively. The rate in Nab-PTX group was clearly higher than the PTX group, and the difference was statistically significant (P = 0.023).

Safety profile
Of the 50 enrolled patients in the two different groups, all completed eight cycles of NAC. No severe AEs were reported during treatment. No discontinuation for adverse reaction, treatment delay, dose reduction, or delayed surgery occurred in either group. The incidence of treatment-related AEs is shown in Table 2. In the Nab-PTX group, the incidence of neutropenia was 20.0% (5/25); in the PTX group, the incidence was 52% (13/25). The difference was statistically significant between the two groups (P = 0.038). In the Nab-PTX group, 12 patients (48%) experienced peripheral sensory neuropathy, manifested by tingling, numbness, or paresthesia in the hands and feet. In the PTX group, only 16% (4/25) of patients experienced peripheral sensory neuropathy, which was a statistically significant difference (P = 0.032). The incidence of arthralgia and myalgia in the Nab-PTX group was lower than in the PTX group (P = 0.018). Neuropathy Grade 3 or 4 (P = 0.609), peripheral sensory neuropathy (P = 0.349), and arthralgia and myalgia (P = 0.49) were observed in both groups. Other common side effects were nausea and vomiting (P = 0.742), baldness (P = 0.166), and anaphylaxis (P = 0.49). However, there was no statistical difference between the two groups.

Secreted protein acidic rich in cysteine expression and response to nanoparticle albumin-bound paclitaxel
In patients treated with Nab-PTX, the expression of SPARC protein was analyzed using IHC [Figure 2]. SPARC protein was found predominantly in the cytoplasm of tumor cells, and

| Table 1: Patients’ characteristics |
|----------------------------------|
|                                | Nab-PTX group | PTX group | P    |
| Age (years)                    |               |           |      |
| <60                             | 16 (64)       | 18 (72)   | 0.762|
| ≥60                             | 9 (36)        | 7 (28)    |      |
| Menopausal status              |               |           |      |
| Premenopausal                  | 17 (68)       | 19 (76)   | 0.754|
| Postmenopausal                 | 8 (32)        | 6 (24)    |      |
| Stage                           |               |           |      |
| IIA                             | 9 (36)        | 12 (48)   | 0.725|
| IIB                             | 10 (40)       | 9 (36)    |      |
| IIIA                            | 3 (12)        | 3 (12)    |      |
| IIIB                            | 3 (12)        | 1 (4)     |      |
| ECOG PS=0                      | 23 (92)       | 21 (84)   | 0.667|
| PS=1                            | 2 (8)         | 4 (16)    |      |
| ER and/or PR status            |               |           |      |
| Positive                       | 15 (60)       | 17 (68)   | 0.769|
| Negative                       | 10 (40)       | 8 (32)    |      |

PTX=Paclitaxel, Nab-PTX=Nanoparticle albumin-bound PTX, ECOG=Eastern Cooperative Oncology Group, PR=Progesterone receptor, ER=Estrogen receptor
68% (17/25) of cases showed strong cytoplasmic staining. Patients with positive SPARC expression had higher cCR (11/17, 64.7%) than those with negative SPARC expression (1/8, 12.5%), \( P = 0.03 \) [Table 3]. Patients with positive SPARC expression had a better 3-year PFS rate (94.1% vs. 75%, \( P = 0.231 \)) than those with negative SPARC expression. However, there was no statistical difference between the two groups.

**DISCUSSION**

In this study, we evaluated the safety and efficacy of preoperative NAC with EC followed by Nab-PTX in patients with operable breast cancer. We found the treatment with Nab-PTX to be safe, effective, and to yield a high pCR rate.

