Clinical Cancer Research

Efficacy of Neoadjuvant Carboplatin plus Docetaxel in Triple-Negative Breast Cancer: Combined Analysis of Two Cohorts

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Abstract

Purpose: Recent studies demonstrate that addition of neoadjuvant (NA) carboplatin to anthracycline/taxane chemotherapy improves pathologic complete response (pCR) in triple-negative breast cancer (TNBC). Effectiveness of anthracycline-free platinum combinations in TNBC is not well known. Here, we report efficacy of NA carboplatin + docetaxel (CbD) in TNBC.

Experimental Design: The study population includes 190 patients with stage I–III TNBC treated uniformly on two independent prospective cohorts. All patients were prescribed NA chemotherapy regimen of carboplatin (AUC 6) + docetaxel (75 mg/m^2) given every 21 days × 6 cycles. pCR (no evidence of invasive tumor in the breast and axilla) and residual cancer burden (RCB) were evaluated.

Results: Among 190 patients, median tumor size was 35 mm, 52% were lymph node positive, and 16% had germline *BRCA1/2* mutation. The overall pCR and RCB 0 + 1 rates were 55% and 68%, respectively. pCRs in patients with *BRCA*-associated and wild-type TNBC were 59% and 56%, respectively ($P = 0.83$). On multivariable analysis, stage III disease was the only factor associated with a lower likelihood of achieving a pCR. Twenty-one percent and 7% of patients, respectively, experienced at least one grade 3 or 4 adverse event.

Conclusions: The CbD regimen was well tolerated and yielded high pCR rates in both *BRCA*-associated and wild-type TNBC. These results are comparable with pCR achieved with the addition of carboplatin to anthracycline–taxane chemotherapy. Our study adds to the existing data on the efficacy of platinum agents in TNBC and supports further exploration of the CbD regimen in randomized studies. *Clin Cancer Res; 23(3); 649–57. ©2016 AACR.*

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Pathologic and molecular similarities between germline BRCA mutation–associated breast cancer and triple-negative breast cancer (TNBC) have led to the exploration of DNA-damaging agents like platinum compounds in TNBC. In this article, we report robust pathologic complete response (pCR) rates in 190 patients treated with anthracycline-free chemotherapy regimen of carboplatin plus docetaxel. Germline *BRCA*1/2 mutations may be an important biomarker of response to platinum agents in TNBC. It has been speculated that improvement in pCR noted with the addition of carboplatin to traditional chemotherapy in TNBC may be driven primarily by high responses in germline BRCA mutation carriers. However, this platinum–taxane chemotherapy regimen rendered equally high pCR rates in *BRCA*-associated (pCR of 59%) and *BRCA* wild-type (pCR of 56%) TNBC. The results of our study support further evaluation of platinum chemotherapy in both *BRCA*-associated and wild-type TNBC.

Introduction

Triple-negative breast cancer (TNBC) accounts for 15% of all breast cancers and is associated with poor long-term outcomes compared with other breast cancer subtypes (1–5). TNBC is a chemosensitive disease, and therefore adjuvant chemotherapy is generally recommended for patients with TNBC with stage I (T > 1 cm)–III disease (6, 7). However, despite receiving standard anthracycline–taxane based chemotherapy, a significant proportion (30%–40%) of patients with early-stage TNBC develop metastatic disease and succumb to the cancer (4, 5, 8). Thus, improved therapeutic approaches are desired for TNBC. As no molecular actionable targets have been identified in TNBC so far, modifications of the traditional breast cancer chemotherapy regimens (i.e., the addition of carboplatin) are a potential way of improving patient outcomes.

Sporadic and germline BRCA mutation–associated TNBCs share several pathologic and molecular similarities (9–13). These similarities have led to the exploration of DNA-damaging agents like platinum compounds in the general population of patients with TNBC (14–17). Although only 15% to 20% of patients with TNBC harbor germline *BRCA* mutations, homologous recombination DNA repair deficiency is likely present in a much larger fraction of patients with TNBC (15, 17–21). Currently, it is not very clear whether the efficacy of platinum salts will predominantly be restricted to *BRCA* mutation–associated TNBC or if these agents will provide meaningful benefit in a larger fraction of sporadic TNBC (15, 22–24). Recent studies demonstrate that addition of carboplatin to anthracycline and taxane-based neoadjuvant chemotherapy (NAC) improves pathologic complete response (pCR) in unselected patients with TNBC (14, 16, 25, 26). However, this improvement in pCR rate comes at the cost of a significant increase in toxicity (14, 16). Furthermore, anthracyclines and cyclophosphamide, although very active for treatment of breast cancer, have established small but serious long-term risks (secondary leukemia/myelodysplastic syndrome, cardiomyopathy; refs. 27–29).

