Journal of
Clinical and Experimental Pharmacology

Li et al., Clin Exp Pharmacol 2016, 6:3
DOI: 10.4172/2161-1459.1000209

Research Article Open Access

Combination of Nab-Paclitaxel with Trastuzumab as Neoadjuvant Chemotherapy for HER2-positive Breast Cancer Patients: Experience from a Single Center

Li T, Yang M*, Ren C, Lao H and Zeng Y

Medical Research Center of Guangdong General Hospital, Guangdong Provincial Cardiovascular Institute, Guangdong Academy of Medical Sciences, Guangzhou, China

***Corresponding author:** Yang M, Medical Research Center of Guangdong General Hospital, Guangdong Provincial Cardiovascular Institute, Guangdong Academy of Medical Sciences, Guangzhou, China, E-mail: mnmyang@aliyun.com

Received date: March 08, 2016; **Accepted date:** May 12, 2016; **Published date:** May 18, 2016

Abstract

Background: Several phase II and pilot studies showed that neoadjuvant nab-paclitaxel-based chemotherapy and trastuzumab treatment was effective and safe. However, combination of nab-paclitaxel alone with trastuzumab has not been investigated.

Methods: This is a retrospective analysis. From July 2009 to June 2014, Patients with histologically confirmed, nonmetastatic HER2-positive breast cancer who received a 3-week regimen of nab-paclitaxel with trastuzumab in Guangdong General Hospital were screened. Baseline and pathological data and blood test results were collected from the electronic patient medical records. Survival data, severe adverse events and cardiac events were collected by telephone follow-up. The primary endpoint was pCR. The secondary endpoints included pCR in breast, DFS during follow-up period, breast conserving rates, tolerance, adverse events and symptomatic cardiac events.

Results: 23 patients who met the eligibility criteria were indentified. 21 (91.3%) patients completed NC courses and received surgery. The breast conserving rates were 19.0%. 10 (47.6%) patients achieved a pCR and 13 (61.9%) achieved a pCR in breast. 7 (53.8%) of the 13 patients with clinical stage IIB-IIIC before surgery achieved a pCR. The pCR rates among hormone-receptor-negative and hormone-receptor-positive patients were 58.3% (7/12) and 33.3% (3/9) respectively. During a median follow-up of 31.3 months, no death was indentified and the 3-year estimated DFS was 81.2%. Two patients reported cardiac events during and after adjuvant chemotherapy. No severe adverse events that required hospitalization were identified during NC period. Grade 3 events were rare.

Conclusion: The combination of nab-paclitaxel and trastuzumab as NC lead to related high pCR rates and was well tolerated. No cardiac events or severe adverse events were indentified during NC period. The studied regimen may be a potential NC therapy for HER2-positive patients. Further study is recommended in the future.

Keywords: HER2-positive breast cancer; Neoadjuvant chemotherapy; Nab-paclitaxel; Pathologic complete response

Introduction

Early stage human epidermal growth factor receptor 2 (Her2)-positive breast cancer is characterized by its higher risk of early metastasis and recurrence [1-3]. Neoadjuvant chemotherapy (NC) is a well-established approach for locally advanced breast cancer. It can downstage tumors before surgery; increase the likelihood of breast conservation; and provide prognostic information on sensibility of breast cancer to a certain chemotherapy regimen [4,5]. Treated with anti-Her2 agents plus chemotherapy regimen, patients with HER2-positive/estrogen-receptor (ER)-negative breast cancer are reported to have the highest rate of pathological complete respond (pCR), which is proved to be a robust predictor of better prognosis [5-7]. Nowadays the most commonly used neoadjuvant regimen for HER2-positive breast cancer is an anthracycline-based chemotherapy followed by taxane plus an anti-Her2 agent (mostly trastuzumab), for example, doxorubicin/cyclophosphamide (AC) followed by docetaxel plus trastuzumab [4,5,8,9]. However, beyond the favorable therapeutic effect, cardiac toxicity of these regimens is a serious concern. Cardiotoxicity is a well-known side effect of anthracyclines, mostly dose cumulative. The cardiac damage induced by anthracyclines could be irreversible and thus may result in permanent heart failure and arrhythmia [10-12]. Trastuzumab also has cardiac toxicity which is usually reversible and of low rate when using alone [13,14]. The concurrent administration of anthracyclines and trastuzumab raises the risk of cardiac toxicity dramatically [15]. Even the sequential administration of trastuzumab following anthracycline-based chemotherapy can lead to a high rate of left ventricular ejection fraction (LVEF) decrease [16-19]. Clinical researches showed that the incidence of severe heart failure during the AC regimen followed by trastuzumab plus paclitaxel is 3-4%. Quite a few patients failed to receive trastuzumab as they developed cardiac toxicity during anthracycline-based treatment. Additionally, the mean age at diagnosis of breast cancer is around 50 year-old in China [20]. The risk of heart fail developed from left ventricular ejection fractions (LVEF) decline may increase with age and thus worsen the quality of patients' survival life. In order to minimize the cardiac toxicity, researchers began to explore the anthracycline-free regimens for breast cancer patients, of which the most attention was paid to taxane-based ones [21-24].

