Neoadjuvant bevacizumab, docetaxel, and capecitabine combination therapy for HER2/neu-negative invasive breast cancer: efficacy and safety in a phase II pilot study

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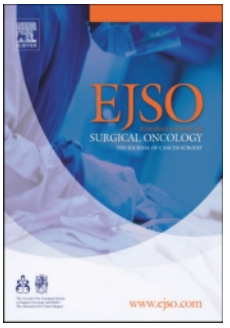

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Neoadjuvant bevacizumab, docetaxel, and capecitabine combination therapy for HER2/neu-negative invasive breast cancer: efficacy and safety in a phase II pilot study

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Abstract

Purpose: To evaluate the triplet combination of bevacizumab, capecitabine, and docetaxel (XTA) as neoadjuvant therapy for breast cancer.

Experimental design: Patients with invasive, HER2-negative, nonmetastatic breast cancer (T2–4c >2 cm) and no prior systemic therapy received six 21-day cycles of XTA (bevacizumab 15 mg/kg, day 1, cycles 1–5; docetaxel 75 mg/m^2, day 1 of each cycle; capecitabine 950 mg/m^2 twice daily for 14 days of each cycle). Patients underwent surgery 2–4 weeks after completing XTA, followed by radiotherapy, chemotherapy and hormone therapy according to institution guidelines. Pathologic complete response (pCR), the primary endpoint, was defined as no evidence of invasive tumour in the final surgical sample. Secondary endpoints included rates of clinical response and breast-conserving surgery, and safety.

Results: Median age of the 18 enrolled patients was 48 years (range 34–69). Most patients (72%) received six cycles of neoadjuvant therapy. pCR rate was 22% (95% confidence interval [CI]: 6–48). Nine of the patients without pCR achieved clinical partial response, giving a 72% overall clinical response rate (95% CI: 47–90). Fifteen patients underwent breast-conserving surgery (83%; 95% CI: 59–96). One additional patient had breast-conserving surgery, followed by mastectomy 1 month later. The remaining 2 patients underwent modified radical mastectomy. XTA was reasonably well tolerated, with no unexpected toxicities or treatment-related deaths.

Conclusions: The 22% pCR rate in a HER2-negative population suggests that addition of bevacizumab increases the activity of neoadjuvant capecitabine-docetaxel. Further evaluation of this regimen in early breast cancer is recommended.

Keywords: Anti-angiogenic; Targeted; Preoperative; Breast cancer; Neoadjuvant; Bevacizumab

Introduction

Chemotherapy for breast cancer

Taxanes are widely used in the treatment of breast cancer in the neoadjuvant, adjuvant, and metastatic settings [1, 2]. Capecitabine, an oral fluoropyrimidine, is an established monotherapy option for metastatic breast cancer (MBC) and the combination of capecitabine and docetaxel significantly improves overall survival versus docetaxel alone in anthracycline-pretreated MBC [3].

Role of bevacizumab in breast cancer

More recently the integration of biologic agents into the treatment of MBC has dramatically improved clinical outcomes. Bevacizumab, which targets all isoforms of vascular endothelial growth factor-A, significantly improves progression-free survival (PFS) in patients with MBC when added to paclitaxel (hazard ratio 0.48, $p < 0.0001$; median 11.3 months versus 5.8 months with paclitaxel alone) [4]. Response rate was also significantly superior in the bevacizumab-containing arm (50% versus 22% with paclitaxel; $p < 0.0001$). Similarly, the AVADO trial met its primary objective, to demonstrate significantly superior PFS with the addition of bevacizumab to docetaxel [5].

Rationale for combining bevacizumab, capecitabine and docetaxel

Supported by the activity of each of the doublets bevacizumab plus a taxane [4, 5], capecitabine plus docetaxel [3], and bevacizumab plus capecitabine [6, 7] in MBC, the triple combination of capecitabine, docetaxel, and bevacizumab (XTA) has been evaluated as first-line therapy for MBC in a single-arm, North Central Cancer Treatment Group (NCCTG)

phase II study. The response rate was 53% (95% confidence interval [CI]: 38–68) and 6-month PFS and overall survival rates were 77% and 96%, respectively [8].

Capecitabine in early breast cancer

In a randomised, phase III trial in patients with node-positive, stage II/III breast cancer, neoadjuvant capecitabine-docetaxel resulted in a significantly higher pathologic complete response (pCR) rate than doxorubicin plus cyclophosphamide (AC; 21% versus 10%, respectively; $p = 0.024$) [9]. In the adjuvant setting, the addition of capecitabine to an anthracycline- and docetaxel-containing regimen significantly improved recurrence-free survival in the recently reported FinXX trial [10].