Therefore, the exploration of the activity of anthracycline-free chemotherapy regimens in TNBC is desired. Taxanes exhibit significant activity in TNBC and also demonstrate preclinical synergy with platinum agents, thus providing a rationale for evaluation of platinum–taxane combination in TNBC (30–33). Herein, we report a combined analysis of two separate TNBC cohorts (University of Kansas and Spanish MMJ-CAR-2014-01) treated with a uniform NAC regimen of carboplatin and docetaxel.

Patients and Methods

Patient population

University of Kansas cohort. Patients with stage I (T $\geq$ 1 cm), II, and III TNBC presenting at an academic center and five community practices within the Kansas City metropolitan area were approached for participation in an Institutional Review Board (IRB)-approved prospective registry protocol (P.R.O.G.E.C.T. NCT02302742). Eligible female patients had biopsy-proven invasive breast cancer not previously treated with taxanes, anthracyclines, or carboplatin for any malignancy. Triple negativity was defined as estrogen receptor (ER) and progesterone receptor (PgR) immunohistochemical nuclear staining of less than 10% and HER2 immunohistochemical staining 0 to 1+ or FISH ratio <2.0 if IHC 2+ or IHC not performed (ASCO/CAP guideline recommendations for HER2 testing in breast cancer; ref. 34). From 2011 to 2015, 69 enrolled patients with stage I (T > 1 cm), II, and III TNBC were treated with an NAC regimen of carboplatin + docetaxel.

MMJ-CAR-2014-01 cohort. GOMHGUGM022011 is a prospective, multicenter, nonrandomized trial exploring the antitumor activity of neoadjuvant carboplatin + docetaxel (CbD; AEMPS code MMJ-CAR-2014-01, NCT01560663). Eligible patients included females with pathologically confirmed diagnosis of primary invasive breast cancer, stage II–III (T $\geq$ 2 cm) aged >18 years, and not previously treated with taxanes, anthracyclines, or carboplatin for any malignancy. The patients were diagnosed at any of the participant academic institutions (see Supplementary Material for a list of participating institutions) and were able to sign the IRB-approved informed consent at each of the centers. Triple negativity was defined as ER and PgR nuclear staining of less than 1% by IHC and HER2 IHC staining 0 to 1+ or FISH ratio <2.0 if IHC 2+ or IHC not performed [ASCO/CAP guideline recommendations for HER2 testing in breast cancer (34)]. Between 2010 and 2015, 123 patients with stage II and III TNBC were enrolled and treated with an NAC regimen of CbD.

Study procedures

Patients in both cohorts were prescribed an NAC regimen of carboplatin (AUC 6) + docetaxel (75 mg/m^2) given every 21 days for six cycles. All patients received myeloid growth factor support [University of Kansas (KU) cohort, 6 mg pegfilgrastim on D2; Spanish cohort, filgastrim 300 μg/day × 5 to 7 days after chemotherapy according to the guidelines of each institution). In patients with clinically suspicious axillary lymph node/s, histologic confirmation by biopsy or fine-needle aspiration was encouraged. Patients with clinically negative axillary lymph nodes could undergo pretreatment sentinel lymph node (SLN) sampling. Following NAC, all patients underwent breast surgery. Axillary sampling was required except in patients with pretreatment-negative SLNs, but the extent of axillary surgery and subsequent irradiation was determined by the treating physician, as was postoperative adjuvant therapy.

Pathologic evaluation

Pathologic response was determined locally, without central pathologic review. All surgical pathology reports were centrally reviewed by the principal investigators of the respective cohorts. pCR was defined as the absence of residual invasive disease with or without ductal carcinoma *in situ* in the breast and axilla (ypT0/isN0). Patients with pCR in the breast and negative pretreatment SLNs were considered to have achieved pCR. Residual cancer burden (RCB) was recorded by local pathologists for all patients using the classification by Symmans and colleagues (35). Patients achieving pCR (RCB 0) or near pCR (RCB 1) are assessed within the group RCB 0 + 1.

Germline BRCA1/2 testing

KU cohort. Germline testing for *BRCA1/2* was done utilizing commercially available tests and laboratories. The majority of patients (97%) had testing through Myriad Genetic Laboratories (Comprehensive BRACAnalysis or myRisk Hereditary Cancer test), and 3% had testing through other laboratories (BreastNext, Ambry Genetics; OncoGeneDx, GeneDx).