Taxane plays an important role in the treatment of breast cancer, including solvent-based paclitaxel (sb-paclitaxel), docetaxel and 130 nm albumin-bound paclitaxel (Nab-paclitaxel). Sb-paclitaxel and docetaxel are water-insoluble and thus formulated with polyoxyethylated castor oil and polysorbate 80 respectively. These two amphoteric surfactants are suggested to be associated with acute hypersensitivity reactions, peripheral neuropathy, hepatotoxicity and renal toxicity [25,26]. In contrast, nab-paclitaxel is a nano-particle created by linking paclitaxel to human serum albumin through high-pressure homogenization, which make it water soluble [26]. As a surfactant-free formulation, nab-paclitaxel can be administered without premedication. Furthermore, it has a higher maximum tolerance dose and shorter injection time [27]. Clinical studies suggest that nab-paclitaxel is more effective and relatively safe in treatment of metastatic breast cancer compared with sb-paclitaxel [28,29]. Phase II and pilot studies showed that the pCR rates under NC treatment of nab-paclitaxel-based chemotherapy and trastuzumab reached 50% [30,31], which was comparable with anthracycline-based regimens. We retrospectively analyzed the data of breast cancer patients who received co-administration of nab-pacltaxel and trastuzumab as NC therapy from July 2009 to June 2014 at Guangdong General Hospital. We assessed the pCR rates, toxicity and disease-free survival (DFS) after a median follow-up period in order to evaluate the efficacy and safety of this regimen.

Patients and Methods

Eligibility criteria

Patients with histologically confirmed, primary, unilateral, nonmetastatic HER2-positive breast cancer who received a 3-week regimen of nab-paclitaxel with trastuzumab as NC were eligible for this retrospective analysis. Histopathological examinations were performed by the pathologists from pathology department of Guangdong General Hospital. HER2-positive cancer was define as 3+ on immunohistochemistry (IHC) test or amplified on fluorescence in situ hybridization (FISH) test. Tumors with <10% positive cancer cells by IHC were classified as ER negative and PR negative. Other inclusion criteria were age ≥18 years and female. Exclusion criteria were prior chemotherapy for this cancer, concurrence with other cancers (such as ovarian cancer and thyroid cancer), other chemotherapeutic agents except nab-paclitaxel, other anti-Her2 agents except trastuzumab, weekly therapeutic regimen. This study complies with the principles of the Declaration of Helsinki and was approved by institutional research ethics committee of Guangdong General Hospital.

Therapy

Patients received nab-paclitaxel 260 mg/m^2 intravenously over 30 minutes every 21 days with trastuzumab simultaneously (8 mg/kg loading dose, and then 6 mg/kg). The NC was scheduled as a 4-course treatment but may be adjusted according to the outcomes of tumor measurements by imaging or physical examination during NC courses. If tumors were found to be progressive, patients might change NC regimen or receive surgery immediately at the discretion of the treating physician; if patients achieved a clinical complete respond before completing 4 courses of treatments, they might receive surgery immediately or continue the remaining treatments at the discretion of the treating physician. Prophylactic recombinant human granulocyte-colony stimulating factor was given after each cycle of NC. Dose modification or treatment discontinuation was performed at the discretion of the treating physician when excess toxicity events occurred. After completion of chemotherapy, patients underwent surgical resection. Adjuvant chemotherapy was at the discretion of the treating physician. Radiation was given to patients who received breast conserving therapy or patients with large tumors or positive axillary nodes after NC treatment. Radiotherapy scheme for each patient was at the discretion of the radiation oncologist. All patients with hormone-receptor-positive cancer received endocrine therapy.

