Cancer Chemother Pharmacol (2012) 69:1363–1368
DOI 10.1007/s00280-012-1841-y

ORIGINAL ARTICLE

A phase II study of neoadjuvant chemotherapy with docetaxel, cisplatin and trastuzumab for T2 breast cancers

Che Lin · Dar-Ren Chen · King-Jen Chang · Tsai-Wang Chang · Hwei-Chung Wang

Received: 31 July 2011 / Accepted: 30 January 2012 / Published online: 19 February 2012

Abstract
Purpose Preclinical data indicate that the combination of docetaxel, cisplatin and trastuzumab (TCH) may have the potential for clinically significant activity against breast cancers that overexpress the her2/neu gene (HER2). An open-label phase II trial was designed to investigate the response rate and toxicity profile of TCH in breast cancer patients with a primary tumor 2–5 cm in diameter (T2) in its original size.
Methods Thirty breast cancer patients with HER2-overexpressing tumors were enrolled. Patients received 6 cycles of docetaxel at 60 mg/m^2 and cisplatin at 50 mg/m^2 given on day 1 and then every 21 days. Trastuzumab was given on day 1, cycle 1 (4 mg/kg), and then continued weekly at 2 mg/kg for 1 year or until disease progression. Tumor measurements were obtained at baseline as well as after 3 and 6 cycles of chemotherapy.
Results We identified 29 breast cancer patients in Taiwan, of whom 13 (44.8%) had pathological complete responses. No cardiac toxicity was observed. Hematologic grade 4 or 3 toxicities were observed in 1 of 28 patients. Non-hematologic grade 4 or 3 toxicities with a reverse pattern were observed in 6 of 29 patients.
Conclusions The results of our study indicate that TCH neoadjuvant chemotherapy is feasible and active in T2 HER2-overexpressing breast cancer patients in terms of pathological complete response rate, complete response, partial response and manageable toxicities.

Keywords Breast cancer · HER2 · Docetaxel · Cisplatin · Trastuzumab

C. Lin · D.-R. Chen (✉)
Comprehensive Breast Cancer Center, Changhua Christian Hospital, 135, Nanhsiao Street, Changhua 500, Taiwan, ROC
e-mail: darren_chen@cch.org.tw

C. Lin
Department of Environmental Engineering, National Chung-Hsing University, Taichung, Taiwan, ROC

K.-J. Chang
Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan, ROC

T.-W. Chang
Department of Surgery, National Cheng Kung University Hospital, Tainan, Taiwan, ROC

H.-C. Wang
Department of Surgery, China Medical University Hospital, Taichung, Taiwan, ROC

Introduction

Preclinical data indicate that the combination of docetaxel, cisplatin and trastuzumab (TCH) may have the potential for clinically significant activity against breast cancers that overexpress the her2/neu gene (HER2) [1–3]. The potential advantage of neoadjuvant chemotherapy is in the ability to assess the response rate in vivo and in downstaging the primary tumor and regional lymphatic metastases, which improves the cosmetic result. Neoadjuvant chemotherapy may also kill tumor cells before drug resistance develops. Clinical and pathological responses may remain the most important variables in predicting breast cancer outcome after chemotherapy. Furthermore, patients experiencing a pathologic complete response (pCR) have a statistically significant survival benefit [1, 2]. Liedtke [1] reported that triple-negative breast cancer with a pCR has excellent

survival. Ezzat demonstrated a high clinical and pathological response rate (24%) for paclitaxel and cisplatin in patients with locally advanced breast cancer and concluded that adjuvant paclitaxel and cisplatin in a multidisciplinary strategy were highly effective [2].

