Multicentre phase II trial of bevacizumab combined with docetaxel–carboplatin for the neoadjuvant treatment of triple-negative breast cancer (KCSG BR-0905)

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Background: This phase II neoadjuvant trial evaluated bevacizumab–docetaxel and carboplatin in triple-negative breast cancer.

Patients and methods: Women with hormone receptor- and human epidermal growth factor receptor 2 (HER2)-negative, stage II/III breast cancer received six cycles of 75 mg/m^2 docetaxel, carboplatin (AUC = 5) and 15 mg/kg bevacizumab every 21 days. The primary end point was pathological complete response (pCR) in breasts and axillary lymph nodes (ALN).

Results: Forty-five patients were recruited from the Korean Cancer Study Group. The median age was 45 (range 30–72) years. ALNs were positive in 80% of patients ($n = 36$) at diagnosis. Overall, 98% of patients ($n = 44$) completed therapy and underwent surgery. The pCR rate was 42% ($n = 19$); clinical response rate 96% ($n = 43$); complete 13% ($n = 6$); partial 82% ($n = 37$); stable disease 2% ($n = 1$). Breast-conserving surgery was undertaken in 78% of patients ($n = 35$). Most frequent grade 3/4 adverse events were neutropenia (84%, $n = 38$) and febrile neutropenia (9%, $n = 4$). One patient experienced delayed wound healing after surgery.

Conclusions: Neoadjuvant bevacizumab, docetaxel and carboplatin resulted in an encouraging pCR rate and negligible wound healing problems after surgery.

Key words: bevacizumab, carboplatin, docetaxel, neoadjuvant chemotherapy, pathological complete response, triple-negative breast cancer

introduction

Triple-negative breast cancer (TNBC) is characterised as the lack of expression of oestrogen receptor (ER) and progesterone receptor (PgR), and the lack of human epidermal growth factor receptor 2 (HER2) over-expression and/or amplification [1, 2], and accounts for 15%–20% of all breast cancers [3]. The prognosis for patients with TNBC is poor owing to the aggressive nature of the disease, including short disease-free intervals and survival duration after recurrence, high-grade histology and frequent visceral metastases [4]. Owing to the lack of an appropriate target, patients with TNBC are not indicated for treatment with endocrine therapy or with the anti-HER2 monoclonal antibody trastuzumab. Thus, systemic treatment options are currently limited to cytotoxic chemotherapy.

Patients with TNBC who achieve pathological complete response (pCR) with neoadjuvant therapy have comparable survival outcomes to patients with non-TNBC. However, patients with TNBC with residual disease after neoadjuvant chemotherapy have higher recurrence risk and significantly decreased survival compared with patients with non-TNBC [4]. Currently, data from clinical studies support the use of neoadjuvant anthracyclines and taxanes as standard therapy regardless of breast cancer subtype [3, 5–8]. Recent studies have suggested overlap between cancers occurring in women

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with *breast cancer type 1* (*BRCA1*) mutations, basal-like breast cancer and TNBC, but the nature of such links remains unclear [1]. Because of its direct DNA damaging nature, TNBC appears to be particularly sensitive to platinum analogues [9–12], especially *BRCA1* mutation-associated TNBC [2, 13].

Inhibiting angiogenesis may be another strategy for the treatment of TNBC, as genes involved in angiogenesis are frequently activated in basal-like tumours [14]. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF) A, has demonstrated clinical efficacy in combination with chemotherapy in patients with HER2-negative metastatic breast cancer [15], including in subgroups of patients with metastatic TNBC [16, 17], as well as in the neoadjuvant setting [18–20]. Indeed, early adoption of bevacizumab as a neoadjuvant or adjuvant therapy could maximise its benefit, because trapping of VEGFA, a key angiogenic factor, would be most effective in the early carcinogenesis niche where only a few angiogenic factors exist [21].