Spanish cohort. Germline testing for *BRCA1/2* was done at Sistemas Genómicos facilities using Targeted Next Generation by sequencing of seven genes (*BRCA1*, *BRCA2*, *PALB2*, *BARD1*, *RAD50*, *RAD51C*, *RAD51D*) and MLPA by quantification of probes corresponding to *BRCA1*, *BRCA2* genes using the MLPA Kit according to the manufacturer's recommendations (MRC-Holland), fragment analysis by ABI 3730xl genetic analyzer, and data normalization and interpretation of results using Coffalyser.net software as recommended by MRC-Holland. Only *BRCA1* and *BRCA2* testing are available and reported for this analysis.

According to *BRCA1* and *2* results, patients were counseled in both cohorts as per institutional guidelines.

Data collection and statistical methods

Relevant demographic, treatment, and outcome variables of the Spanish and KU cohorts were combined for analysis. An independent statistical analysis of the combined dataset was performed by both groups, and any discrepancies between the two independent analyses were resolved by review of source documents.

Statistical section. Primary objective was to determine the rate of pCR and near pCR as defined previously. All analyses were conducted using SPSS statistics version 22 (IBM Corporation). All reported *P* values were two-sided without corrections for multiple comparisons. *P* values less than 0.05 were considered to indicate statistically significant results. Overall frequencies and percentages were summarized for race, ethnicity, menopausal status, T-stage, lymph node status, tumor–node–metastasis (TNM) stage, hormone receptor status, germline *BRCA* mutation status, surgery type, and family history of breast/ovarian cancer (36). Patient outcomes were summarized in terms of pCR and RCB. Confidence intervals (CIs) for the proportion of patients who achieved pCR and RCB 0 + 1 were calculated according to the exact two-sided binomial test. Categorical variables were compared between the two cohorts by Fisher exact test. Continuous variables were compared by nonparametric Mann–Whitney test. Logistic regression analysis was used to examine the effect of multiple variables on attainment of pathologic response (pCR; RCB 0 + 1).

Results

Study cohort

A consort diagram depicting cohort identification has been provided (Fig. 1). Two patients in the Spanish cohort were found to have metastatic disease after enrollment and were excluded

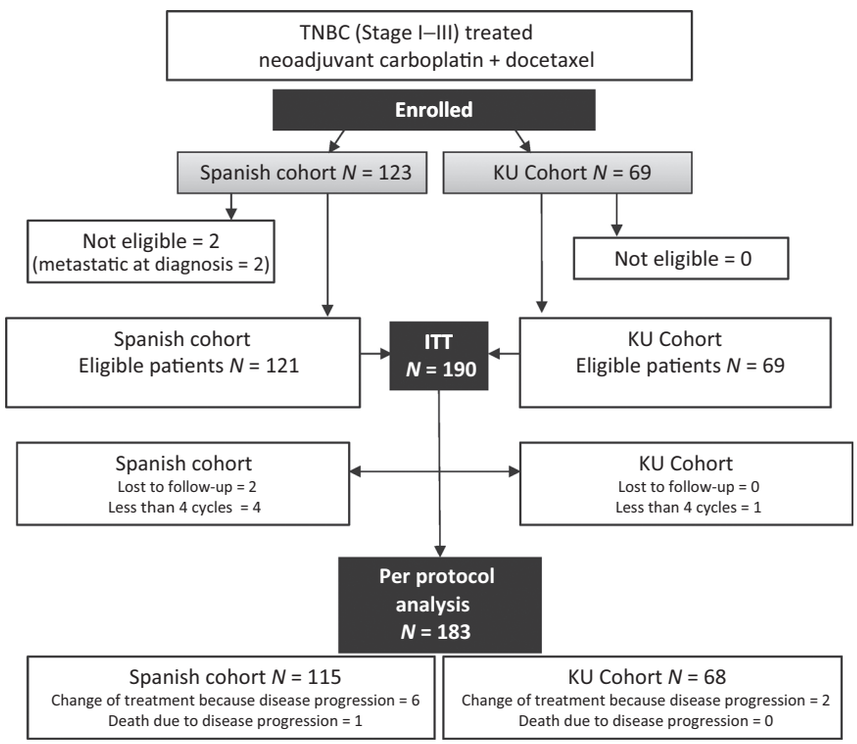


Figure 1.
CONSORT diagram. In addition to the various centers in Spain, the Spanish cohort includes a center from Lima, Peru.

from the intention-to-treat (ITT) population. Seven patients in the ITT population were not included in the per-protocol analysis (received less than four cycles of NAC without progression = 5, lost to follow-up = 2). Eight patients switched to a different chemotherapy regimen due to clinically progressive disease and are designated as "no pCR" in per-protocol analysis. In addition, one subject died due to disease progression during NAC chemotherapy and is also included in per-protocol analysis (designated as "no pCR").