Of interest, some recent studies have suggested that there might be a significantly higher pCR after trastuzumab target therapy [3–6]. Pegram [3] showed that combinations of docetaxel, a platinum salt, and trastuzumab are feasible and active in patients with advanced breast cancers that overexpress the her2/neu gene (HER2). Buzdar [4] reported a higher pCR after neoadjuvant therapy with paclitaxel, epirubicin and trastuzumab chemotherapy in human epidermal growth factor receptor 2-positive operable breast cancer. Robert [6] showed that the addition of carboplatin to paclitaxel and trastuzumab improved the objective response rate and progression-free survival in women with HER2-overexpressing metastatic breast cancer. However, whether TCH neoadjuvant chemotherapy is feasible remains an open question. Information on TCH neoadjuvant chemotherapy is still confusing and limited [7–19].

Traditionally, breast carcinoma classification using gene expression profiles and IHC biomarkers has identified at least 4 subtypes [20]. These subtypes are luminal A (estrogen receptor [ER]-positive and/or progesterone receptor [PgR]-positive and HER2-negative), luminal B (ER-positive and/or PgR-positive and HER2-positive), basal-like (ER-negative, PgR-negative and HER2-negative) and HER2-positive (ER-negative, PgR-negative and HER2-positive) [14–20]. In this study, luminal B and the so-called HER2-positive subtypes were defined as HER2-overexpressing breast cancer. An open-label phase II trial was designed to investigate the response rate and toxicity profile of TCH in HER2-overexpressing breast cancer patients with a primary tumor 2–5 cm in diameter (T2) in its original size.

Materials and methods

Patients

Patients were enrolled from National Taiwan University Hospital (Taipei, Taiwan), China Medical University Hospital (Taichung, Taiwan), National Cheng Kung University Hospital (Tainan, Taiwan) and Changhua Christian Hospital (Changhua, Taiwan) aggregately, between January 2007 and July 2009. The inclusion criteria were as follows: (1) women aged 18 years or older, cooperative patients with informed consent and histologically confirmed invasive ductal breast cancer (T2, N0-N1, M0) with needle core biopsy; (2) HER2 overexpression detected by fluorescence in situ hybridization (FISH) + or immunohistochemistry (IHC) 3+, and measurable disease; (3) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; (4) white cell count of at least 4,000 cells/μl and platelet count of at least 100,000 cells/μl; total bilirubin level within the institutional normal range; aspartate transaminase of not greater than 2 times the upper limit of normal; serum creatinine levels less than 1.5 mg/dl; and (5) left ventricular ejection fraction of at least 50%. The exclusion criteria were as follows:(1) distant metastases; (2) previous chemotherapy for breast cancer; (3) prior malignancy not treated with curative intent; (4) synchronous breast cancer; (5) pregnancy or nursing; (6) uncontrolled infection, active cardiovascular or pulmonary disease, uncontrolled diabetes mellitus or peripheral neuropathy of any etiology exceeding grade 1; and (7) hepatitis B or hepatitis C carriers. The primary endpoint of this phase II trial was the objective response rate for the regimen. The secondary endpoints included treatment-related toxicity. Estimated time for patient accrual was 3 months. All the patients received at least 3 courses of TCH therapy. This study was approved by the institutional review board of Changhua Christian Hospital. All patients enrolled on this study gave the written informed consent to take part in the trial.

Study design

The baseline data were based on the availability of demographic characteristics (e.g., age) and tumor characteristics (e.g., tumor size, ER/PgR/HER2 information and histology).

Tumor size was determined based on pathological reports from National Taiwan University Hospital, China Medical University Hospital, National Cheng Kung University Hospital and Changhua Christian Hospital. Staging in this study was in accordance with the American Joint Committee on Cancer staging group guidelines. ER and PgR statuses were assessed by IHC, which was performed with anti-ER (NeoMarkers, SP1 clone, dilution: 1:200, Fremont, California) and anti-PgR antibody (NeoMarkers, SP2 clone, dilution: 1:250, Fremont, California) using an autostaining system (Ventana Medical Systems, Tucson, Arizona). IHC analysis was carried out on all preneoadjuvant and most of the post-neoadjuvant chemotherapy-treated specimens. IHC was performed on paraffin-embedded and formalin-fixed breast cancer tissue; 10% or greater of cells with nuclear staining for ER and PgR, respectively, was considered a positive result. HER2 overexpression was defined as being scored as either 3+ (IHC) or HER2 gene amplification (FISH). HER2 overexpression on each tumor was assessed according to the current 2007 CAP/ASCO guideline scoring system.