Bevacizumab in early breast cancer

Several phase II studies in the neoadjuvant setting have shown that addition of bevacizumab to anthracycline- and taxane-containing neoadjuvant regimens is feasible and active. Regimens tested in this setting include bevacizumab, doxorubicin and docetaxel, followed by bevacizumab monotherapy [11], docetaxel, cyclophosphamide, and bevacizumab, followed by doxorubicin [12], and bevacizumab, trastuzumab, nanoparticle albumin-bound paclitaxel and carboplatin in HER2-positive disease [13].

In the adjuvant setting, rigorous cardiac monitoring revealed no safety concerns when bevacizumab was integrated into sequential regimens of dose-dense AC followed by paclitaxel [14] or nanoparticle albumin-bound paclitaxel [15]. Furthermore, preliminary results of a multicentre, randomised trial in the adjuvant setting revealed no additional or unexpected toxicities when bevacizumab was combined with three docetaxel-based adjuvant regimens, with or without trastuzumab [16].

Since all three agents in various doublet combinations have shown activity in early breast cancer, we initiated a pilot phase II study of neoadjuvant XTA.

Materials and methods

Study design and endpoints

This single-centre, pilot, phase II study was designed to determine the efficacy of neoadjuvant XTA in patients scheduled to receive preoperative chemotherapy. The primary endpoint was pCR rate, defined as no evidence of invasive tumour in the final surgical sample (T0 or ductal carcinoma in situ). Secondary endpoints included clinical objective response rate (by Response Evaluation Criteria In Solid Tumors [RECIST]), rate of breast-conserving surgery, and tolerability according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0.

The protocol was approved by an Independent Ethics Committee. The study was conducted in full concordance with the principles of the Declaration of Helsinki and Guideline for Good Clinical Practice ICH Tripartite Guideline, 1997.

Patient population

Eligible patients were female, aged 18–70 years, with invasive HER2-negative breast cancer (fluorescence in situ hybridisation [FISH] or chromogenic in situ hybridisation [CISH] negative, or immunohistochemistry [IHC] 0 or 1+, or IHC 2+ confirmed by negative FISH/CISH), T2–4 (except T4d) >2 cm, any N stage, no evidence of distant metastases or secondary carcinoma, no prior systemic therapy, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and normal cardiac, renal and hepatic function. Patients with pre-existing motor or sensory neurotoxicity of grade >2 (NCI CTCAE, version 3.0) were excluded, as were patients with evidence of wound-healing complications, bone fracture, ulcer or clinically significant peripheral vascular disease.

All patients provided written informed consent before starting study-specific procedures.

Treatment

The planned treatment course comprised six 21-day cycles of XTA. Bevacizumab 15 mg/kg was administered as a 30–90-minute intravenous (i.v.) infusion on day 1 of cycles 1–5. Docetaxel 75 mg/m^2 was given via a 1-hour i.v. infusion on day 1 for all six cycles. Capecitabine 950 mg/m^2 twice daily was given for 14 days followed by a 7-day rest period for six cycles, with the first dose on the evening of day 1 and the last on the morning of day 15. Treatment with corticosteroids (e.g., dexamethasone) was recommended to prevent docetaxel-induced hypersensitivity reactions. Antiemetic premedication, dosing and schedule were at the investigators' discretion.

The bevacizumab dose was not to be modified. If patients experienced a grade 3/4 bevacizumab-related toxicity, bevacizumab was held until resolution to grade ≤1. If the patient experienced grade 3/4 haemorrhagic toxicity, symptomatic grade 4 arterial thromboembolism, grade 4 hypertension or proteinuria, grade 3/4 congestive heart failure, gastrointestinal perforation, or a second episode of a grade 3 bevacizumab-related toxicity, bevacizumab was discontinued permanently. Capecitabine therapy was interrupted at the first appearance of any grade ≥2 toxicity. After resolution, treatment could be continued at the same or a reduced dose, depending on the severity of the adverse event. Treatment was discontinued permanently if patients experienced a grade 4 event, a second grade 3 event, or a third grade 2 event. The docetaxel dose was reduced in the event of severe haematologic or nonhaematologic toxicities.

Surgery was performed 2–4 weeks after completing study therapy. All patients underwent adequate local surgery with axillary lymph node clearance (minimum of eight lymph nodes). Complete axillary lymph node dissection was performed in all patients

because node negative status was determined only clinically at baseline. At the time the study was designed, sentinel node biopsy after neoadjuvant chemotherapy was not standard.Breast-conserving surgery was attempted if possible according to the institution's guidelines. Tumour resection was directed by clipping tumours. Adjuvant radiotherapy, chemotherapy and/or hormone therapy were given according to institution guidelines.