In a phase II trial of docetaxel and carboplatin-based neoadjuvant chemotherapy for stage II/III breast cancer, a differential response was observed, with highest pCR rates achieved in patients with TNBC [10]. Based on these results, and given the sensitivity of TNBC to platinum analogues [9–12], we designed a single-arm phase II trial of docetaxel, carboplatin and bevacizumab as neoadjuvant treatment in patients with stage II/III TNBC. Given the potential for cardiac toxicity with anthracyclines, we chose a non-anthracycline chemotherapy regimen for the study.

methods

patients

Women aged ≥20 years (the legal adult age in Korea) with histologically confirmed stage II/III TNBC were eligible. Patients were required to have tumours measurable by breast magnetic resonance imaging (MRI), mammography and physical examination. Axillary lymph node (ALN) status was defined as positive based on imaging studies including MRI, or clinical examination followed by confirmed positive aspiration cytology findings. Triple negativity was defined as <1% nuclear staining for ER and PgR by immunohistochemistry (IHC), HER2-negativity of 0 or 1+ by IHC or HER2 non-amplification by fluorescent *in situ* hybridisation analysis. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–1 and normal organ function. Further relevant eligibility criteria were normal cardiac function showing left ventricular ejection fraction (LVEF) ≥55% by echocardiography or multi-gated acquisition scan, no previous thromboembolic event, no known haemorrhagic diathesis or coagulopathy, and no major surgery within the past 28 days or anticipation of a major surgery during the study treatment period. Patients with active uncontrolled infection were excluded.

The trial was carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the Protocol Review Committee of the Korean Cancer Study Group and by the Institutional Review Board in each participating institute. All patients provided written informed consent before any study-related procedure (ClinicalTrials.gov identifier: NCT01208480; protocol number: KCSG BR-0905).

study design

This was a single-arm, phase II, multicentre study of bevacizumab, docetaxel and carboplatin as neoadjuvant treatment in patients with TNBC. Patients received six cycles of 15 mg/kg bevacizumab, 75 mg/m^2 docetaxel and carboplatin (AUC = 5) on the first day of every 21 days. Bevacizumab was omitted in the last cycle to avoid wound complications. Patients were to undergo breast surgery 4–6 weeks after administration of the last cycle of chemotherapy to prevent wound complications. Treatment continued for six cycles unless there was disease progression, unacceptable toxicity or withdrawal of consent. If there was tumour progression during treatment, study treatment was discontinued and further local or systemic treatment was permitted at the investigator's discretion. During the first cycle, complete blood counts and biochemistry tests were carried out on days 10–14. Thereafter, if there were no adverse events, they were carried out before each cycle and as clinically indicated.

Chemotherapy dose adjustments were made if, on the planned day of therapy, absolute neutrophil count was $<1.5 \times 10^9$/l and/or platelet count was $<100 \times 10^9$/l, chemotherapy was delayed until these criteria were met. A maximum postponement of 3 weeks was allowed. Chemotherapy dose reductions were carried out in patients who had grade 4 neutropenia or thrombocytopenia lasting >7 days and in patients with febrile neutropenia (>38.5°C) associated or not associated with documented infection. Study treatment was interrupted and the dose reduced for patients who experienced a second occurrence of grade 2 non-haematological toxicity (except alopecia, nausea/vomiting or peripheral neuropathy) or any grade 3 toxicity. All non-haematological toxic effects must have subsided to grade ≤1 before re-starting treatment. Subsequent treatment such as adjuvant chemotherapy and radiotherapy were allowed at the discretion of the investigator. Granulocyte colony-stimulating factor (G-CSF) support was used according to standard guidelines and at the investigator's discretion.

study end points

The primary end point of the study was pCR rate, defined as the absence of invasive disease in the primary breast and ALN (i.e. pathology stage T0N0 or TisN0). Secondary end points were: clinical response rates of breast tumours and ALNs, as assessed by physical examination and imaging studies; toxicity; the rate of breast pCR, regardless of ALN; and the rate of breast-conserving surgery (BCS).