Response and toxicity assessment

The primary objective of this study was to assess the pCR rates. pCR was defined as an absence of invasive tumor cells in both the breast and axilla at the time of surgery, including residual ductal carcinoma in situ. The secondary objectives included pCR in breast, breast conservation rates, DFS during follow-up and safety profile. With respect to the incompleteness of electronic medical records and the effect of anthropogenic factors, safety profile was assessed based only on the laboratory examination results. Patients were scheduled to take complete blood count (CBC) at local medical institutions or at our hospital on the forth, sixth, eighth and tenth day of chemotherapy and whenever needed. Patients were scheduled to take CBC, liver function and renal function examinations at our hospital before each cycle of NC. We assessed safety of the NC regimen based on the laboratory results before each chemotherapy treatment and telephone follow-up. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE 4.0).

After collecting patients' baseline and pathological response data and blood-test outcomes, we performed a telephone follow-up. The objectives of the telephone follow-up were to confirm 1) patients' survival and relapse; 2) severe adverse events (required hospitalization) during NC; 3) symptoms of cardiac toxicity such as palpitation, cardiodynia and physical stamina decline during and after NC.

Statistics

Data were collected from the electronic medical record system of Guangdong General Hospital by Excel 2003. Statistical analyses were performed using SPSS statistical software package 21.0. Continuous data were expressed as medians, ranges, or means and categorical data as frequency percentages. DFS was defined as the time elapsed between the date of the NC initiation and the date of first time recurrence, excluding second primary tumor. Survival analyses were performed using the Kaplan and Meier method. The differences between patients achieved and not achieved pCR with regard to DFS were evaluated by the log-rank test.

Results

Patient and tumor characteristic

According to the eligibility and exclusion criteria, 25 patients received combination of nab-paclitaxel and trastuzumab as NC from July 2009 to June 2014 were identified. One patient was found to have indications of vertebral metastasis on admission during data check phase. Another patient was found to co-administrate with lapatinib during telephone follow-up phase. Thus 23 patients were included in evaluation. The basic characteristics of the 23 patients were summarized in Table 1.

Age (years)	
Mean	44.9
Range	28-64
Median	44
Age distribution, n (%)	
≥40 years	16 (69.6)
<40 years	7 (30.4)
Menopausal status, n (%)	
Premenopausal	16 (69.6)
Postmenopausal	7 (30.4)
Tumor stage, n (%)	
cT1	2 (8.7)
cT2	17 (73.9)
cT3	2 (8.7)
cT4	2 (8.7)
Lymph node stage, n (%)	
cN0	10 (43.5)
cN1	10 (43.5)
cN2	2 (8.7)
cN3	1 (4.3)
Clinical stage, n (%)	
IIA	10 (43.5)
IIB	8 (34.8)
IIIA	2 (8.7)
IIIB	2 (8.7)
IIIC	1 (4.3)
Histological subtype, n (%)	
Invasive ductal cancer (IDC)	21 (91.3)
IDC+ILC	1 (4.3)
Mucinous carcinoma	1 (4.3)
Histological grade, n (%)	
I	1 (4.3)
II	10 (43.5)
III	10 (43.5)
Unknown	2 (8.7)
ER, n (%)	
Positive	7 (30.4)
Negative	16 (69.6)
PR, n (%)	
Positive	8 (34.8)
Negative	15 (65.2)

Table 1: Patient and tumor characteristics before NC.