All treatments were given intravenously. In the first cycle, a trastuzumab loading dose (4 mg/kg) was given for over

90 min on day 1; docetaxel at 60 mg/m^2 was infused intravenously for 60 min on day 1, followed by cisplatin at a 50 mg/m^2 infusion intravenously for 24 h. Trastuzumab at 2 mg/kg was subsequently given for 30 min on days 8 and 15. In the remaining cycles, docetaxel and cisplatin were infused on day 1 immediately following trastuzumab. Prophylactic steroid consisted of dexamethasone at 8 mg administered orally the night before docetaxel infusion, the morning of the infusion, 1 h before docetaxel and twice daily for 36 h thereafter. All patients received intravenous hydration with at least 1 l of normal saline before and after receiving cisplatin. Treatment continued for 6 cycles unless there was unacceptable toxicity or disease progression. Trastuzumab was continued weekly at 2 mg/kg for 1 year after chemotherapy ended. For all toxicities, treatment was discontinued until recovery to grade 1. After recovery, treatment was resumed in subsequent cycles. Treatment after recurrence was based on the St. Gallen or NCCN guidelines and multidisciplinary discussions. The patients with recurrence underwent adjuvant systemic chemotherapy.

Patients with invasive breast carcinoma, whose needle core biopsy and subsequent excision biopsy specimens (lumpectomy or mastectomy) were pathologically evaluated, were identified. "No change" was defined as no significant difference found in the same patient between pre- and post-neoadjuvant chemotherapy. Tumor response was classified according to World Health Organization criteria. Response was assessed and reported by the investigators. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

Statistics

Statistical analyses were performed using PASW 18 software (SPSS, Inc., Chicago, IL). We expressed data as mean ± standard deviation for continuous variables. Independent t tests were used for the comparison of continuous variables, and categorical variables were normally tested with the χ^2 test when appropriate. All *P* values were two-tailed; a *P* value of less than 0.05 was considered to indicate statistical significance. A Simon two-stage optimal design was used for definition of the total number of patients required for this phase II trial. The study was designed to have 80% power to accept the hypothesis and 5% significance to reject the hypothesis.

Ethical aspects

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of the participating institutions. All patients provided their written informed consents prior to the study enrollment.

Table 1 Descriptive statistics of patients

Features	Total
Age, years (SD)	52 (5.66)
Tumor size, cm (SD)***	
Before TCH	2.885 (0.83)
After TCH	1.3 (1.70)
ER[a] status	
Negative	18
Positive	11
PgR[a] status	
Negative	20
Positive	9
Subgroup	
ER+ and/or PgR+ and HER2+[a]	11
ER−, PgR− and HER2+[a]	18
Menopausal status	
Premenopause	17
Postmenopause	12
Extent of surgery	
Total mastectomy	20
Partial mastectomy	9
Histological positive nodes after TCH	
Positive	3
Negative	26

SD standard deviation, *ER* estrogen receptor, *PgR* progesterone receptor

*** A *P* value <0.0001

[a] The statuses of hormone receptors and HER2 were determined on primary tumor tissue

Results

We enrolled 30 breast cancer patients with HER2-overexpressing tumors and excluded one due to lack of availability of data. The study group included 29 assessable women with an average age of 52 years (standard deviation 5.66 years, Table 1). All patients had HER2 overexpression documented by IHC (2+ or 3+) or evidence of HER2 gene amplification by FISH. Twenty-eight (96%) of 29 patients in this trial had an IHC score of 3+ or positive by FISH at the time of initial screening for study entry. Ninety-six percent of patients received 6 courses of TCH chemotherapy. Thirteen patients (44.8%) had pCR, 9 (31.0%) had a complete response, 13 (44.8%) had a partial response, 2 (6.9%) had stable disease, and 1 (3.4%) had progressive disease (Table 2). In this study, pCR was defined as pathological complete response without residual invasive disease. Therefore, we included one patient with residual ductal carcinoma in situ following neoadjuvant chemotherapy in the