assessment of end points

Radiological imaging tests, medical history and physical examination were carried out within 14 days before treatment. Tumour measurements were scheduled at baseline, and after cycles 3 and 6 for lesions assessed radiographically. The target lesion and regional lymph nodes were examined by palpation at every cycle. Pathological responses of the breast tumour and infiltration of regional lymph nodes were assessed and staged according to the tumour-node-metastatic system. Clinical complete response was assessed by breast MRI and Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [22]. Toxic effects were assessed at the end of each cycle according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. Patients were considered to have had BCS if the final surgical procedure was tumourectomy, segmentectomy or quadrantectomy.

statistical design

All patients who received at least one cycle of bevacizumab, docetaxel and carboplatin were included in the intent-to-treat (ITT) population. The Fleming single-stage design assumed the expected pCR to be at least 37% and the minimum acceptable pCR as 20% [4]. Thus, 45 patients were required to provide a power of 80% and a 5% chance of type I error.

Table 1. Baseline demographic and clinical characteristics

	ITT population ($N = 45$)
Female, n (%)	45 (100)
Median age, years (range)	45 (30–72)
Invasive ductal carcinoma, n (%)	45 (100)
ECOG performance status, n (%)	
0	44 (98)
1	1 (2)
Median largest tumour diameter, cm (range)	3.9 (0.6–11.3)
Pre-chemotherapy T stage, n (%)	
cT1	2 (4.4)
cT2	31 (68.9)
cT3	12 (26.7)
Pre-chemotherapy N stage, n (%)	
Node positive	36 (80.0)
Node negative	9 (20.0)
AJCC clinical stage, n (%)	
IIA	7 (15.6)
IIB	29 (64.4)
IIIA	9 (20.0)
Histological grade, n (%)	
1	1 (2.2)
2	12 (26.6)
3	28 (62.2)
Not available	4 (8.9)

ITT, intent-to-treat; ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer.

results

baseline characteristics

From October 2010 to December 2011, 45 women with stage II/III TNBC were enrolled at seven centres in Korea; these 45 patients received at least one dose of study treatment and were included in all efficacy and safety analyses (ITT population). Forty-four patients completed six cycles of therapy followed by surgery (per protocol population). One patient declined further treatment after cycle 3 and was withdrawn from the study; this patient showed complete response after the third cycle of study treatment, as assessed by breast MRI.

Baseline characteristics of the 45 eligible patients are shown in Table 1. The median patient age was 45 (range 30–72) years and the median tumour size was 3.9 cm, as assessed by breast MRI. Overall, 4%, 69% and 27% of patients had stage cT1, cT2 and cT3 disease, respectively. ALNs were clinically positive in 80% of patients at diagnosis (16 patients were diagnosed based on aspiration cytology). Based on preoperative breast MRI, 16% of patients had stage IIA tumours, 64% had stage IIB tumours and 20% had stage IIIA tumours. All patients had histological type invasive ductal carcinoma. Additionally, 2.2%, 26.6% and 62.2% of patients had tumours of histological grade 1, 2 and 3, respectively.

efficacy outcomes

The primary end point, the rate of pCR in both breast and ALN, in the ITT population was 42% [95% confidence interval (CI) 27.8–56.6] ($n = 19$) (Table 2). Thus, the null hypothesis

Table 2. Summary of treatment outcomes

n (%) [95% CI]	ITT population ($N = 45$)
pCR (absence of invasive disease in breast and ALN)	19 (42.2) [27.8–56.6]
pCR (absence of invasive disease in breast irrespective of ALN)	20 (44.4) [29.9–58.9]
Clinical response	
Complete response	6 (13.3) [3.4–23.2]
Partial response	37 (82.2) [71.0–93.4]
Stable disease	1 (2.2) [−2.1–6.5]
Progressive disease	0
Not evaluable	1 (2.2) [−2.1–6.5]
BCS	
Yes	35 (77.7) [65.5–89.9]
No	9 (20.0) [8.3–31.7]
No surgery[a]	1 (2.2) [−2.1–6.5]

