Weekly Paclitaxel/Carboplatin/Trastuzumab Therapy Improves Pathologic Complete Remission in Aggressive HER2-Positive Breast Cancers, Especially in Luminal-B Subtype, Compared With a Once-Every-3-Weeks Schedule

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Disclosures of potential conflicts of interest may be found at the end of this article.

ABSTRACT

Background. The efficacy and tolerability of two different schedules of paclitaxel, carboplatin, and trastuzumab (PCarH) for HER2-positive, locally aggressive (stage IIB–IIIC) breast cancers were evaluated in this phase II trial.

Methods. Patients were randomly assigned to receive either weekly (12 doses over 16 weeks) or once-every-3-weeks (4 doses over 12 weeks) treatment. The primary endpoint was pathologic complete remission (pCR) in the breast and axilla. To detect an assumed 35% pCR absolute difference between the two schedules, a minimum of 26 assessable patients in each group was required (two-sided $\alpha = 0.05$, $\beta = 0.2$).

Results. A total of 56 patients were enrolled (weekly group, $n = 29$; every-3-weeks group, $n = 27$). In the intent-to-treat analysis, pCR in the breast/axilla were found in 31 patients (55%; 95% confidence interval [CI]: 41%–69%). Compared with the every-3-weeks schedule, the weekly administration achieved higher pCR (41% vs. 69%; $p = .03$). After adjustment

for clinical and pathological factors, the weekly administration was more effective than the every-3-weeks schedule, with hazard ratio of 0.3 (95% CI: 0.1–0.9; $p = .03$). Interestingly, weekly administration resulted in high pCR rates in both luminal-B (HER2-positive) and ERBB2+ tumors (67% vs. 71%; $p = .78$), whereas luminal-B (HER2-positive) tumors benefited less from the every-3-weeks schedule compared with the ERBB2+ tumors (21% vs. 62%, $p = .03$). These results remain after multivariate adjustment, showing weekly administration was more effective in the luminal-B (HER2-positive) subgroup ($p = .02$) but not in the ERBB2+ subgroup ($p = .50$).

Conclusion. A more frequent administration might improve the possibility of eradicating invasive cancer in the breast and axilla, especially in the luminal-B (HER2-positive) subtype. Further studies to validate our findings are warranted. *The Oncologist* 2013;18:511–517

Implications for Practice: In the present phase II trial, we evaluated the difference in efficacy as well as tolerability between two different schedules of paclitaxel, carboplatin, and trastuzumab (PCarH) for HER2-positive, locally aggressive (stage IIB–IIIC) breast cancers. The results showed that a more frequent (weekly) administration of PCarH achieved a significantly higher pathologic complete remission (pCR) rate in the breast and axilla compared with the every-3-weeks schedule. The weekly regimen was also delivered as planned in most patients and well-tolerated. More interestingly, the weekly schedule increased the likelihood of achieving pCR mainly in luminal-B (ER/PR-positive and HER2-positive) tumors. As we know, the ER/PR-positive (luminal-A/B) tumors were relatively chemoresistant when treated with every-3-weeks neoadjuvant chemotherapy regimens. Our results indicate that the luminal-B (HER2-positive) subtype might benefit more from a more frequent schedule of paclitaxel-containing chemotherapy.

INTRODUCTION

Response to neoadjuvant chemotherapy (NCT), especially achievement of a pathologic complete remission (pCR) in the breast and axillary lymph nodes, is highly predictive of diminished risk of disease recurrence. This suggests that a treatment regimen that significantly increases the pCR rate could improve recurrence-free survival as well as overall survival [1, 2]. Although both National Surgical Adjuvant Breast and

Bowel protocols B-18 and B-27 demonstrate that NCT is equivalent to adjuvant chemotherapy, patients who achieved a pCR continue to have significantly superior survival outcomes compared with patients who did not [3].

The combination of a chemotherapeutic regimen and a recombinant monoclonal antibody against HER2, trastuzumab, has formed the cornerstone of therapy for HER2-positive

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breast cancer. The superiority of the addition of trastuzumab to a taxane-based chemotherapy to the chemotherapy regimen itself is supported by data from metastatic, neoadjuvant, and adjuvant studies [4–7]. Weekly paclitaxel plus trastuzumab has proven to be highly active, safe, and superior to paclitaxel alone in patients with HER2-positive advanced breast cancer [4, 8]. Moreover, weekly administration of paclitaxel seems more effective than once-every-3-weeks schedule [9, 10].