Study assessments

Prestudy screening within 4 weeks before enrolment included assessment of HER2 and hormone receptor status, tumour histology and grading, computed tomography scan of the thorax and abdomen, and bilateral mammography. Baseline histological assessment was by jour-cut biopsy. Vascular and lymphatic invasion was assessed in the surgical specimens. Information on baseline predictive characteristics, such as Ki67, was not collected. Patients were evaluated clinically for response before each cycle. Mammography (and sonography) and magnetic resonance imaging (MRI) were performed after the third and sixth cycles, respectively. Electrocardiogram and left ventricular ejection fraction (LVEF) were performed at baseline and after the third and sixth cycles. LVEF was performed in the event of symptomatic cardiac failure. Dipstick or 24-hour urine proteinuria assessment was performed before each bevacizumab administration.

Statistics

With an expected pCR rate of 20%, a sample size of 18 patients would enable calculation of a 95% CI with a precision of ±19%. Descriptive statistical methods were applied in this exploratory trial. Exact 95% CIs were calculated for the primary response endpoint. Statistical Analysis Software (SAS version 9.1.3, Cary, NC, USA) was used for all statistical analyses.

Safety and efficacy analyses were based on the intent-to-treat population, which included all patients who received at least one dose of all three study drugs.

Results

Patient population

Between 28 February 2006 and 25 September 2007, 18 patients were enrolled and treated. The last patient was entered in October 2006 and the present analysis was performed in April 2008. Table 1 shows baseline characteristics. At study entry, breast-conserving surgery was considered appropriate in 8 patients; in the remaining 10 patients, radical mastectomy was planned.

Treatment delivered

All six cycles of docetaxel were delivered in 13 patients. Three patients received five cycles, 1 received four cycles, and 1 received three cycles. All five planned cycles of bevacizumab were given in 15 patients and all six planned cycles of capecitabine were given in 11 patients (Fig. 1). The median duration of neoadjuvant therapy was 120 days (range 54–133). Reasons for early discontinuation are described in the safety section below. The median dose delivered at the last cycle of therapy was 15.00 mg/kg (range 14.95–16.54) for bevacizumab, 1848 mg/m^2/day (range 1156–1987) for capecitabine, and 75 mg/m^2 (range 58–80) for docetaxel.

After surgery, all patients received adjuvant therapy, predominantly radiotherapy alone (n = 5), anastrozole alone (n = 4), or tamoxifen and radiotherapy, with or without goserelin (n = 6).

Efficacy

The pCR rate was 22% (95% CI: 6–48). All pCRs occurred in patients with node-negative disease at study entry and showed no surgical margin involvement. Thirteen of 14 patients without pCR were evaluable for clinical response by RECIST. Of these, 9 achieved clinical partial response and the remaining 4 showed disease stabilisation. Thus the rate of objective response (pCR or clinical complete or partial response) was 72% (95% CI: 47–90).

All four pCRs were observed in patients with hormone receptor-negative disease, giving a pCR rate in this subpopulation of 67%. One of the remaining 2 patients achieved clinical partial response, giving a clinical response rate of 83%, and the other achieved clinical stable disease. Among the 12 patients with hormone receptor-positive disease, there were no pCRs; 8 patients achieved clinical partial response (67% clinical response rate), 3 achieved clinical stable disease and 1 was not evaluable.

Tumour size was substantially reduced after XTA therapy. The mean largest tumour diameter assessed by MRI after XTA was 2.3 cm (range 0.0–8.0), compared with 4.6 cm (range 2.5–10.0) before treatment. Tumour shrinkage is summarised in Table 2. Median tumour shrinkage (calculated from the sum of median tumour diameters at screening and end of treatment) was 77% by ultrasound, 74% by MRI, 86% by mammography, and 96% by palpation.

Breast-conserving surgery was performed in 15 patients (83%; 95% CI: 59–96). One additional patient had breast-conserving surgery, followed by mastectomy 1 month later because of marginal involvement. The remaining 2 patients underwent modified radical mastectomy. Among 15 patients undergoing sentinel biopsy, sentinel lymph nodes were negative in 10. Lymph node dissection, performed in all patients, revealed no positive lymph nodes in 11 patients, two positive lymph nodes in 2 patients and in the remaining patients, one, three, four, five and 11 positive nodes, respectively.