Response to NC

21 (91.3%) of the 23 patients completed the NC courses and received surgery. 17 (81.0%) of the 21 patients received modified radical mastectomy and the other 4 patients (19.0%) received breast conserving surgery. Of the 21 patients who had surgery records, 10 (47.6%) achieved a pCR and 13 (61.9%) achieved a pCR in breast. Of the 11 patients who did not achieve pCR, 8 achieved clinical partial response and 3 remained clinically stable. Of 13 patients with clinical stage IIB-IIIC at diagnosis, 7 (53.8%) achieved a pCR and 9 (69.2%) achieved a pCR in breast. 7 (58.3%) out of 12 hormone-receptor-negative patients as well as 3 (33.3%) out of 9 hormone-receptor-positive patients achieved a pCR. Since only 3 patients received axillary nodes biopsies before surgery, the pathological responses of axillary nodes were not assessed. Positive axillary nodes were observed in 8 of the 21 patients, including 3 with ≥9 positive axillary nodes (pN3) and 5 with 1-3 positive axillary nodes (pN1). After surgery, 20 of the 21 patients continued to receive combination of nab-paclitaxel and trastuzumab as adjuvant chemotherapy. One patient who did not achieve pCR at the time of surgery changed to nab-paclitaxel and carboplatin as adjuvant chemotherapy.

Follow-up and disease-free survival

Until Dec 2014, the median follow-up time was 31.3 months (range, 11.5-56.6 months). One of the 21 patients was lost to follow-up. No death was identified during follow-up period. 3 patients had metastatic recurrence and none had local recurrence. Of the 3 recurrences, one occurred in patients with a pCR at the time of surgery. Two occurred in patients with ER/PR-negative tumors. Based on the Kaplan-Meier survival analysis, the estimated 3-year DFS was 81.2% (Figure 1). There was no significant difference in DFS on the basis of achievement of pCR at the time of surgery (Figure 2).

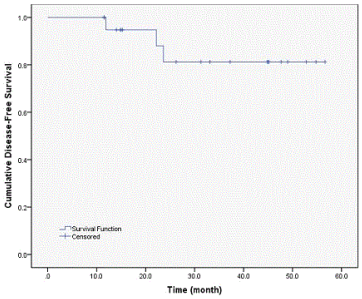

Figure 1: Kaplan-Meier curve showing cumulative DFS of the 21 patients.

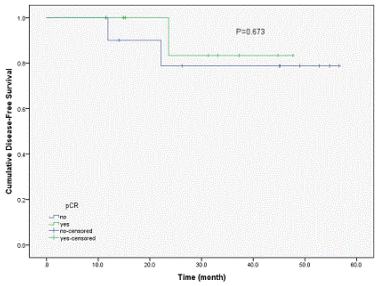

Figure 2: Kaplan-Meier curves showing cumulative DFS according to pCR.

Tolerance and toxicity

23 patients were included in tolerance and toxicity assessment. 21 patients completed all NC courses before surgery; 2 patients discontinued after 2 cycles of NC without a surgery record. One was lost to follow-up and the other discontinued NC because of intolerance. A total of 89 doses of NC were administrated. Dose delays ≥5 days were required in 8 (9.0%) NC courses while dose reduction was required in only one patient. According to the results of blood tests, grade 3 events were indentified in 2 patients, including 1 neutropenia and 1 alanine aminotransferase elevation. Grade 2 events, including 2 leukocytopenia, 2 neutropenia, 2 alanine aminotransferase elevation, 1 aspartate translocase elevation and 1 hemoglobin concentration decline, were observed in 5 patients. No grade 4 or Grade 5 event was identified. Cases with increased creatinine were not observed.

Of 21 patients who completed the NC, 14 had echocardiography records both before and after NC. Among the 14 patients, no LVEF decline after NC was identified. According to the outcomes of telephone follow-up, no cardiac event during NC therapy was reported. A 34 year-old patient reflected that she had had palpitation accompanied with amaurosis approximately once a month since June 2014 but had not taken any ultrasound cardiogram check yet. She received paclitaxel and trastuzumab as adjuvant chemotherapy after surgery and completed the trastuzumab courses in 2012. Another woman reflected that she developed premature beat after the first cycle of adjuvant chemotherapy but recovered after completing adjuvant chemotherapy. No patient except these 2 patients reported symptoms of cardiac toxicity. No severe adverse event that required hospitalization during NC was reported.