Thus far, the combination of a taxane, a platin, and trastuzumab has been used in the metastatic, neoadjuvant, and adjuvant settings [6, 11, 12]. In the neoadjuvant field, a regimen of four cycles of once-every-3-weeks docetaxel, cisplatin, and trastuzumab is clinically active and leads to excellent survival [11]. If cisplatin is replaced by carboplatin and docetaxel is replaced by paclitaxel, the combination of paclitaxel (P), carboplatin (Car), and trastuzumab (H) has also achieved high pCR rates and encouraging recurrence-free survival [13]. To our knowledge, the optimal schedule of PCarH administration is unknown in the neoadjuvant setting.

We previously conducted a phase II trial evaluating the activity and safety of a weekly paclitaxel plus carboplatin (PCar) regimen as NCT in women with locally advanced breast cancer (ClinicalTrials.gov NCT01203267) [14]. The clinical response rate was 86% and the pCR rate was 19%. Because PCar is an active and safe regimen, we designed further neoadjuvant clinical trials based on this regimen. We hypothesized that a weekly scheduled PCar with weekly H might be superior to a once-every-3-weeks schedule in women with HER2-positive aggressive breast cancers. We performed a two-arm randomized phase II trial to compare the efficacy and safety between the two schedules (ClinicalTrials.gov NCT01170143). The primary endpoint was pCR in the breast and axillary lymph nodes; secondary endpoints were safety, recurrence-free survival, and overall survival. Because of short follow-up time, we here present the outcomes of response and safety.

PATIENTS AND METHODS

Eligibility

Untreated HER2-positive patients with histologically confirmed (via core needle biopsy) locally advanced or large breast cancers (stage IIB–IIIC) were considered eligible. Other inclusion criteria included the following: age between 18–70 years; no inflammatory breast cancer; assessable tumor in the breast without evidence of distant metastasis measured by bilateral breast mammogram, bilateral breast magnetic resonance imaging (MRI), chest computed tomography scan, abdominal ultrasound, and bone scan; Eastern Cooperative Oncology Group performance status ≤ 1 ; left ventricular ejection fraction $>55\%$ by multiple gated acquisition scan or echocardiography; no history of cancer other than in situ uterine cervix cancer or skin basal cell carcinoma. Patients were required to have an adequate hematopoietic function (absolute neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, and hemoglobin level ≥ 100 g/L), adequate hepatic and renal function (bilirubin level, aspartate aminotransferase, and alanine aminotransferase <1.5 times of the normal upper limit, and serum creatinine <110 $\mu\text{mol/L}$).

Patients with sensorial neurotoxicity greater than grade 1 according to the National Cancer Institute–Common Toxicity

Figure 1. Treatment plan.

Abbreviations: AUC, area under the concentration-time curve; BC, breast cancer; Car, carboplatin; FISH, fluorescence in situ hybridization; H, trastuzumab; IHC, immunohistochemistry; P, paclitaxel.

Criteria (NCI–CTC) score system (<http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx>) were ineligible. Women of child-bearing potential were required to have a negative pregnancy test and to agree to take adequate contraceptive measures. The protocol was reviewed and approved by the independent Ethical Committee and Institutional Review Board of Shanghai Cancer Center, Fudan University. All patients provided written informed consent before inclusion in this trial.

Treatment Plan

The treatment plan is illustrated in Figure 1. Patients were randomly assigned by computer to receive the weekly PCarH for four cycles (12 doses over 16 weeks) or the once-every-3-weeks schedule for four cycles (4 doses over 12 weeks). The carboplatin dose was calculated using the Calvert formula [15] and creatinine clearance was calculated by the Jelliffe formula [16]. With the weekly schedule, patients received an 80 mg/m² dose of paclitaxel (Taxol; Bristol-Myers Squibb, Wallingford, CT, <http://www.bms.com>) followed by carboplatin dosed at an area under the concentration-time curve (AUC) of 2 on days 1, 8, and 15 of a 28-day cycle, with trastuzumab given at a dose of 2 mg/kg (loading dose, 4 mg/kg) every week. With the every-3-weeks schedule, patients received 175 mg/m² paclitaxel followed by carboplatin at an AUC of 6 on day 1 of a 21-day cycle, with trastuzumab of 6 mg/kg (loading dose, 8 mg/kg) every 3 weeks. Pretreatment was administered as previously reported [14].

