Clinical Cancer Research

Pathological Response and Survival in Triple-Negative Breast Cancer Following Neoadjuvant Carboplatin plus Docetaxel

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Abstract

Purpose: Prognostic value of pathologic complete response (pCR) and extent of pathologic response attained with anthracycline-free platinum plus taxane neoadjuvant chemotherapy (NAC) in triple-negative breast cancer (TNBC) is unknown. We report recurrence-free survival (RFS) and overall survival (OS) according to degree of pathologic response in patients treated with carboplatin plus docetaxel NAC.

Patients and Methods: One-hundred and ninety patients with stage I–III TNBC were treated with neoadjuvant carboplatin (AUC6) plus docetaxel (75 mg/m^2) every 21 days × 6 cycles. pCR (no evidence of invasive tumor in breast and axilla) and Residual cancer burden (RCB) were evaluated. Patients were followed for recurrence and survival. Extent of pathologic response was associated with RFS and OS using the Kaplan–Meier method.

Results: Median age was 51 years, and 52% were node-positive. pCR and RCB I rates were 55% and 13%, respectively. Five percent of pCR patients, 0% of RCB I patients, and 58% of RCB II/III patients received adjuvant anthracyclines. Three-year RFS and OS were 79% and 87%, respectively. Three-year RFS was 90% in patients with pCR and 66% in those without pCR [HR = 0.30; 95% confidence interval (CI), 0.14–0.62; $P = 0.0001$]. Three-year OS was 94% in patients with pCR and 79% in those without pCR (HR = 0.25; 95% CI, 0.10–0.63; $P = 0.001$). Patients with RCB I demonstrated 3-year RFS (93%) and OS (100%) similar to those with pCR. On multivariable analysis, higher tumor stage, node positivity, and RCB II/III were associated with worse RFS.

Conclusions: Neoadjuvant carboplatin plus docetaxel yields encouraging efficacy in TNBC. Patients achieving pCR or RCB I with this regimen demonstrate excellent 3-year RFS and OS without adjuvant anthracycline. *Clin Cancer Res; 24(23); 5820–9. ©2018 AACR.*

Introduction

Triple-negative breast cancer (TNBC), which is defined by the lack of expression of estrogen receptor (ER), progesterone receptor (PgR), and absence of ERBB2 (HER2) overexpression and/or gene amplification, accounts for 15% of all the breast cancers in the United States. Compared with other breast cancer subtypes, TNBC is associated with inferior long-term outcomes (1–3). Adjuvant chemotherapy reduces the risk of distant recurrence and death in

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Translational Relevance

Phenotypic and molecular similarities between sporadic and *BRCA* mutation–associated triple-negative breast cancer (TNBC) have prompted the exploration of DNA-damaging agents like platinum compounds in TNBC. We report survival outcomes with neoadjuvant carboplatin plus docetaxel, an anthracycline-free chemotherapy regimen, in TNBC. Robust pathologic complete response (pCR) and near-complete response (RCB I) rates were noted with this regimen. Patients who achieved pCR or RCB I had excellent 3-year recurrence-free rate and overall survival (OS) without adjuvant anthracyclines, suggesting that the composite of pCR + RCB I may accurately identify patients at low risk of recurrence who can avoid further adjuvant chemotherapy and associated toxicities. This platinum–taxane chemotherapy regimen rendered equally high pCR and survival rates in *BRCA*-associated TNBC as in *BRCA* wild type TNBC. The results of our study support further evaluation of platinum-based chemotherapy in both *BRCA*-associated and wild type TNBC as well as the role of extent of pathologic response in risk stratification of patients undergoing neoadjuvant chemotherapy.

patients with TNBC and is generally recommended for TNBC patients with stage I (T>1 cm)–III disease (4–6). Even so, despite receiving standard anthracycline–taxane-based chemotherapy, a significant proportion (20%–40%) of patients with early-stage TNBC develop metastatic disease (7, 8). Improved therapeutic approaches are thus desired for TNBC. In the absence of available actionable molecular targets, modifications of traditional chemotherapy regimens (i.e., the addition of platinum agents) may be potential means of improving outcomes for this breast cancer subtype.