Patient characteristics

The study population included 190 subjects treated in KU and Spanish cohorts between 2010 and 2015. Table 1 describes the demographic and baseline clinical characteristics of the study population. For the overall study population, median age was 51 years (range, 29–81 years), 14% were Hispanic, and 7% were black. Fifty-six percent had clinical stage II disease, and 52% were clinically node positive. Germline BRCA testing results were available for 87% of the study population, and 16% of the study population carried a deleterious *BRCA1/2* mutation. A small percentage (5%, all from KU cohort) of patients had ER/PgR expression between 1% to 10%. Compared with the KU cohort, patients in the Spanish cohort had larger tumors and a higher percentage of node-positive and stage III disease. Family history was assessed in the two cohorts based on the local guidelines (specific guidelines are provided

Table 1. Patient demographics

	All patients ($N = 190$)	KU ($N = 69$)	Spanish ($N = 121$)	P[a]
Age at diagnosis (years; median, range)	51 (29–81)	52 (30–80)	50 (29–81)	0.86
Race				<0.001
Caucasian	174 (92%)	57 (83%)	117 (96%)	
Black	14 (7%)	12 (17%)	2 (2%)	
Asian	2 (1%)	0 (0%)	2 (2%)	
Ethnicity				0.001
Hispanic	26 (14%)	2 (3%)	24 (20%)	
Non-Hispanic	163 (86%)	67 (97%)	97 (80%)	
Menopausal status				0.59
Pre/peri	86 (45%)	30 (44%)	56 (46%)	
Post	98 (52%)	38 (55%)	60 (50%)	
Unknown	6 (3%)	1 (1%)	5 (4%)	
T stage number				<0.001
1	23 (12%)	19 (27%)	4 (3%)	
2	104 (55%)	37 (54%)	67 (55%)	
3	34 (18%)	11 (16%)	23 (19%)	
4	29 (15%)	2 (3%)	27 (23%)	
Median tumor size (mm; range)	35 (9–180)	30.5 (10–111)	41 (9–180)	<0.001
Lymph node status				<0.001
Negative	90 (47%)	47 (68%)	43 (35%)	
Positive	98 (52%)	22 (32%)	76 (63%)	
Unknown	2 (1%)	0 (0%)	2 (2%)	
TNM stage				<0.001
I	20 (11%)	18 (26%)	2 (2%)	
II	107 (56%)	41 (59%)	66 (54%)	
III	63 (33%)	10 (15%)	53 (44%)	
ER/PgR				0.001
0%	184 (97%)	63 (91%)	121 (100%)	
1%–10%	6 (3%)	6 (9%)	0 (0%)	
Germline BRCA mutation				0.084
Absent	136 (71%)	49 (71%)	87 (72%)	
Present	30 (16%)	15 (22%)	15 (12%)	
Unknown	24 (13%)	5 (7%)	19 (16%)	
Surgery type[b]				0.045
Lumpectomy	84 (45%)	23 (33%)	61 (53%)	
Mastectomy	101 (55%)	46 (67%)	55 (47%)	
Axillary surgery				<0.001
Pre-NAC SLNB	24 (13%)	0 (0%)	24 (20%)	
Post-NAC				<0.001
SLNB without ALND	50 (27%)	46 (66%)	4 (3%)	
SLNB plus ALND	15 (8%)	6 (9%)	9 (8%)	
ALND	94 (50%)	15 (22%)	79 (66%)	
No axillary procedure	5 (2%)	2 (3%)	3 (3%)	
Positive family history[c]				0.11
Yes	52 (28%)	27 (39%)	25 (21%)	
No	136 (72%)	42 (61%)	94 (79%)	

Abbreviations: ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

[a]Mann–Whitney nonparametric test for continuous data; Pearson χ^2/Fisher exact test for categorical data.

[b]Surgical information was not available for 5 patients in the IIT population.

[c]Family history information was not available for 2 patients from the Spanish cohort. Family history is reported utilizing cohort-specific definitions of positive family history as outlined in patient characteristics section. Upon application of Spanish family history definition to the entire study population, 24% of patients had positive family history.

in Supplementary Material). Twenty-eight percent of patients reported a positive family history of breast or epithelial ovarian cancer (KU, 39%; Spanish cohort, 21%). To provide consistent evaluation of family history, when the Spanish family history criteria were applied to the entire study population, 24% (45/190) of patients demonstrated positive family history.