Table 2 Descriptive statistics of patients, clinical and pathological responses

Features	Total (%)
Pathological complete response	13 (44.8)
Complete response	9 (31.0)
Partial response	13 (44.8)
Stable disease	2 (6.9)
Progressive disease	1 (3.4)

pCR group. There was no patient with lymph nodes involvement after neoadjuvant chemotherapy in the pCR group.

No cardiac toxicity was observed (Table 3). Hematologic grades 4 or 3 toxicities were observed in 1 of 28 patients, and grades 2 or 1 toxicities were observed in 18 of 28 patients. Non-hematologic grades 4 or 3 toxicities were observed in 6 of 29 patients, and grades 2 or 1 were observed in 20 of 29 patients. For all toxicities, treatment was discontinued until recovery to grade 1. After recovery, treatment was resumed in subsequent cycles. All patients recovered within a short time. In 1 patient with severe hematologic toxicity, docetaxel doses were modified to 45 mg/m^2. Overall, the TCH regimen was well tolerated, with manageable toxicities.

One patient had brain metastasis, received whole brain radiotherapy and then died of breast cancer in May 2010. Another patient had lung metastasis and local recurrence and was alive at the latest follow-up in July 2010.

The data on biomarker changes showed that ER status remained unchanged in the majority of cases, 58.6%, when comparing preneoadjuvant and post-neoadjuvant chemotherapy-treated specimens (Table 4); 41% of PgR status, 34.5% of HER2 IHC status and 60.0% of HER2 FISH status remained unchanged.

The analyses of ER subgroups, ER-positive versus ER-negative, revealed that there was no statistically significant difference in pCR, in addition to partial response, stable disease and progressive disease, between ER subgroups (Table 5).

Discussion

The use of the TCH combination had the following rationales: First, each component has good activity against breast cancer. Second, the major toxicities of each component in this novel regimen are generally non-overlapping. Finally, the synergistic reactions of these active agents have been well established. We hypothesized that this regimen should have high clinical and pathological response rates with acceptable and manageable toxicities.

Table 3 Descriptive statistics of patients, toxicity

Features	Total (%)
Cardiac toxicity (n = 28)	
Cardiac death	0 (0)
Ventricular arrhythmia	0 (0)
Cardiac hypotension	0 (0)
Hematologic grade 4 or 3 toxicities	
Neutropenia (n = 28)	0 (0.0)
Leukopenia (n = 28)	0 (0.0)
Anemia (n = 27)	1 (3.7)
Thrombocytopenia (n = 28)	0 (0)
Hematologic grade 2 or 1 toxicities	
Neutropenia (n = 28)	1 (3.5)
Leukopenia (n = 28)	1 (3.6)
Anemia (n = 27)	18 (66.7)
Thrombocytopenia (n = 27)	1 (3.7)
Non-hematologic grade 4 or 3 toxicity (n = 28)	
Diarrhea	2 (7.1)
Nausea/Vomiting	4 (14.3)
Alopecia	2 (7.1)
Skin rash	0 (0)
Hypersensitivity	1 (3.6)
Non-hematologic grade 2 or 1 toxicity (n = 28)	
Diarrhea	12 (42.9)
Nausea/Vomiting	21 (75.0)
Alopecia	17 (60.7)
Skin rash	1 (3.6)
Hypersensitivity	0 (0)