Platinum compounds generate the double-stranded DNA breaks that are preferentially repaired by the mechanism of homologous recombination. Phenotypic and molecular similarities between *BRCA*-associated and sporadic TNBC suggest that homologous recombination deficiency may be a shared alteration that can be targeted in a larger subset of TNBC (7, 9–13). Germline *BRCA1/2* mutations are the prototype molecular alterations that confer homologous recombination deficiency and sensitivity to DNA-damaging therapy. Only 15% to 20% of patients with TNBC harbor germline *BRCA* mutations; however, additional mechanisms such as promoter methylation, transcript instability/attenuation, or somatic/germline mutations in other homologous recombination pathway genes may compromise DNA repair machinery (14–17). It has recently been reported that comprehensive evaluation of factors beyond germline *BRCA* mutation reveals homologous recombination deficiency in 50% to 60% of TNBC, expanding the therapeutic potential of DNA-damaging agents like platinum compounds within the general population of TNBC (16, 18). Neoadjuvant studies demonstrate that the addition of carboplatin to anthracycline and taxane-based neoadjuvant chemotherapy (NAC) improves pathologic complete response (pCR) in TNBC (11, 19–22). However, the improvement in pCR rate comes at the cost of increased toxicity (11, 19, 21, 22). Exploration of a platinum-based chemotherapy regimen with an improved toxicity profile in TNBC is therefore warranted. Taxanes demonstrate significant activity in TNBC as well as preclinical and clinical synergy with platinum agents, providing rationale for evaluation of a platinum-taxane combination in TNBC (23–28).

We have recently reported encouraging efficacy of a carboplatin plus docetaxel NAC regimen in TNBC (29). In this study, overall pCR rates were 55% and were not influenced by germline *BRCA* mutation status (pCR 59% in *BRCA*-associated TNBC, 56% in *BRCA* wild type TNBC). Here, we report 3-year recurrence-free survival (RFS) and overall survival (OS) from the same study population. We also present the correlation between survival outcomes and degree of pathologic response as assessed by residual cancer burden (RCB).

Patients and Methods

Patient population

The study population includes patients with stage I–III TNBC treated with a NAC regimen of carboplatin plus docetaxel in two separate and independent prospective cohorts. Details of the study population have been published previously (29). A brief description of the study population is provided below.

This study was conducted in accordance with the U.S. Common Rule and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. Human Investigations were performed after approval by the Institutional Review Board at each institution, and all subjects provided written informed consent.

University of Kansas (KU) cohort. Patients with stage I (T≥1 cm), II, and III TNBC were enrolled in an IRB-approved multisite prospective registry protocol (NCT02302742). Triple negativity was defined as ER and PgR IHC nuclear staining of less than 10% and HER2 IHC staining of 0 to 1+ or FISH ratio <2.0 if IHC 2+ or if IHC not performed (30). From 2011 to 2015, 69 enrolled patients with stage I (T > 1 cm), II, and III TNBC were treated with a NAC regimen of carboplatin plus docetaxel.

MMJ-CAR-2014-01 (Spanish) cohort. Female patients with pathologically confirmed diagnosis of stage II–III (T ≥ 2 cm) TNBC were enrolled on a prospective, multicenter, nonrandomized trial exploring the antitumor activity of neoadjuvant carboplatin plus docetaxel (NCT01560663). See Supplementary Material for a list of participating institutions. Triple negativity was defined as ER and PgR nuclear staining of less than 1% by IHC and HER2 IHC staining of 0 to 1+ or FISH ratio <2.0 if IHC 2+ or if IHC not performed (30). Between 2010 and 2015, 123 patients with stage II and III TNBC were enrolled and treated with neoadjuvant carboplatin plus docetaxel.

This study was conducted in accordance with the U.S. Common Rule and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. Human investigations were performed after approval by the Institutional Review Board at each institution, and all subjects provided written informed consent.