Breast surgery with level I–II axillary dissection was performed at 2–4 weeks after the last chemotherapy dose. Surgery type was at the surgeon's discretion. Adjuvant chemotherapy began within 4 weeks postoperatively. An additional two cycles of PCar were delivered to patients who achieved pCR; otherwise, four cycles of epirubicin and cyclophosphamide (EC) were administered. Trastuzumab for 1 year in total was recommended for all patients.

Assessment

Immunohistochemical (IHC) assessment of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression was conducted in paraffin-embedded tumor samples biopsied before neoadjuvant treatment according to the guidelines from the American Society of Clinical Oncology and the College of American Pathologists [17, 18]. HER2 positivity was determined by IHC 3+ (HerceptTest; Dako, Glostrup, Copenhagen,

Figure 2. Consolidated Standards of Reporting Trials diagram.

Abbreviations: Car, carboplatin; H, trastuzumab; ITT, intention-to-treat; P, paclitaxel.

Denmark, <http://www.dako.com>) or fluorescence in situ hybridization (FISH) positive status (PathVysion HER2 DNA probe kit; Vysis Inc., Downers Grove, IL).

The clinical response in the breast was assessed using a breast magnetic resonance imaging (MRI) after the second cycle and the fourth (the last) cycle of NCT and categorized as a clinical complete response, clinical partial response, stable disease, and progressive disease according to the Response Evaluation Criteria in Solid Tumors. Pathologic response was assessed postoperatively: pCR in the breast was defined as the disappearance of residual invasive disease (residual ductal carcinoma in situ allowed) in the breast by pathologic examination, and pCR in the axilla was assessed as the absence of positive lymph nodes by hematoxylin and eosin staining. The primary endpoint of this study was pCR in the breast and axilla. Toxicity was evaluated at every cycle of chemotherapy treatment and recorded according to the NCI-CTC version 3.0.

Statistics

Sample size was calculated according to the anticipated pCR rates in the breast and axilla. There were two previous studies showing that preoperative administration of weekly and every-3-weeks paclitaxel plus trastuzumab has a pCR rate of 30% [19] and 18% [20], respectively, with an odds ratio of 1.7 for an every-3-weeks versus weekly schedule. In addition, weekly paclitaxel with every-4-weeks carboplatin plus trastuzumab had a pCR rate of 76% [13]. Taken together, our trial was designed to detect about 35% absolute difference of pCR between the weekly schedule (~75%) and the every-3-weeks schedule (~40%, calculated by 75%/1.7). Thus, a minimum of 26 assessable patients in each group were required for a 0.05 two-sided significance level with an 80% power. If a 0.05 one-

Table 1. Characteristics of the enrolled patients

Characteristic at baseline	Weekly PCarH (n = 29)	Every-3-weeks PCarH (n = 27)	p value
Median age, yr (range)	50 (26–71)	50 (26–67)	.9 ^a
Mean tumor size (cm)	4.2	4.1	.7 ^a
Menopausal status			
Premenopausal	15 (51.7)	13 (48.1)	.8 ^b
Postmenopausal	14 (48.3)	14 (51.9)	
Clinical lymph nodes			
N0–1	24 (82.8)	20 (74.1)	.4 ^b
N2–3	5 (17.2)	7 (25.9)	
Estrogen receptor			
Negative	16 (55.2)	17 (63.0)	.6 ^b
Positive	13 (44.8)	10 (37.0)	
Progesterone receptor			
Negative	17 (58.6)	14 (51.9)	.6 ^b
Positive	12 (41.4)	13 (48.1)	

Data are n (%) unless noted.

^aMann-Whitney test.

^bPearson's χ^2 test.

Abbreviation: PCarH, paclitaxel/carboplatin/trastuzumab.

sided significance level was set as a superiority design (weekly schedule probably better than every-3-weeks schedule [9, 10]), the current sample size had 88% power to detect the assumed difference. The characteristics and adverse events were presented as percentages or mean/median and ranges. Categorical variables were compared using Pearson's χ^2 test

or Fisher's exact test where appropriate. Multivariate analysis was performed using logistic regression analysis. The response rates and odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Statistical analysis was performed using STATA v.10.0 (StataCorp, College Station, TX, <http://www.stata.com>) and SPSS v.12.0 (SPSS, Chicago, IL, <http://www.spss.com>).