Treatment response

pCR and RCB 0 + 1 for the per-protocol study population were 55% (95% CI, 48%–62%) and 68% (95% CI, 61%, 75%), respectively. Both pCR and RCB 0 + 1 rates were higher in the KU cohort compared with the Spanish trial (Table 2). pCR and RCB 0 + 1 rates were lower in stage III disease compared with stage I–II disease (pCR: 37% vs. 63%, $P = 0.002$; RCB 0 + 1: 49% vs. 77%, $P \leq 0.001$). When assessed by individual TNM stage, the pCR rates were similar in the KU and Spanish cohorts (Table 2). When assessed by germline *BRCA* status, pCR rate was 56% in *BRCA* wild-type and 59% in *BRCA* mutation–associated TNBC ($P = 0.83$; Fig. 2). Family history of breast and ovarian cancer did not have an impact on pCR or RCB 0 + 1 rates using individual cohort–positive family history criteria (Supplementary Table S1) or using Spanish trial–positive family history criteria (data not shown).

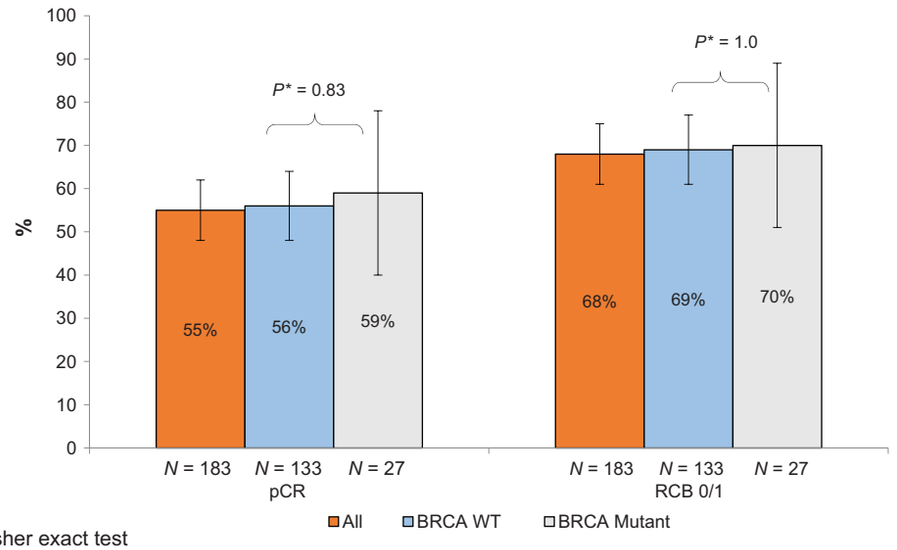
Because of the inclusion of a small number of patients with 1% to 10% ER/PgR expression (KU cohort), pCR analysis was also performed according to ER/PgR expression status. Fifty percent and 55% of patients with ER/PgR 1% to 10% ($n = 6$) and ER/PgR <1% ($n = 177$) achieved pCR, respectively ($P = 1.0$; Supplementary Table S2).

On univariate analysis, presence of lower T stage (T1/2 vs. T3/4), lower TNM stage (I/II vs. III), and being treated in the KU cohort were associated with higher likelihood of achieving a pCR (Table 3). For RCB 0 + 1, presence of lower T stage (T1/2 vs. T3/4), lower TNM stage (I/II vs. III), lymph node–negative status, and being treated in the KU cohort were associated with higher likelihood of achieving a RCB 0 + 1 (Supplementary Table S3). Age, germline *BRCA* mutation, and family history of breast/ovarian cancer did not influence the likelihood of achieving pCR or RCB 0 + 1. Compared with the KU cohort, the Spanish cohort had a higher proportion of patients with