NAC has been used widely, not only to reducing tumor loading and downstaging in breast-conserving surgery but also for chemosensitivity testing in vivo.\(^\text{5}\) Compared with monotherapy, the combination of Nab-PTX with other chemotherapeutics provides better clinical outcomes, both in response rate and survival.\(^\text{9,10}\) The efficacy of neoadjuvant therapy can be assessed using the pCR rate, which can predict the long-term clinical benefit.\(^\text{11-13}\) As several reports have published, sequential anthracycline and taxane combinations remain the main regimen for early and locally advanced breast cancer, with pCR rates of 15%–25%.\(^\text{14-18}\) Taxanes were proven to increase pCR rates for operable breast cancer when used in a neoadjuvant setting.\(^\text{19}\) Paclitaxel is the most common taxane used for NAC in patients with breast cancer.\(^\text{20}\) However, paclitaxel requires emulsification with polyoxyethylated castor oil and ethanol to increase drug solubility. These solvents have been associated with frequent toxicities, including hypersensitivity reactions and peripheral neuropathy. The solvent-associated toxicities may limit the paclitaxel dose that can be administered safely and have a negative impact on the efficacy of paclitaxel.\(^\text{21}\)

Nab-PTX is a form of paclitaxel bound to albumin nanoparticles. It avoids the use of prophylactic antihistamines and corticosteroids as premedication and lower percentages of patients experience neutropenia, myalgia, and arthralgia compared with patients administered paclitaxel. Furthermore, Nab-PTX results in quicker recovery from peripheral neuropathy than with PTX.\(^\text{22}\)

Our treatment protocol, which comprised the administration of EC q3w followed by Nab-PTX, was based on these advantages. Our tested regimen showed a good safety profile with a cRR of 100%. The most common AE observed in the Nab-PTX group was an increased risk of peripheral sensory neuropathy.

Recent reports on NAC with Nab-PTX showed a favorable pCR rate of between 29% and 37%.\(^\text{5-7}\) These findings were...
consistent with our results and illustrated the superiority of Nab-PTX as neoadjuvant treatment.

The albumin-binding protein known as SPARC is a key regulator for cellular interaction with the extracellular matrix as it binds to structural matrix proteins that are homologous to gp60. The binding of albumin to the gp60 receptor is known to mediate endothelial caveolar transcytosis and facilitate the transport of paclitaxel across endothelial cell layers. Studies have indicated that SPARC was overexpressed in breast cancer and that high SPARC expression in tumor cells was associated with a higher pCR rate to NAC. In previous experimental models, Nab-PTX achieved a 33% higher intratumoral paclitaxel concentration than conventional paclitaxel. It has also been hypothesized that SPARC expression and its binding to albumin caused the enrichment of Nab-PTX accumulation in tumors and enhanced its antitumor effects. However, in another trial, the difference in the benefit of neoadjuvant Nab-PTX in the SPARC-overexpressing group was not remarkable compared with the SPARC-negative cohort. More evidence from larger prospective trials is warranted to identify predictive markers for Nab-PTX treatment.

We performed IHC to investigate the association between SPARC expression and the response to Nab-PTX and found that there was a significant difference in pCR between patients with positive SPARC expression and patients with negative SPARC expression after Nab-PTX therapy. SPARC may increase the PTX concentration in tumor cells, and our data demonstrated that high SPARC expression in tumor cells might enhance the effectiveness of Nab-PTX.

The results of our study are limited by the small sample size and the lack of long-term follow-up. Further prospective and randomized controlled trials with larger sample sizes and long-term observations are necessary. More precise predictive factors should be assessed to help avoid the adverse effects of Nab-PTX.

CONCLUSIONS

We have demonstrated the effects of a novel preoperative NAC treatment with EC followed by Nab-PTX. The regimen achieved a high pCR rate, with a good safety profile. Moreover, SPARC expression was associated with pCR and may affect the efficacy of Nab-PTX. Sensory neuropathy, neutropenia, arthralgia, and myalgia were common AEs induced by Nab-PTX therapy. However, these AEs were tolerable and controllable. Therefore, Nab-PTX appears to be a promising alternative to NAC in patients with operable breast cancer.

Acknowledgment

We would like to express our sincere gratitude to the patients and their families for agreeing to participate in this work.

Financial support and sponsorship

This work has been supported by Yantai Municipal Science and Technology Project (No.2018FGY114).

Conflicts of interest

There are no conflicts of interest.

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