RESULTS

The Consolidated Standards of Reporting Trials diagram is displayed in Figure 2. Of the 56 patients enrolled between August 2009 and August 2011 (Table 1), 29 were randomized into the weekly group and 27 were placed in the once-every-3-weeks group. Twenty-eight patients (50%) were premenopausal. The mean tumor size was 4.2 cm. ER-positive and PR-positive tumors accounted for 41% and 45% of cases, respectively. Seven patients did not complete the planned treatment. Two patients halted the treatment due to toxicity; one patient received two cycles, whereas the other received three cycles. Two patients halted the treatments after two cycles because of economic reasons. Three patients discontinued NCT and insisted on undergoing surgery after two or three cycles with obvious tumor shrinkage.

Efficacy

In the intent-to-treat evaluation, there were 19 clinical complete responses (34%; 95% CI: 22%–48%), 35 partial responses (63%; 95% CI: 49%–75%), and 2 patients had stable disease, with an objective response rate of 96% (95% CI: 88%–99%). At surgery, pCR in the breast was found in 35 patients (63%; 95% CI: 49%–75%) and pCR in the breast and axilla was found in 31 patients (55%; 95% CI: 41%–69%). Generally, ER-negative and PR-negative tumors tended to achieve higher pCR rates, with ORs of 3.1 (95% CI: 1.0–9.4; $p = .04$) and 3.2 (95% CI: 1.1–9.5; $p = .04$) compared with their positive counterparts, respectively. Among the 21 patients (37.5%) with residual invasive cancer (non-pCR) in the breast, 14 patients had adequate preoperative and postoperative specimens to detect IHC ER and HER2. Two of the four (50%) ER-negative tumors at baseline became ER-positive after NCT, but no ER-positive tumors changed to ER-negative. Three of the 13 (18%) HER2 IHC 3+ became IHC 0–2+ after NCT, and one with HER2 IHC 2+ kept its original status. No postoperative specimens were examined for HER2 status using FISH.

The pCR results of the two schedules are shown in Figure 3A. In the intent-to-treat analysis for the weekly group, 76% of patients had no residual invasive disease in the breast and 69% had no residual invasive disease in the breast and axilla; for the every-3-weeks schedule, 48% of patients achieved pCR in the breast and 41% achieved pCR in the breast and axilla ($p = .03$ and $.03$, respectively). Our results suggested the superiority of a more frequent administration of PCarH in HER2-positive breast cancer. After adjustment for clinical and pathological factors (age, clinical tumor size before NCT, tumor ER/PR status before NCT, and clinical lymph node status before NCT), the weekly administration of PCarH was more effective than the every-3-weeks schedule (HR: 0.3, 95% CI: 0.1–0.9; $p = .03$). Subgroup analyses are shown in Figure 3B, indicating that a weekly schedule is more effective in the small tumors and luminal-B (HER2-positive) tumors.

Figure 3. Pathological response of the two schedules in overall subjects and subgroups. **(A):** pCR in the breast and in the breast and axilla according to treatment groups. $*p = .03$; $**p = .03$. **(B):** Forest plot of univariate analysis. The odds ratios (ORs) with 95% confidence intervals (CIs) for the patients assigned to the weekly schedule, as compared with the every-3-weeks schedule, were assessed using unadjusted logistic regression by different clinical and pathologic parameters. The dashed vertical line denotes an OR of 1.0. The diamond/square denotes the OR of each subgroup. An OR <1.0 means achieving higher pCR rate from the weekly schedule; an OR >1.0 means achieving higher pCR rate from the every-3-weeks schedule. **(C):** Each bar represents one patient, with the green bar denoting the patient achieving pCR and the yellow denoting non-pCR. The p values of the pCR difference between luminal-B (HER2-positive) tumors and ERBB2+ tumors were .78 and .03 for the weekly schedule and every-3-weeks schedule, respectively. The p values of the pCR difference between the weekly schedule and every-3-weeks schedule were .01 and .59 for luminal-B (HER2-positive) tumors and ERBB2+ tumors, respectively.

Abbreviations: CI, confidence interval; ER, estrogen receptor; LN, lymph node; OR, odds ratio; PcarH, paclitaxel, carboplatin, and trastuzumab; pCR, pathologic complete remission; Post., postmenopausal; PR, progesterone receptor; Pre., premenopausal.