Table 2. Pathologic response by germline BRCA mutation status and stage

All patients	All Patients *N* = 183	KU *N* = 68	Spanish *N* = 115	*P*[a]
pCR	*N* (%; 95% CI)	*N* (%; 95% CI)	*N* (%; 95% CI)	
Yes	100 (55%; 48%–62%)	44 (65%; 54%–76%)	56 (49%; 40%–58%)	0.046
No	83 (45%; 38%–52%)	24 (35%; 24%–46%)	59 (51%; 42%–60%)	
RCB 0 + 1				
Yes	125 (68%; 61%–75%)	55 (81%; 72%–90%)	70 (61%; 52%–70%)	0.005
No	58 (32%; 25%–39%)	13 (19%; 10%–28%)	45 (39%; 30%–48%)	
BRCA wild-type	*N* = 133	*N* = 48	*N* = 85	
pCR				
Yes	75 (56%; 48%–64%)	31 (65%; 52%–78%)	44 (52%; 41%–63%)	0.20
No	58 (44%; 36%–52%)	17 (35%; 22%–48%)	41 (48%; 37%–59%)	
RCB 0 + 1				
Yes	92 (69%; 61%–77%)	39 (81%; 70%–92%)	53 (62%; 52%–72%)	0.031
No	41 (31%; 23%–39%)	9 (19%; 8%–30%)	32 (38%; 28%–48%)	
BRCA mutation positive	*N* = 27	*N* = 15	*N* = 12	
pCR				
Yes	16 (59%; 40%–78%)	11 (73% 51%–95%)	5 (42%; 14%–70%)	0.13
No	11 (41%; 22%–60%)	4 (27%; 5%–49%)	7 (58%; 30%–86%)	
RCB 0 + 1				
Yes	19 (70%; 53%–87%)	12 (80%; 60%–100%)	7 (58%; 30%–86%)	0.40
No	8 (30%; 13%–47%)	3 (20%; 0%–40%)	5 (42%; 14%–70%)	
BRCA status unknown	*N* = 23	*N* = 5	*N* = 18	
pCR				1
Yes	9 (39%; 19%–59%)	2 (40%; 3%–83%)	7 (39%; 16%–62%)	
No	14 (61%; 41%–81%)	3 (60%; 17%–103%)	11 (61%; 38%–84%)	
RCB 0 + 1				
Yes	14 (61%; 41%–81%)	4 (80%; 45%–115%)	10 (56%; 33%–79%)	0.61
No	9 (39%; 19%–56%)	1 (20%; 15%–55%)	8 (44%; 21%–67%)	
TNM stage I and II	*N* = 124	*N* = 58	*N* = 66	
pCR				
Yes	78 (63%; 54%–71%)	40 (69%; 57%–81%)	38 (58%; 46%–70%)	0.20
No	48 (37%; 29%–46%)	18 (31%; 19%–43%)	28 (42%; 30%–54%)	
RCB 0 + 1				
Yes	95 (77%; 70%–84%)	50 (86%; 77%–95%)	45 (68%; 57%–79%)	0.02
No	29 (23%; 16%–30%)	8 (14%; 5%–23%)	21 (32%; 21%–43%)	
TNM stage III	*N* = 59	*N* = 10	*N* = 49	
pCR				
Yes	22 (37%; 25%–49%)	4 (40%; 10%–70%)	18 (37%; 23%–51%)	1.0
No	37 (63%; 51%–75%)	6 (60%; 30%–90%)	31 (63%; 49%–77%)	
RCB 0 + 1				
Yes	29 (49%; 36%–62%)	5 (50%; 19%–81%)	24 (49%; 35%–63%)	1.0
No	30 (51%; 38%–64%)	5 (50%; 19%–81%)	25 (51%; 37%–65%)	

[a]Fisher exact test.



*Fisher exact test

Figure 2.
Carboplatin plus docetaxel pathologic response by germline BRCA (gBRCA) status. WT, wild-type.

stage III disease, and on multivariable logistic regression analysis, the presence of TNM stage III disease was the only factor associated with a lower likelihood of achieving a pCR (HR, 0.35; 95% CI, 0.19–0.67; factors included in multivariable analysis: age, lymph node status, T stage, TNM stage, germline BRCA mutation status, family history, and cohort type).

Adverse events

Twenty-eight percent (54/190) of patients experienced one or more grade 3/4 adverse events (grade 3 = 21%, grade 4 = 7%; Table 4). Eighty-three percent of patients completed all six cycles of treatment. Twelve percent (22/183) of patients discontinued treatment prematurely: 4.4% (8/183) because of progressive disease, 6.0% (11/183) because of toxicity, and 1.6% (3/183) because of other reasons. No treatment-related deaths were reported.

Table 3. Predictors of pCR on univariate analysis[a]

	OR (95% CI)	P[b]
Age		
≤50	1	0.37
>50	0.74 (0.4–1.33)	
LN status		
Negative	1	
Positive	0.71 (0.39–1.27)	0.30
T stage		
T1/2	1	
T3/4	0.39 (0.21–0.73)	0.003
TNM stage		
I/II	1	
III	0.35 (0.19–0.67)	0.001
gBRCA mutation		
Negative/unknown	1	
Positive	1.25 (0.54–2.86)	0.68
Family history		
No	1	
Yes	0.96 (0.5–1.85)	1.0
Cohort		
Spanish	1	
KU	1.93 (1.04–3.50)	0.046

Abbreviations: gBRCA, germline BRCA; LN, lymph node.
[a]ORs and two-sided *P* values from Fisher exact test.
[b]On multivariable logistic regression analysis (factors included: age, lymph node status, T stage, TNM stage, germline BRCA mutation status, family history, and cohort type), presence of TNM stage III disease was the only factor associated with a lower likelihood of achieving a pCR (HR, 0.35; 95% CI, 0.19–0.67).