Safety

All patients were evaluable for safety. There were no surgical complications. In general, the safety profile of XTA was consistent with the known toxicities of each agent. The most commonly reported adverse events of any grade, irrespective of relationship to study treatment, were alopecia (17 patients), nail disorders (12 patients), constipation, lymphopenia, hyperglycaemia and elevated lactate dehydrogenase concentrations (each in 8 patients). Diarrhoea and hand-foot syndrome (HFS) occurred in 4 patients and 3 patients, respectively. There were no cases (any grade) of congestive heart failure, hypertension or wound-healing disorders.

The most frequent severe adverse events (NCI CTCAE grade 3/4, World Health Organization [WHO] severe or life threatening, or severity grade missing), irrespective of relationship to study treatment, were alopecia (17 patients), polyneuropathy, neutropenia (each in 3 patients), stomatitis, fatigue and leukopenia (each in 2 patients). The remaining severe adverse events each occurred in only 1 patient: HFS, asthenia, dry mouth, neutropenic infection, intestinal perforation, deep vein thrombosis, anorexia, pain in extremity, oral pain, vertigo, menorrhagia and general physical health deterioration.

Five patients discontinued all three component drugs before completing the six planned cycles. In cycle 3, 1 patient discontinued treatment because of reversible grade 4 neutropenic fever, classified as a serious adverse event. In cycle 4, 1 patient discontinued treatment because of reversible grade 2 fatigue and grade 3 polyneuropathy. Three patients discontinued therapy in cycle 5 (due to grade 4 intestinal perforation, which recovered with sequelae due to colostomy; reversible grade 1 melena; and reversible grade 3 fatigue and grade 2 polyneuropathy).

Discussion

Findings from this study

Our single-centre, pilot, phase II study demonstrated that XTA is an active, well-tolerated preoperative regimen, producing a 22% pCR rate, 72% clinical response rate and substantial tumour reduction. Breast-conserving surgery was possible in 83% of patients.

Neoadjuvant XTA was reasonably well tolerated at the doses used in our study. Clinically relevant severe adverse events were relatively infrequent and no unexpected toxicities were observed. Typical of a docetaxel-containing regimen, almost all patients experienced alopecia, and nail toxicities were common. Grade 3/4 neuropathy and neutropenia each occurred in 17% of patients and in some cases, resulted in treatment discontinuation. However, HFS and diarrhoea, both characteristic of capecitabine, were infrequent, with no grade 3/4 diarrhoea and only 1 patient reporting grade 3 HFS. Unlike previous reports of bevacizumab plus chemotherapy in the metastatic setting [4, 6, 17], hypertension was infrequent and there were no grade 3/4 episodes. Among the 5 patients who did not complete the planned six cycles, all adverse events resolved completely except for sequelae due to colostomy in the patient with grade 4 intestinal perforation. Although the proportion of patients discontinuing therapy before completing all planned cycles was unexpectedly high, the adverse events leading to early treatment discontinuation were rarely of major concern and in three of the five cases, were typical of taxane-based therapy.

In the present study, bevacizumab and docetaxel were given at the doses evaluated by Perez et al. as first-line therapy for MBC, but the capecitabine dose was slightly higher (950 mg/m^2 twice daily versus 825 mg/m^2 twice daily in the NCCTG study) [8]. The two regimens exhibited quite different tolerability. In our study, the most frequent clinically relevant grade 3/4 adverse events were neuropathy, neutropenia, stomatitis and fatigue, whereas in the MBC study, the most common grade 3/4 toxicities were neutropenia (77%),

HFS (29%), fatigue (20%) and diarrhoea (18%). This variation in safety profiles might be due in part to regional differences in fluoropyrimidine tolerability, with US populations tolerating fluoropyrimidines less well than European and Asian populations [18].

Subpopulation analyses

As well as the obvious limitations of cross-trial comparison, there are difficulties in comparing our data with other neoadjuvant regimens. Definitions of pCR and eligibility criteria vary greatly. For example, most studies in the literature include mixed populations of patients (HER2-positive or -negative disease). HER2 overexpression and hormone receptor-negative status are associated with substantially higher pCR rates [19–22]. In an analysis of 103 patients receiving neoadjuvant anthracycline-taxane therapy for locally advanced breast cancer (mostly stage III), the pCR rate was 14% among patients with HER2-negative disease versus 29% in those with HER2-positive disease [21].

The 22% pCR rate in our study falls within the range reported for anthracycline- and taxane-containing regimens in populations unselected for HER2 status [1, 23–25] and at the upper end of the 10–21% range reported for capecitabine-docetaxel in unselected populations [9, 26]. Furthermore, it compares favourably with the 9–19% pCR rates reported with neoadjuvant capecitabine-docetaxel specifically in HER2-negative disease [27, 28].