Study procedures

As described previously (29), patients in both cohorts were prescribed an NAC regimen of carboplatin (AUC 6) + docetaxel (75 mg/m^2) given every 21 days for 6 cycles. All patients received myeloid growth factor support (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

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patients with clinically suspicious axillary lymph node/s, histologic confirmation by biopsy or fine-needle aspiration was encouraged. Following NAC, all patients underwent breast surgery. Axillary sampling was required except in patients with pretreatment negative sentinel lymph nodes. Twenty-two percent (41/183) of the per-protocol population underwent pretreatment sentinel lymph node biopsy; completion dissection was required in case of positive pretreatment sentinel lymph node biopsy (additional information regarding pretreatment axillary lymph node assessment is included as Supplementary Text). Extent of axillary surgery, subsequent irradiation, and postoperative adjuvant chemotherapy were otherwise determined by the treating physician. Patients were prospectively followed for recurrence and survival status.

Pathologic evaluation

As described previously (29), 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 in the breast and axilla with or without ductal carcinoma *in situ* (ypT0/isN0). Patients with pCR in the breast and negative pretreatment sentinel lymph nodes were considered to have achieved pCR. RCB for all the patients was calculated centrally (utilizing parameters reported on individual patient pathology reports), blinded to enrollment site, using the classification by Symmans *et al* (31). Patients achieving pCR (RCB 0) or near-pCR (RCB I) were assessed within the group RCB 0/I.

Germline BRCA1/2 testing

KU cohort. Germline testing for *BRCA1/2* was done utilizing commercially available tests and laboratories.

Spanish cohort. Germline testing for *BRCA1/2* was done at Sistemas Genómicos facilities using targeted next-generation sequencing of 7 genes (*BRCA1*, *BRCA2*, *PALB2*, *BARD1*, *RAD50*, *RAD51C*, and *RAD51D*) and multiplex ligation-dependent probe amplification (MLPA) by quantification of probes corresponding to *BRCA1* and *BRCA2* genes using the MLPA Kit (MRC-Holland) according to the manufacturer's recommendations, fragment analysis by ABI 3730xl genetic analyzer (Applied Biosystems), and data normalization and interpretation of results using Coffalyser.net software as recommended by MRC-Holland. Only *BRCA1* and *BRCA2* results are available and reported for this analysis.

Patients with germline *BRCA1* or *BRCA2* mutation were counseled in both cohorts as per institutional guidelines.

Statistical analysis

Relevant demographic, treatment, and outcome variables of the Spanish and KU cohorts were combined for analysis. Demographic and toxicity data depict the intent-to-treat population, whereas all other analyses reflect the per-protocol patient population. RFS was defined as the time from diagnosis to first recurrence (invasive ipsilateral breast, invasive local/regional, or distant) or to death as a result of any cause (32). OS was defined as time from diagnosis to death as a result of any cause. Patients were censored on the date of last contact if an event had not been observed. Confidence intervals (CI) for the proportion of patients with pCR and RCB 0/I were calculated according to the exact two-sided binomial test. Survival curves were assessed by the Kaplan–Meier method, and unadjusted survival comparisons were conducted using log-rank tests. Cox regression modeling was used for univariate and multivariable analysis of factors associated with risk of recurrence and death. All reported *P* values and CIs are from two-sided tests. All analyses were conducted using SPSS Statistics version 22 (IBM Corporation).

Results

Study cohort

A CONSORT diagram depicting cohort identification has been provided (Fig. 1). As reported previously (29), the study population included 190 subjects treated in KU and Spanish cohorts between 2010 and 2015. Two patients were found to have metastatic disease after enrollment and were excluded from the intent-to-treat population. Seven patients in the intent-to-treat population were not included in the per-protocol analysis (consent withdrawn or lost to follow-up prior to definitive breast surgery).

Patient characteristics

Table 1 describes the demographic and baseline clinical characteristics of the study population. For the overall study