Discussion

TNBC, which is defined by the lack of ER and PgR expression and absence of HER2 overexpression and/or gene amplification, is currently the most lethal subtype of breast cancer. Because of the lack of molecular targets, chemotherapy is the only available treatment for TNBC. Despite achieving higher rates of pCR with conventional neoadjuvant chemotherapy, TNBC phenotype is associated with higher relapse rates than luminal tumors among patients with residual disease (1, 4, 5, 37). Although current guidelines recommend anthracycline and taxane-based chemotherapy for (neo)adjuvant treatment of TNBC, these schedules have limitations (6, 7). First of all, the studies that support this recommendation included patients regardless of HER2 and/or ER status. Second, anthracyclines are associated with established irreversible and long-term adverse events, and finally, 30% to 40% of patients with early TNBC experience relapse despite receiving anthracycline–taxane based (neo)adjuvant treatment (8, 27–29, 38, 39). Thus, there is a need to design clinical trials in this population of patients incorporating new drugs and/or optimizing the administration of standard chemotherapy to improve the efficacy and reduce the toxicity.

Recent studies demonstrate that the addition of platinum salts, namely carboplatin, to anthracycline and taxane–based neoadjuvant chemotherapy improves pCR in TNBC (14, 16, 25, 26). However, this improvement in pCR rate comes at the cost of an increase in toxicity and decrease in tolerability of chemotherapy (14, 16). The efficacy of anthracycline-devoid neoadjuvant combinations in sporadic and BRCA-associated TNBC has not been properly explored so far. Over a decade ago, a few neoadjuvant studies evaluated platinum–taxane combination chemotherapy in unselected patients with locally advanced breast cancer. These studies demonstrated overall modest pCR rates of 14% to 22%, with higher pCR rates noted in the ER-negative subgroup (40, 41). Over the last few years, improved understanding of biology of breast cancer subtypes coupled with the preclinical

Table 4. Grade 3 or 4 treatment-related toxicities

N = 190	G3/4 *n* (%)	G3 *n* (%)	G4 *n* (%)
Leukopenia	2 (1%)	2 (1%)	0 (0%)
Neutropenia	22 (12%)	13 (7%)	9 (5%)
Thrombocytopenia	11 (6%)	9 (5%)	2 (1%)
Anemia	7 (4%)	6 (3%)	1 (1%)
Febrile neutropenia	8 (4%)	6 (3%)	2 (1%)
Nausea	5 (3%)	5 (3%)	0 (0%)
Vomiting	5 (3%)	4 (2%)	1 (1%)
Mucositis	2 (1%)	2 (1%)	0 (0%)
Diarrhea	5 (3%)	5 (3%)	0 (0%)
Peripheral neuropathy	3 (2%)	3 (2%)	0 (0%)
Fatigue	2 (1%)	2 (1%)	0 (0%)
Other[a]	9 (5%)	9 (5%)	0 (0%)

[a]Other: Hepatic/transaminase elevation ($n = 3$), rash ($n = 2$), hyponatremia ($n = 1$), thrombosis ($n = 1$), allergic reaction ($n = 1$), dehydration ($n = 1$).

data supporting activity of platinum agents in TNBC has led to reemergence of interest in exploration of platinum agents for treatment of TNBC (14, 16, 25, 26). Taxanes are an integral part of adjuvant/neoadjuvant chemotherapy regimens for breast cancer treatment and appear to contribute particularly among patients with TNBC (30). On the other hand, there is abundant preclinical and clinical data demonstrating synergy between platinum compounds and taxanes in several solid tumor types (31–33). An interesting study, the randomized TNT trial, compared single-agent carboplatin to single-agent docetaxel in patients with metastatic TNBC. The trial showed both significant single-agent activity of docetaxel and carboplatin in unselected TNBC and non–cross resistance between these agents (22). Furthermore, in a randomized neoadjuvant study comparing single-agent docetaxel versus single-agent doxorubicin, the taxane demonstrated a significant superior activity with respect to single-agent doxorubicin in cDNA microarray-defined basal-like TNBC, but not in the remaining subtypes (42). The above clinical and preclinical data provided the rationale for the two different studies (the KU and the Spanish trials) that were conducted in parallel and whose merged results are presented in this article. Both evaluated the antitumor activity of an identical neoadjuvant combination chemotherapy regimen of carboplatin plus docetaxel in TNBC.

The merged results presented here show that the pCR rates achieved with this CbD chemotherapy regimen in TNBC seem to be numerically higher than those reported in several trials using classical neoadjuvant anthracycline–taxane combinations, in which 28% to 39% of patients with TNBC achieved a pCR (14, 43, 44). This pCR rate of 55% was achieved even though more than half of the patients had node-positive disease, and one-third had stage III disease. Previous studies have demonstrated that pCR is a very robust surrogate for improved long-term outcomes, specifically for aggressive tumor subtypes like TNBC (1, 45). Thus, pCR is considered as a good endpoint for early evaluation of new treatment approaches for TNBC.