Cumulative incidence, all chemotherapy cycles

In this study, we reported 0% cardiac toxicity. Our findings supported those from other studies in terms of cardiac toxicity. In the study by Buzdar et al. [4], they investigated the effects of trastuzumab addition on neoadjuvant chemotherapy in operable breast cancer patients with HER2-overexpressing disease and found that none of these patients developed clinical congestive heart failure (95% CI, 0% to 14.8%). A greater than 10% decrease in the left ventricle ejection fraction was observed in five and seven patients in the chemotherapy alone and trastuzumab plus chemotherapy arms, respectively, when trastuzumab was administered concurrently with paclitaxel and epirubicin, a possibly toxic combination for the heart [4]. Gianni reported that the NOAH trial results that revealed only 2 patients (2%) developed symptomatic cardiac failure and both responded to cardiac drugs. Our data contrasted with those of the series of Slamon et al. [14] in which 13% of 92 patients with paclitaxel plus trastuzumab developed heart failure; the race factor and the sample size factor could have contributed to the difference.

Table 4 Biomarker changes in women with T2 breast cancer given TCH neoadjuvant chemotherapy

Biomarker	Total, *n* (%)
ER status (*n* = 29)	
3 + to 2+	1 (3.4)
2 + to x	1 (3.4)
+ to x	2 (6.9)
− to x	8 (27.6)
No change (%)	17 (58.6)
PgR status (*n* = 29)	
3 + to −	1 (3.4)
+ to 2+	1 (3.4)
+ to −	2 (6.9)
+ to x	2 (6.9)
− to x	9 (31.0)
− to +	2 (6.9)
No change (%)	12 (41.4)
HER2 status by immunohistochemistry (*n* = 29)	
3+ to 2+	3 (10.3)
3+ to +	3 (10.3)
3+ to −	3 (10.3)
3+ to x	10 (34.5)
No change (%)	10 (34.5)
HER2 status by fluorescence in situ hybridization (*n* = 25)	
+ to −	2 (8.0)
+ to x	7 (28.0)
− to +	1 (4.0)
No change (%)	15 (60.0)

ER estrogen receptor, *PgR* progesterone receptor

Table 5 Data on ER-positive versus ER-negative subgroups of women with T2 HER2-overexpressing breast cancer given TCH neoadjuvant chemotherapy

	ER-positive (*n* = 11)	ER-negative (*n* = 18)	*P*[a]
Pathological complete response (%)	3 (27.3)	10 (55.6)	>0.05
Complete response (%)	3 (27.3)	6 (33.3)	>0.05
Partial response (%)	8 (72.7)	5 (27.8)	>0.05
Stable disease (%)	0	2 (11.1)	>0.05
Progressive disease (%)	0	1 (5.6)	>0.05

ER estrogen receptor, *PgR* progesterone receptor

[a] The *P* values were calculated by Fisher's exact test

Emerging data show that patients with operable, HER2-overexpressed breast carcinoma have significantly better responses when treated with trastuzumab simultaneously with neoadjuvant chemotherapy than with chemotherapy alone. The inclusion of trastuzumab as part of a neoadjuvant chemotherapy regimen yields a higher pCR rate and a greater percentage of patients that are disease free than neoadjuvant chemotherapy alone [9, 21–23]. The increasing number of patients with breast cancer being treated in the TCH neoadjuvant setting gives rise to a need to assess biomarkers accurately in the needle biopsy material, which is usually the only available tissue before treatment. However, concordance rates between FISH-determined HER2 status on needle core biopsies and on subsequent excision biopsies of the same tumor have not been well studied. Our findings support the results of the D'Alfonso study [23] that HER2 status remains unchanged in the majority of cases when comparing preneoadjuvant and post-neoadjuvant chemotherapy-treated specimens. D'Alfonso found that excellent overall concordance was achieved between the FISH-determined HER2 status in the needle core biopsy and that determined in the subsequent excision biopsy of the same tumor. D'Alfonso [23] also mentioned that there is a surprising lack of published evidence showing the concordance rate between the FISH-determined HER2 status of the two types of biopsy specimens from the same tumor.