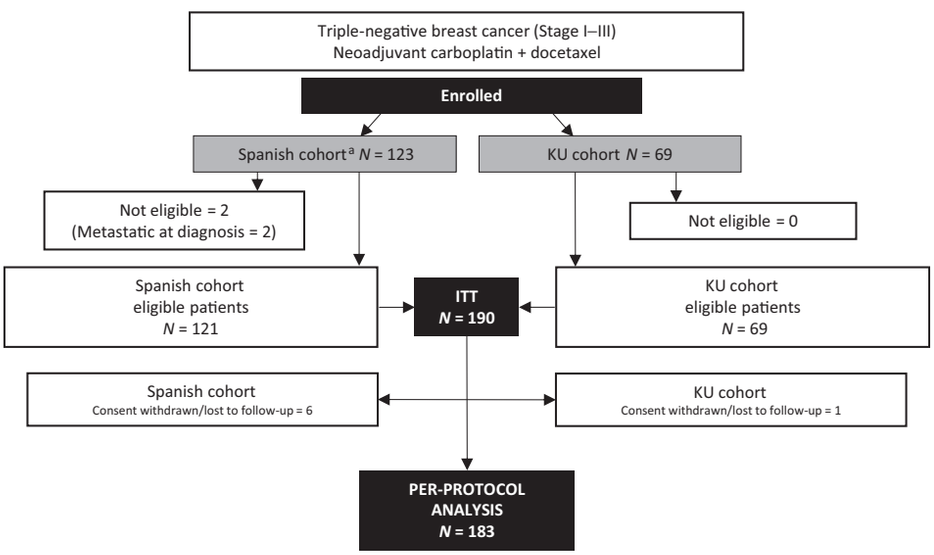

Figure 1.
CONSORT diagram. [a]In addition to the various centers in Spain, the Spanish cohort includes a center from Lima, Peru.

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Table 1. Patient characteristics

	All patients (*N* = 190)
Age at diagnosis, years – Median (range)	51 (29–81)
Race – *n* (%)	
Caucasian	174 (92%)
Black	14 (7%)
Asian	2 (1%)
Ethnicity[a]	
Hispanic	26 (14%)
Non-Hispanic	163 (86%)
Menopausal status	
Pre/peri	86 (45%)
Post	98 (52%)
Unknown	6 (3%)
Histologic grade	
1	1 (1%)
2	39 (21%)
3	140 (78%)
T stage	
1	23 (12%)
2	104 (55%)
3	34 (18%)
4	29 (15%)
Lymph node status	
Negative	90 (47%)
Positive	98 (52%)
Unknown	2 (1%)
ER/PR IHC	
0%	184 (97%)
1–10%	6 (3%)
Germline *BRCA* mutation	
Absent	136 (71%)
Present	30 (16%)
Unknown	24 (13%)
Surgery type[b]	
Lumpectomy	84 (45%)
Mastectomy	101 (55%)
pCR (*n* = 183)[b]	
Yes	100 (55%)
No	83 (45%)
RCB 0/I (*n* = 180)[c]	
Yes	123 (68%)
No	57 (31%)
Adjuvant chemotherapy in patients with RCB II+III (*n* = 57)	
Yes	33 (58%)
No	24 (42%)

[a]Ethnicity is not known for one patient.
[b]Surgical information is not available for 5 patients.
[c]RCB status is not available for 3 patients.

population, median age was 51 years (range, 29–81 years), 14% were Hispanic, 7% were black, and 52% had clinically node-positive disease. Sixteen percent of the study population carried a deleterious *BRCA1/2* mutation (germline *BRCA* testing results were available for 87% of patients). A small percentage (3%, all from KU cohort) had ER/PgR expression between 1% and 10%.

Pathologic response

Pathologic complete response and RCB I for the per-protocol study population ($N = 183$) were 55% (100/183; 95% CI, 48–62) and 13% (23/183; 95% CI, 8–18), respectively (Supplementary Fig. S1), as reported previously (29). Taken together, this yields a RCB 0/I rate of 68% (123/183; 95% CI, 61–75). When assessed by germline *BRCA* status, pCR rate was 56% (75/133) in *BRCA* wild type and 59% (16/27) in *BRCA* mutation-associated TNBC ($P = 0.83$). Because of the inclusion of a small number of patients with 1% to 10% ER/PgR expression, pCR assessment 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% ($n = 177$), respectively, achieved pCR ($P = 1.0$).