Exploratory Analysis of Efficacy

An exploratory analysis based on ER/PR status is displayed in Figure 3C. Patients with luminal-B (HER2-positive) tumors and

ERBB2+ tumors had comparable pCR rates when administered on the weekly schedule (71% vs. 67%, $p = .78$). However, luminal-B (HER2-positive) tumors were resistant to the every-3-weeks schedule compared with ERBB2+ tumors (21% vs. 61%, $p = .03$). It appears that the overall pCR difference between these two schedules is mainly because of the higher pCR rate of the weekly schedule in luminal-B (HER2-positive) tumors relative to the every-3-weeks regimen ($p = .01$). However, the pCR rates of these two schedules were comparable in the ERBB2+ group ($p = .59$). After adjustment for clinical and pathological factors (age, clinical tumor size before NCT, and clinical lymph node status before NCT), the weekly administration was still more effective than the every-3-weeks schedule for luminal-B (HER2-positive) tumors ($p = .02$) rather than for ERBB2+ tumors ($p = .50$). Taken together, the unadjusted and adjusted results consistently showed that weekly administration was more effective than the every-3-weeks schedule in the luminal-B (HER2-positive) subgroup (unadjusted $p = .01$ and adjusted $p = .02$). After correction for multiple comparisons (there were two subgroups, luminal-B [HER2-positive] and ERBB2+), the corrected p values were still significant (unadjusted $p = .02$, adjusted $p = .04$).

Safety

Two patients stopped treatment due to toxicity: one in the weekly group who developed grade 4 neutropenia and the other in the every-3-weeks group who developed grade 4 thrombocytopenia. No deaths or life-threatening events were recorded. The incidence of grade 3/4 neutropenia was 48% (41% of grade 3 and 7% of grade 4) in the weekly group and 49% (37% of grade 3 and 12% of grade 4) in the every-3-weeks group. One patient in the weekly group reported developing febrile neutropenia; this patient also eventually halted the treatment. Grade 3 leukopenia was observed in 27% of the weekly group and 17% of the every-3-weeks group, whereas no grade 4 leukopenia was recorded. No severe (grade 3/4) anemia occurred. Grade 1/2 alopecia was almost universal in both groups. Peripheral neuropathy was frequent in both groups but never severe. The incidence of gastrointestinal toxic effects (nausea and vomiting and diarrhea) was frequent and comparable in the two groups, whereas no cases suffered from severe gastrointestinal (grade 3/4) toxicity.

DISCUSSION

These results from a phase II trial compared two schedules of a neoadjuvant PCarH regimen in patients with stage IIB–IIIC HER2-positive breast cancer. A more frequent administration of PCarH achieved a significantly higher pCR rate in the breast and axilla compared with the every-3-weeks schedule. Specifically, a weekly schedule increased the likelihood of achieving pCR of luminal-B (ER/PR-positive and HER2-positive) tumors.

The overall pCR rate in the breast and axilla was 55% in our study, consistent with previous reported results (ranging from 18% to 81% [21–23]) of preoperative administration of trastuzumab and chemotherapy. The high pCR rate of 69% observed in the weekly group is encouraging, and it is greater than the every-3-weeks rate of approximately 30%. This high pCR improvement might result from a more frequent administration, addition of trastuzumab to chemotherapy, effective and dense paclitaxel/carboplatin, and a potential synergetic interaction between trastuzumab and paclitaxel/carboplatin [24].

Notably, without trastuzumab, the pCR rates in the breast and axilla were 28% and 16% for weekly paclitaxel and every-3-weeks paclitaxel, respectively, even with four subsequent cycles of fluorouracil, doxorubicin, and cyclophosphamide (FAC) [25].

Several other phase II–III trials have evaluated the combination of trastuzumab and paclitaxel-based cytotoxic therapy (with or without platin) in HER2-positive breast cancer. One study reported a high pCR rate of 76% for weekly paclitaxel and once-every-4-weeks carboplatin with trastuzumab [13]. Another phase III trial demonstrated that the addition of trastuzumab to NCT (paclitaxel followed by fluorouracil, epirubicin, and cyclophosphamide [FEC]) in HER2-positive patients resulted in a more than doubled pCR rate compared with chemotherapy alone (65% vs. 26%, $p = .016$) [26]. Our weekly PCarH not only has a comparable pCR with the aforementioned regimens, but also has a shorter administration time of 16 weeks (paclitaxel followed by FAC/FEC takes 24 weeks). In addition, our weekly schedule appears to be well-tolerated, with the most frequent grade 4 toxicity of neutropenia being manageable.