[a]One patient refused surgery and was subsequently withdrawn.
CI, confidence interval; ITT, intent-to-treat; pCR, pathological complete response; ALN, axillary lymph nodes; BCS, breast-conserving surgery.

according to the Fleming design was rejected. The rate of pCR in the breast only was 44% (95% CI 29.9–58.9) ($n = 20$). Based on RECIST and breast MRI, 96% of patients ($n = 43$) experienced a clinical response [six complete responders (13%) and 37 partial responders (82%)], one patient showed stable disease, and one patient was not evaluated due to withdrawn consent.

The median sum of target lesions in the breast and ALN was 4.35 cm at baseline, 1.83 cm after the third cycle and 1.30 cm after the sixth cycle. Most patients showed remarkable tumour shrinkage during the first three cycles; however, in an exploratory finding, a few patients responded to the last three cycles of treatment despite having stable disease during the first three cycles (supplementary Figure S1, available at Annals of Oncology online). Following surgery, besides a pCR rate of 42%, 49% of patients ($n = 22$) exhibited a T stage of I or II. BCS was carried out in 78% (95% CI 65.5–89.9) of patients ($n = 35$) (Table 2).

safety

All grade treatment-emergent adverse events are listed in Table 3. Treatment was generally well tolerated. Twelve patients (27%) experienced grade 1 bleeding events (epistaxis, $n = 8$; oral mucosal bleeding, $n = 3$; menorrhagia, $n = 1$) and one patient (2%) experienced grade 2 bleeding (anal bleeding). Bevacizumab-related arterial hypertension developed in eight patients (18%) at the grade 1 level. Only one patient (2%) experienced delayed wound healing after breast surgery; the wound was completely recovered 3 weeks after the operation and did not affect the radiation therapy schedule. The most frequently reported grade 3/4 adverse events were neutropenia (84%, $n = 38$), febrile neutropenia (9%, $n = 4$) and vomiting (7%, $n = 3$). No cases of congestive heart failure (CHF) were reported.

Table 3. All grade treatment-emergent adverse events

n (%)[a]	Safety population (N = 45)			
	Grade 1	Grade 2	Grade 3	Grade 4
Haematological toxicity				
Neutropenia	0	1 (2.2)	6 (13.3)	32 (71.1)
Febrile neutropenia	NA	NA	4 (8.9)	–
Anaemia	2 (4.4)	3 (6.7)	1 (2.2)	–
Thrombocytopenia	2 (4.4)	–	1 (2.2)	–
Non-haematological toxicity				
Stomatitis/mucositis	24 (53.3)	9 (20.0)	1 (2.2)	–
Fatigue	9 (20.0)	5 (11.1)	–	–
Infection	1 (2.2)	1 (2.2)	–	–
Hypertension	8 (17.6)	–	–	–
Bleeding	12 (26.7)	1 (2.2)	–	–
Conjunctivitis	–	3 (6.7)	–	–
Diarrhoea	14 (31.1)	8 (17.8)	–	–
Constipation	16 (35.6)	5 (11.1)	–	–
Skin discolouration	13 (28.9)	7 (15.6)	–	–
Anorexia	10 (22.2)	5 (11.1)	–	–
Nausea	27 (60.0)	6 (13.3)	2 (4.4)	–
Vomiting	7 (15.6)	3 (6.7)	3 (6.7)	–
Increased ALT	–	–	1 (2.2)	–
Peripheral neuropathy	20 (44.4)	3 (6.7)	–	–
Alopecia	9 (20.0)	26 (57.8)	–	–
Arthralgia	1 (2.2)	1 (2.2)	–	–
Myalgia	16 (35.6)	7 (15.6)	–	–
Allergic reaction	2 (4.4)	2 (4.4)	–	–
Oedema	10 (22.2)	–	–	–

[a]Patients may have experienced more than one adverse event.
ALT, alanine aminotransferase.