Survival outcomes

At a median follow-up of 36 months (range, 4–97 months), there have been 36 RFS events (distant $n = 26$, local/regional $n = 5$, site of metastasis unknown $n = 5$) and 25 deaths, with estimated 3-year RFS and OS of 79% (95% CI, 73–85) and 87% (95% CI: 82–92), respectively (Supplementary Fig. S2). Figure 2 shows Kaplan–Meier curves for RFS and OS by pCR (Fig. 2A and B) and RCB 0/I (Fig. 2C and D) status. Patients achieving pCR demonstrated significantly better RFS and OS compared with patients without pCR. Estimated 3-year RFS was 90% and 66% in patients with and without pCR, respectively (HR = 0.30; 95% CI, 0.14–0.62; $P = 0.0001$). Estimated 3-year OS was 94% (95% CI, 89–99) and 79% (95% CI, 70–88) for patients with and without pCR, respectively (HR = 0.25; 95% CI, 0.10–0.63; $P = 0.001$). Similar to those who achieved pCR, patients who achieved RCB 0/I status also demonstrated significantly superior RFS and OS compared with patients with RCB II/III. Estimated 3-year RFS was 91% (95% CI, 86–96) and 59% (95% CI, 45–73) in patients with RCB 0/I and RCB II/III, respectively (HR = 0.20; 95% CI: 0.10–0.41, $P < 0.0001$). Estimated 3-year OS was 95% (95% CI: 91–99) and 75% (95% CI: 63–87) for patients with RCB 0/I and RCB II/III, respectively (HR = 0.16; 95% CI: 0.06–0.42, $P < 0.0001$). Figure 3 shows RFS and OS by the four RCB classes. Estimated 3-year RFS was 90% (95% CI: 84–96) for RCB 0 (pCR), 93% (95% CI: 79–100) for RCB I, 69% (95% CI: 54%–84) for RCB II, and 21% (95% CI, 0–46) for RCB III. Estimated 3-year OS was 94% (95% CI, 89–99) for RCB 0 (pCR), 100% for RCB I, 83% (95% CI, 71–95) for RCB II, and 43% (95% CI, 11–75) for RCB III. Compared with patients with RCB II, patients with RCB III had inferior RFS (HR = 4.70; 95% CI, 1.97–11.20; $P < 0.0001$) and OS (HR = 4.34; 95% CI, 1.59–11.84; $P = 0.002$). RFS appeared similar between RCB 0 (pCR) and RCB I groups (HR = 2.48; 95% CI, 0.32–19.36; $P = 0.37$). Because of the absence of OS events in the RCB I group, no formal statistical analysis was done to compare OS between RCB 0 and RCB I groups.

When analyzed by *BRCA* status, estimated 3-year RFS was 88% (95% CI, 75–100) in patients with germline *BRCA1/2* mutation and 79% (95% CI, 72–86) in patients who were *BRCA* wild type (HR = 0.69; 95% CI, 0.24–1.99; $P = 0.48$). Similar to RFS, estimated 3-year OS was similar between patients with germline *BRCA1/2* mutation (95%; 95% CI, 86–100) and those who were *BRCA* wild type (87%, 95% CI, 81–93; HR = 0.37; 95% CI, 0.12–2.21; $P = 0.33$)

Adjuvant chemotherapy use and survival

Only 5 of 100 patients with pCR received postsurgical adjuvant chemotherapy (all 5 received doxorubicin and cyclophosphamide, AC). Adjuvant chemotherapy use in patients with pCR did not impact RFS or OS (data not shown). None of the 23 patients with RCB I status received adjuvant chemotherapy. Fifty-eight percent (33/57) of patients with RCB II/III received adjuvant anthracyclines, and the survival outcomes in this group were not significantly different compared with those patients who did not receive adjuvant anthracycline (Supplementary Fig. S3). No patients received adjuvant capecitabine.