There are potential limitations to this study. In Taiwan, trastuzumab-targeted therapy has been administered only to metastatic breast cancer patients, up to August 2010, due to this country's national health insurance policy. Because of cardiac toxicity and budget concerns, the use of trastuzumab outside of the national health insurance system up to 2006 was rare among Taiwanese women with HER2-overexpressing breast cancer, which may have contributed to our dropout rate. One patient in this trial dropped out after only 3 courses of TCH neoadjuvant chemotherapy. Time is needed for patients to accept this costly drug.

Cameron et al. [24] showed the observation that patients whose tumors achieve a pathologic pCR to presurgical treatment have a better outcome gave many hope that it could be a validated surrogate for disease-free, if not overall, survival. Untch et al. [25] reported that pCR was the only significant prognostic factor for three-year disease-free survival (hazard ratio 2.5; 95% confidence interval, 1.2–5.1; $P = 0.013$) in multivariate analysis when breast cancer patients with pCR compared to patients without pCR after neoadjuvant chemotherapy plus trastuzumab.

This study is the first Taiwanese phase II trial on eligibility and toxicity of TCH neoadjuvant chemotherapy. It indicates that T2 breast cancer patients with HER2-overexpressing tumors are eligible for TCH neoadjuvant chemotherapy in terms of pCR, complete response and partial response rates, and manageable toxicities.

Acknowledgments This work was supported by grants from Sanofi-Aventis Taiwan Co. Ltd. and Roche Taiwan Co. Ltd. Editorial support was provided by Ms. Yu-Fen Wang for editing assistance.

Conflict of interests None.