treatment exposure

In total, 98% of patients (n = 44) received all six cycles of treatment, including five cycles of bevacizumab, and underwent breast surgery. G-CSF was supported in 72/267 (27%) cycles. Chemotherapy was delayed in seven patients (16%) due to febrile neutropenia (n = 4), grade 3 stomatitis (n = 1), schedule of response evaluation (n = 1) and grade 3 vomiting (n = 1). The chemotherapy dose was reduced in eight patients (18%) due to febrile neutropenia (n = 4), grade 3 vomiting (n = 3) and grade 3 stomatitis (n = 1). A relative dose intensity >85% was achieved in 78% of patients (n = 35). The median bevacizumab-free interval, defined as the time between the starting date of the last cycle and the date of surgery, was 4.3 (range 3.7–6.0) weeks.

Forty-two patients received radiation therapy after breast surgery. Six patients underwent adjuvant chemotherapy, three patients received cyclophosphamide, methotrexate and fluorouracil, and a further three patients received doxorubicin–cyclophosphamide.

discussion

Results of this phase II study showed that bevacizumab combined with docetaxel and carboplatin as neoadjuvant treatment resulted in an encouraging pCR rate (42%) in patients with TNBC. Adverse events were manageable; the only postoperative complication was a single case of wound healing delay. Our data compare favourably with published data in TNBC, including a pCR rate of 35% reported in the I-SPY trial of sequential neoadjuvant anthracyclines and taxanes [23]. To the best of our knowledge, no other article has reported data on the combination of neoadjuvant bevacizumab and chemotherapy exclusively in patients with TNBC. One neoadjuvant study was presented in abstract form, which is the combination of cisplatin with bevacizumab in patients with TNBC and reported a pCR of 15%; overall, 5% of patients did not complete therapy because of toxic effects [24]. The difference in terms of pCR rate between that study and our study (42% versus 15%) could be attributed to the baseline chemotherapy regimen, as we used docetaxel–carboplatin rather than single-agent cisplatin.

We acknowledge the limitations of our study, given the lack of a control arm and the relatively small sample size, and suggest that results from a randomised study of patients with TNBC would be more informative. Indeed, data from randomised trials investigating the role of platinum and taxane in this setting are awaited. One such study, CALGB 40603, will examine the addition of carboplatin with or without bevacizumab to neoadjuvant paclitaxel followed by doxorubicin–cyclophosphamide (AC) in HER2-negative resectable breast cancer.

Recently, two randomised, phase III studies revealed significant improvements in pCR rates with the addition of bevacizumab to neoadjuvant therapy in operable or locally advanced breast cancer (Table 4) [18, 19]. In GeparQuinto, patients received epirubicin–cyclophosphamide followed by docetaxel with or without bevacizumab [18]. In NSABP B-40, patients received docetaxel alone or in combination with capecitabine or gemcitabine, with or without bevacizumab for the first six cycles, all followed by AC [19]. These trials were conducted in patients with HER2-negative breast cancer, including hormone receptor-positive and -negative tumours. In the NSABP B-40 trial, the combination of bevacizumab with chemotherapy significantly increased the pCR rate in the breast (pT0N0/+/pTisN0/+) from 28% to 35% (P = 0.02), which was the primary end point of the study [19]. Subgroup analyses showed that pCR rates (breast only) in patients with TNBC receiving or not receiving bevacizumab were 52% and 47%, respectively, representing a numerical increase without statistical significance (P = 0.34) [19]. The GeparQuinto trial demonstrated a significant improvement in pCR rate (breast and ALN: pT0N0) with the addition of bevacizumab to neoadjuvant chemotherapy in the overall population (15% versus 18%, respectively, odds ratio 1.29, 95% CI 1.02–1.65; P = 0.04) as well as in patients with TNBC (39% versus 28%, respectively; P = 0.003) [18]. Although patient baseline characteristics in our study, including tumour size, nodal status and tumour grade, differed from NSABP B-40 and GeparQuinto, the pCR rate of 42% (breast and ALN) was comparable with that achieved in patients with TNBC in those studies. Furthermore, the BCS rate of 78% was higher than that in GeparQuinto (62%) and NSABP B-40 (47%), as was the clinical response rate [18, 19]. These results could be attributable to the relatively early-stage tumours included in