Hormone receptor status is another important factor influencing response to neoadjuvant chemotherapy. In our study, 6 of 18 patients were ‘triple negative’ (negative progesterone receptor, oestrogen receptor (ER) and HER2 status; basal-like tumours), a subgroup of patients more likely to achieve pCR [29–31]. XTA produced pCR in 4 of these 6 patients. Notwithstanding the very small patient numbers, this is a very encouraging outcome. In the MD Anderson Cancer Center retrospective analysis, the pCR rate was 22% among patients with triple-negative disease receiving anthracycline-based chemotherapy

with or without a taxane [22]. Rouzier et al. reported a 45% pCR rate in this population of patients receiving paclitaxel- and doxorubicin-containing preoperative chemotherapy [31].

Among the evaluable patients with ER-positive, HER2-negative disease (luminal A subtype), there were no pCRs, but 8 of 11 patients achieved clinical partial response. Although the absence of pCR in these 11 patients is slightly disappointing, it is not entirely unexpected given the reported low pCR rates of 0–7% in this patient subgroup in earlier studies [21, 22, 29, 31].

Future directions

Based on the very high activity, particularly in triple-negative disease, and good tolerability demonstrated in this study, further evaluation of XTA in early disease is strongly recommended. Investigation focusing on patients with triple-negative disease may be of particular interest, since these patients appeared to benefit most from XTA in our study. A single-arm, phase II study (NCT00576901) evaluating a regimen very similar to ours in patients with HER2-negative inflammatory or locally advanced breast cancer has recently begun in Spain. Recruitment is complete for a phase II study (NCT00365417) by the National Surgical Adjuvant Breast and Bowel Project (NSABP) evaluating neoadjuvant AC followed by docetaxel plus capecitabine, with bevacizumab given throughout chemotherapy and as monotherapy after surgery. Results of the study will provide further information on the role of bevacizumab-, capecitabine- and taxane-containing regimens. In the longer term, one of the arms of NSABP-40 is evaluating preoperative XTA followed by AC plus bevacizumab and adjuvant bevacizumab. Further studies in the neoadjuvant and adjuvant settings, including GeparQuinto, BEATRICE and ECOG E5103, are evaluating the incorporation of bevacizumab into anthracycline- and/or taxane-containing regimens. Results of our study represent an encouraging early indicator of activity and feasibility, and the potential of XTA gives reason for optimism when considering future treatments for early breast cancer.

Conflict of interest statement

R Greil has received speaker honoraria from Roche. None of the remaining authors has a conflict of interest to declare.

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Table 1

Baseline characteristics

Median age, years (range)	48 (34–69)
ECOG performance status 0, *n* (%)	18
HER2 status, *n* (%)	
IHC 0 (negative)	16
IHC 2+, FISH–	2
ER positive, *n* (%)	12
PR positive, *n* (%)	11
ER and PR negative, *n* (%)	6
Mean tumour size, cm	
Palpatory	5.6 x 4.6
Mammography[a]	3.0 x 2.8
MRI	4.5 x 4.0
Sonography	4.1 x 3.3
T stage, *n* (%)	
2	10
3	7
4a	1
N stage, *n* (%)	
0	9
1	4
Unknown	5
Grade, *n* (%)	
1	3

2	10
3	5

[a]*n* = 16

ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; MRI, magnetic resonance imaging; PR, progesterone receptor

Table 2

Tumour shrinkage

	MRI			Mammography			Palpation			Sonography		
	Screening	Cycle 3	EOT	Screening	Cycle 3	EOT	Screening	Cycle 3	EOT	Screening	Cycle 3	EOT
n	18	18	16	16	13	15	18	18	15	18	17	15
Median maximum tumour diameter, cm (Q1–Q3)	3.4 (3.0–5.6)	2.6 (1.6–3.6)	1.7 (1.0–3.2)	3.0 (2.3–3.5)	1.2 (0.9–1.9)	1.2 (0.0–1.8)	5.0 (4.0–8.0)	2.0 (1.0–3.0)	1.0 (0.0–1.5)	3.0 (2.7–4.6)	1.2 (0.9–2.4)	1.5 (0.0–2.4)
Difference between consecutive assessments	$p < 0.0001$ $p = 0.0171$			$p = 0.0029$ $p = 0.0313$			$p < 0.0001$ $p = 0.0002$			$p = 0.0002$ $p = 0.0635$		
Difference from screening to EOT	$p < 0.0001$			$p = 0.0003$			$p < 0.0001$			$p < 0.0001$		

Wilcoxon test *p* values

EOT, end of treatment; MRI, magnetic resonance imaging

Figure legend

Figure 1. Treatment administered by cycle and agent. *No bevacizumab dose planned in cycle 6.