References

1. Liedtke C, Mazouni C, Hess KR, Andre F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN, Pusztai L (2008) Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26:1275–1281
2. Ezzat AA, Ibrahim EM, Ajarim DS, Rahal MM, Raja MA, Tulbah AM, Al-Malik OA, Al-Shabanah M, Sorbris R (2004) Phase II study of neoadjuvant paclitaxel and cisplatin for operable and locally advanced breast cancer: analysis of 126 patients. Br J Cancer 90:968–974
3. Pegram MD, Pienkowski T, Northfelt DW, Eiermann W, Patel R, Fumoleau P, Quan E, Crown J, Toppmeyer D, Smylie M, Riva A, Blitz S, Press MF, Reese D, Lindsay MA, Slamon DJ (2004) Results of two open-label, multicenter phase II studies of docetaxel, platinum salts, and trastuzumab in HER2-positive advanced breast cancer. J Natl Cancer Inst 96:759–769
4. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Pusztai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D, Hortobagyi GN (2005) Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 23:3676–3685
5. Buzdar AU (2007) Adjuvant chemotherapy for high-risk operable breast cancer. J Clin Oncol 25:1642–1644
6. Robert N, Leyland-Jones B, Asmar L, Belt R, Ilegbodu D, Loesch D, Raju R, Valentine E, Sayre R, Cobleigh M, Albain K, McCullough C, Fuchs L, Slamon D (2006) Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 24:2786–2792
7. Coudert BP, Arnould L, Moreau L, Chollet P, Weber B, Vanlemmens L, Molucon C, Tubiana N, Causeret S, Misset JL, Feutray S, Mery-Mignard D, Garnier J, Fumoleau P (2006) Pre-operative systemic (neo-adjuvant) therapy with trastuzumab and docetaxel for HER2-overexpressing stage II or III breast cancer: results of a multicenter phase II trial. Ann Oncol 17:409–414
8. Yaal-Hahoshen N, Safra T (2006) Herceptin (trastuzumab): adjuvant and neoadjuvant trials. Isr Med Assoc J 8:416–421
9. Chang JC (2007) HER2 inhibition: from discovery to clinical practice. Clin Cancer Res 13:1–3
10. Untch M, von Minckwitz G (2009) Recent advances in systemic therapy: advances in neoadjuvant (primary) systemic therapy with cytotoxic agents. Breast Cancer Res 11:203
11. Untch M, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H, Bauerfeind I, Hilfrich J, Eidtmann H, Gerber B, Hanusch C, Kuhn T, du Bois A, Blohmer JU, Thomssen C, Dan Costa S, Jackisch C, Kaufmann M, Mehta K, von Minckwitz G (2010) Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. J Clin Oncol 28:2024–2031
12. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, Zambetti M, Vazquez F, Byakhow M, Lichinitser M, Climent MA, Ciruelos E, Ojeda B, Mansutti M, Bozhok A, Baronio R, Feyereislova A, Barton C, Valagussa P, Baselga J (2010) Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 375:377–384
13. Gonzalez RJ, Buzdar AU, Fraser Symmans W, Yen TW, Broglio KR, Lucci A, Esteva FJ, Yin G, Kuerer HM (2007) Novel clinical trial designs for treatment of ductal carcinoma in situ of the breast with trastuzumab (herceptin). Breast J 13:72–75
14. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783–792
15. Lin C, Chien SY, Chen LS, Kuo SJ, Chang TW, Chen DR (2009) Triple negative breast carcinoma is a prognostic factor in Taiwanese women. BMC Cancer 9:192
16. Cheang MC, Voduc D, Bajdik C, Leung S, McKinney S, Chia SK, Perou CM, Nielsen TO (2008) Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res 14:1368–1376
17. Nguyen PL, Taghian AG, Katz MS, Niemierko A, Abi Raad RF, Boon WL, Bellon JR, Wong JS, Smith BL, Harris JR (2008) Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol 26:2373–2378
18. Rakha EA, Reis-Filho JS, Ellis IO (2008) Basal-like breast cancer: a critical review. J Clin Oncol 26:2568–2581
19. Kurebayashi J, Moriya T, Ishida T, Hirakawa H, Kurosumi M, Akiyama F, Kinoshita T, Takei H, Takahashi K, Ikeda M, Nakashima K (2007) The prevalence of intrinsic subtypes and prognosis in breast cancer patients of different races. Breast 16(Suppl 2):S72–S77
20. Perreard L, Fan C, Quackenbush JF, Mullins M, Gauthier NP, Nelson E, Mone M, Hansen H, Buys SS, Rasmussen K, Orrico AR, Dreher D, Walters R, Parker J, Hu Z, He X, Palazzo JP, Olopade OI, Szabo A, Perou CM, Bernard PS (2006) Classification and risk stratification of invasive breast carcinomas using a real-time quantitative RT-PCR assay. Breast Cancer Res 8:R23
21. Adams AL, Eltoum I, Krontiras H, Wang W, Chhieng DC (2008) The effect of neoadjuvant chemotherapy on histologic grade, hormone receptor status, and HER2/neu status in breast carcinoma. Breast J 14:141–146
22. Madarnas Y, Trudeau M, Franek JA, McCready D, Pritchard KI, Messersmith H (2008) Adjuvant/neoadjuvant trastuzumab therapy in women with HER-2/neu-overexpressing breast cancer: a systematic review. Cancer Treat Rev 34:539–557
23. D'Alfonso T, Liu YF, Monni S, Rosen PP, Shin SJ (2010) Accurately assessing her-2/neu status in needle core biopsies of breast cancer patients in the era of neoadjuvant therapy: emerging questions and considerations addressed. Am J Surg Pathol 34:575–581
24. Cameron DA (2011) Chemotherapy, trastuzumab, and pathological complete response: when shall we three meet again? J Clin Oncol 29:3344–3346
25. Untch M, Fasching PA, Konecny GE, Hasmuller S, Lebeau A, Kreienberg R, Camara O, Muller V, du Bois A, Kuhn T, Stickeler E, Harbeck N, Hoss C, Kahlert S, Beck T, Fett W, Mehta KM, von Minckwitz G, Loibl S (2011) Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 29:3351–3357