Table 4. Overview of the efficacy of neoadjuvant bevacizumab-containing regimens in patients with TNBC

	KCSG BR-0905	GeparQuinto[18]	NSABP B-40[19]
Regimen	T + Carbo + Bev	EC → T + Bev	T → AC + Bev
			TX → AC + Bev
			TG → AC + Bev
Enrolled patients, n	45	956	604
Patients with TNBC, n (%)	45 (100.0)	323 (33.8)	244 (40.0)
pCR rate in patients with TNBC, n (%) [95% CI]	19 (42.2) [27.8–56.6]	127 (39.3) [34.0–44.6]	126 (51.5) [45.2–57.8]
Definition of pCR	Primary breast and ALN: pT0N0/ pTisN0	Primary breast and ALN: pT0N0	Primary breast: pT0N0/ pTisN0

TNBC, triple-negative breast cancer; T, docetaxel; Carbo, carboplatin; Bev, bevacizumab; E, epirubicin; C, cyclophosphamide; A, doxorubicin; X, capecitabine; G, gemcitabine; pCR, pathological complete response; CI, confidence interval; ALN, axillary lymph nodes.

our trial, but caution should be exercised when making cross-trial comparisons.

Bevacizumab-related postoperative wound complications are of concern in the neoadjuvant setting. Recent data suggest that neoadjuvant bevacizumab may be associated with an increased risk of major postoperative complications, including wound dehiscence and seroma, especially among women undergoing breast reconstruction with tissue expanders [25]. In contrast, two large randomised, phase III studies and our study recorded few postoperative wound complications with neoadjuvant bevacizumab [10, 19, 26]. To avoid postoperative wound complications our study protocol specified that bevacizumab should be omitted in the last cycle, with surgery carried out at least 28 days after administration of the last cycle. A similar design was employed in the phase III studies.

Most adverse events reported during the study were manageable. Grade 3/4 neutropenia was the most frequently reported adverse event. There were no grade ≥3 bevacizumab-related events, such as hypertension or bleeding. One patient refused further therapy after the third cycle and was withdrawn from the study; this patient had a complete response as assessed by breast MRI.

A recent meta-analysis examining bevacizumab-related cardiac toxicity in patients with metastatic breast cancer demonstrated a 1.6% incidence of high-degree CHF in bevacizumab-treated patients compared with 0.4% for placebo [26]. In our trial, no case of CHF was reported using a non-anthracycline-based regimen in combination with bevacizumab. However, it must be remembered that, while most of the patients treated with bevacizumab in the metastatic setting had been exposed to anthracyclines, none of the patients on the current trial had ever received an anthracycline. The median LVEF of 15 patients, which was not mandatory, was unchanged after treatment compared with baseline (data not shown).

Although TNBC seems to be a heterogeneous disease clustered as several subtypes, as shown in recent gene expression profiles, it would be essential to focus on TNBC in future phase III clinical trials; these patients have a distinct disease that differs from both luminal disease and HER2-positive breast cancer [27]. Data from the ongoing, open-label, randomised, phase III BEATRICE study will define the role of bevacizumab added to standard anthracycline-/taxane-containing adjuvant chemotherapy, specifically in patients with TNBC, with invasive disease-free survival as the primary end point (ClinicalTrials.gov identifier: NCT00528567). Further neoadjuvant clinical trials that enrol only patients with TNBC are warranted to define the role of bevacizumab in this patient group. For this purpose, a docetaxel and carboplatin backbone would be a reasonable choice because of its clinical evidence of sensitivity to TNBC and non-overlapping toxicity with bevacizumab in terms of cardiac function.

disclosure

The authors have declared no conflicts of interest.

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