Discussion

Efficacy and follow-up

According to a recently published study included 12 international neoadjuvant trials [6], the pCR rates of HER2-positive, hormone-receptor-negative population with trastuzumab was 50.3% (45.0-55.5), and those of HER2-positive, hormone-receptor-positive population with trastuzumab was 30.9% (26.3-35.8). In our study, the pCR rates of hormone-receptor-negative patients were 58.3% and those of hormone-receptor-positive ones were 33.3%, which was comparable with standard NC regimens. During a median follow-up of 31.3 months, 3 patients relapsed but no dead was reported. Our study found no significant difference in DFS on the basis of achievement of pCR. This might due to the short-term of follow-up and few cases of relapse.

Toxicity assessment

We indentified the adverse events based on a patient's blood-examination outcomes before each NC cycle, which determined whether the patient could receive the chemotherapy on schedule. According to the results, no Grade 4 event was observed, and grade 3 adverse events were indentified only in two patients. The rates of dose delay and dose reduction were low compared with other taxane and/or anthracycle-based chemotherapeutic regimens [32-34]. No severe adverse event that required hospitalization during NC was reported.

Trastuzumab itself can induce cardiac toxicity [13,14]. Concurrent or sequential administration of trastuzumab with anthracyclines raises the risk of cardiac toxicity. In the cardiac safety report of NSABP B31 clinical trial (N=1664) [16], the absolute cumulative incidence of cardiac events was 4.1% in AC followed by paclitaxel plus trastuzumab (AC-PH) arm; 6.6% patients never received trastuzumab because of LVEF declines during AC therapy. In NCCTG N9831 clinical study [19], the 3-year cumulative incidences of cardiac events were 3.3% in AC-PH arm and 5.0% of the patients developed LVEF declines before receiving trastuzumab. Meta-analysis by Feng et al. [35] showed that concurrent use of anthracycline-based regimen and trastuzumab as NC significantly increased the likelihood of cardiac toxicity. In our study, no cardiac event was reported. Two patients reported cardiac symptoms in telephone follow-up but none of them occurred during NC period. One occurred after the first cycle of adjuvant chemotherapy and recovered after completion of adjuvant chemotherapy. The other occurred one year after completion of trastuzumab therapy. In general, the regimen of nab-paclitaxel plus trastuzumab as NC was well tolerated.

Limitation

Our study has several limitations. First of all, this is a retrospective analysis. Several data were not able to collect. Adverse events such as neuropathy, asthenia, and gastrointestinal symptom and so on were not recorded in the medical records. Quite a few of blood examinations were performed locally, which makes it infeasible for us to collect all the blood-examination outcomes between two NC courses. To compensate, we performed a telephone follow-up for investigated severe adverse events and cardiac events. No severe adverse event or cardiac event during NC was reported. Second, the sample size was relative small in our study. To confirm our results, further prospective studies with larger sample size are needed.

Significance of our study

As long-time survival improving in HER2-positive breast cancer patients, concerns with cardiac toxicity induced by the traditional anthracycline-based regimens raise. Researchers began to explore alternative regimens with similar efficacy and less cardiac toxicity in order to improve patients' survival life quality. According to our knowledge, this is the first report of breast cancer patients received nab-paclitaxel plus trastuzumab as NC regimen. In 2011, Yardley, et al. [30] reported a phase II study of weekly nab-paclitaxel and carboplatin with bevacizumab and trastuzumab as NC for women with locally advanced HER2-positive breast cancer. The pCR rates reached 54%

(14/26) but the bevacizumab-related completions were common. In 2012, Kaklamani, et al. [36] reported a pilot neoadjuvant trial of nab-paclitaxel plus lapatinib in HER2-positive breast cancer. This regimen was well tolerated but the pCR was achieved only in 5 of the 28 patients (17.9%). Our study indicated that nab-paclitaxel alone with trastuzumab as NC could lead to relative high pCR rates and maybe better tolerated. Combination of nab-paclitaxel with trastuzumab may be potential to replace anthracycline-based regimens for HER2-positive patients.

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