An interesting finding came from the unplanned analysis based on the ER/PR status. We demonstrated that luminal-B (HER2-positive) tumors and ERBB2+ tumors had comparably high pCR rates of 67%–71% when treated with a weekly schedule; however, luminal-B (HER2-positive) tumors were likely to resist the every-3-weeks schedule. The ER/PR-positive (luminal-A/B) tumors were chemoresistant and demonstrated to have low pCR rates [27–30]. Luminal-B (HER2-positive) subtype tumors, although a bit more responsive to NCT than luminal-A [14], had a limited benefit from NCT. Interestingly, in our study, we observed that the weekly schedule of PCarH is a highly effective regimen for the luminal-B (HER2-positive) subtype. Although numerous clinical trials show a significantly higher pCR rate in ER-HER2+ disease compared with that in ER+HER2+ disease [19, 23, 31], to the best of our knowledge, there are few clinical studies directly comparing the effectiveness of the weekly schedule with the once-every-3-weeks schedule in the luminal-B (HER2-positive) subtype. Our results indicate that, despite the relative chemoresistance of ER+HER2+ disease, this subtype (also known as luminal-B [HER2-positive]) might benefit more from a more frequent schedule of paclitaxel-containing chemotherapy.

Although some factors such as extension of NCT time [2] and augmentation of drug intensity [26, 32] of the weekly schedule might increase the possibility of pCR in the luminal-B subtype, a speculated biological mechanism may also be a potential explanation of our observations. We propose the following speculation according to the current experimental and preclinical evidence. In luminal-B (HER2-positive) subtype cancer cells, there is a crosstalk between the HER2 pathway and the ER pathway, and the estrogen-independent ER pathway is dominant while the classic estrogen-dependent ER pathway is subordinate [33, 34]. Overactivation of intracytoplasmic kinases in the HER2 pathway can lead to ER phosphorylation, resulting in estrogen-independent activation of ER, which might contribute to hormonal therapy resistance [34] and chemotherapy resistance [29, 35]. When trastuzumab is administered, the inhibited HER2 pathway fails to activate ligand-independent ER pathway. The inactive ER pathway in-

duces a reduction in chemoresistance. During this time, if effective and frequent chemotherapeutic drugs are administered, cancer cells would be eradicated to a large extent. Otherwise, if chemotherapy is administered over a longer timeframe, cancer cells would most likely develop a switch to the estrogen-dependent pathway. Then chemoresistance recovers. The reported half-life of paclitaxel and carboplatin was 6–8 and 2–6 hours, respectively, implying a more frequent schedule is more theoretically effective for the luminal-B (HER2-positive) subtype. Of course, the precise mechanism needs further investigation.

The limitations of the study should be acknowledged. First, although the sample size is sufficient for overall analysis, it is underpowered for the subgroup analysis. The findings from the ER/PR subgroups require further validation. Second, because of the short-term follow-up time, survival data are unavailable. Therefore, it is unclear whether the pCR improvement would transfer to a survival benefit. Third, it may be argued that the total dose of paclitaxel in the weekly schedule was higher than that in the every-3-weeks schedule (960 vs. 700 mg/m²), which may have contributed to the pCR difference. In our trial design, we referred to previous trials as well as NCCN guidelines in which the commonly recommended doses were 175 mg/m² for every-3-weeks and 80 mg/m² for weekly paclitaxel administration. Actually, patients receiving paclitaxel ≥ 175 mg/m² likely had an unacceptable level of grade 3/4 neurotoxicity [25]. Furthermore, the time to surgery is longer in the weekly arm and the duration of neoadjuvant therapy itself might affect pCR. Although the weekly schedule has a longer duration than the every-3-week schedule, they had comparable total drug doses and the same treatment cycles. If the difference is caused by time, both subgroups (luminal-B [HER2-positive] and ERBB2+) would have higher pCR in the longer duration arm, but we failed to observe this.

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In summary, we reported a promising schedule of PCarH regimen, which achieved a high pCR rate in HER2-positive aggressive breast cancers and showed a potential ability to eradicate luminal-B (HER2-positive) cancer cells, a previously recognized chemoresistant subtype. The regimen was delivered as planned in most patients and well tolerated. Because of the short-term follow-up, survival data remain unavailable. Thus, additional clinical and basic investigations of this regimen are warranted.

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