Addition of carboplatin to anthracycline/taxane–based chemotherapy in TNBC increases pCRs from around 40% to 50%–54% (14, 16, 25). However, the impact of this approach on long-term outcomes is not yet clear. In GeparSixto, a 44% improvement in 3-year event-free survival (EFS) was noted with the addition of concurrent carboplatin to anthracycline plus taxane plus bevacizumab chemotherapy backbone. On the other hand, in CALGB 40603 addition of carboplatin to taxane followed by sequential doxorubicin/cyclophosphamide did improve pCR rate, but improvement in 3-year EFS or overall survival (OS) was not noted (46, 47). It is important to point out that neither of these two trials were powered sufficiently for EFS and OS endpoints and thus cannot be considered definitive studies to answer the question of clinical utility of platinum agents for early-stage TNBC. The optimal dose, sequence, and chemotherapy backbone for efficacious incorporation of platinum in treatment of early-stage TNBC are also not yet known. Several ongoing randomized phase III trials are evaluating various schedules and combinations of platinum salts in early-stage TNBC (NCT02488967, NCT02455141, NCT02441933, NCT02445391, NCT02125344, and NCT02032277).

pCR in our study with the CbD regimen was 55%, which is similar to pCR attained with the addition of carboplatin to anthracycline/taxane chemotherapy. However, the addition of carboplatin to anthracycline–taxane regimens is associated with a significant increase in acute toxicity, with only 50% to 76% of patients completing all study treatment (14, 16, 25). In contrast, the chemotherapy regimen of CbD has a much favorable toxicity profile, with 83% of patients completing all six cycles of therapy.

There were some differences between the KU and Spanish cohorts. Compared with the KU cohort, patients in the Spanish cohort had higher disease burden (larger tumors, more node-positive, and stage III disease). Patients in the Spanish cohort were also more likely to undergo SLN biopsy prior to NAC (35% vs. 0%, $P < 0.0001$) and to undergo breast conservation surgery (vs. mastectomy). These surgical differences are a reflection of the local surgical practice patterns and patient preference regarding breast conservation in the respective countries. The percentage of patients with deleterious *BRCA* mutation in the KU series is consistent with other reported studies from the United States (15, 19). The Spanish series reported a slightly lower percentage of patients with deleterious *BRCA* mutations, but this prevalence rate is also consistent with the reported rates in Spanish women with TNBC not selected for family history (48, 49). We noted a pCR rate of 59% in *BRCA* mutation carriers, which is consistent with previously reported pCR rates with single-agent platinum and platinum–anthracyline–taxane combination chemotherapy in *BRCA* mutation carriers (24, 50).

In our study, deleterious *BRCA* mutation and family history were not associated with pCR and RCB 0 + 1, with equally good pathologic response rates noted in *BRCA* wild-type and mutant patients. This might be explained by the idea that docetaxel and carboplatin combination offers antitumor coverage for both sporadic and *BRCA*-associated TNBC. Docetaxel seems to be better in the first group, whereas carboplatin is more active in *BRCA*-mutated patients. Furthermore, it is now becoming increasingly evident that 40% to 50% of BRCA wild-type TNBCs harbor homologous recombination deficiency, and benefit of platinum agents may very well extend much beyond *BRCA* mutation–associated breast cancers (15, 17, 21). The tolerance to CbD was good. Only 6% of patients discontinued therapy because of toxicity. A similar chemotherapy regimen, the TCH regimen (that combines carboplatin and docetaxel with trastuzumab) is widely used for the neo/adjuvant treatment of $HER2^+$ breast cancer.

Although presenting very robust pathologic response data, our study does have several limitations. The decision to combine the two series with the purpose of reporting pathologic response was made *post hoc* and was not preplanned. However, this report includes almost 200 patients with TNBC treated with the same regimen in three different continents. In this combined analysis,

more than half of the patients had node-positive disease, one-third had stage III disease, and 16% harbored deleterious *BRCA* mutation. These patient characteristics are very similar to contemporary randomized neoadjuvant clinical trials in TNBC. We also acknowledge the lack of a control arm in both series; a deficit that can only be addressed in setting of a randomized trial. In fact, an ongoing randomized phase II study is currently comparing neoadjuvant CbD regimen with the anthracycline–taxane–carboplatin regimen used in CALGB 40603 (NCT02413320).

In conclusion, the combination of carboplatin plus docetaxel with G-CSF support yielded a significant antitumor activity in stage I–III TNBC with manageable toxicity. This anthracycline-free regimen should be compared with standard taxane–anthracycline chemotherapy as neoadjuvant therapy of TNBC in a prospective randomized trial.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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