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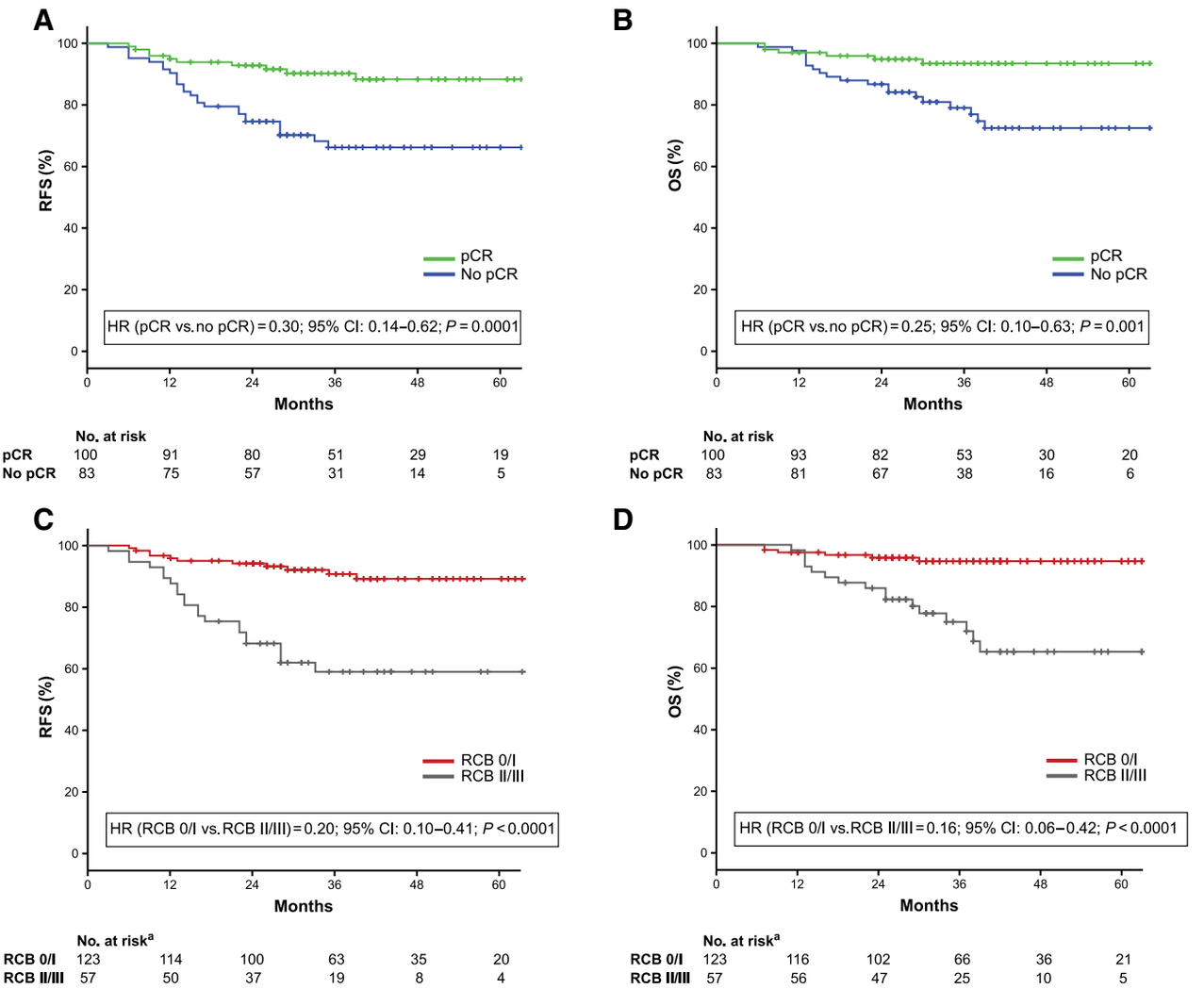

Figure 2.

A, RFS by pCR status; **B,** OS by pCR status; **C,** RFS by RCB 0/I vs. RCB II/III; **D,** OS by RCB 0/I vs. RCB II/III. [a]RCB unavailable for 3 patients.

Factors impacting survival

On univariate analysis, baseline node-positive status, higher baseline T-stage, lack of pCR, and an RCB greater than 0/I were all predictors of a greater risk of recurrence and death, whereas age at diagnosis, *BRCA* mutation status, pathologic grade, and adjuvant chemotherapy use (in patients with RCB II/III) did not impact RFS and OS (Table 2). On multivariable analysis, higher baseline T-stage was associated with greater risk of recurrence and death, whereas RCB 0/I was associated with reduced risk of recurrence and death. Baseline node-positive status was associated with greater risk of recurrence but not of death.

Adverse events

As reported previously (29), 28% (54/190) of patients in the intent-to-treat population experienced one or more grade 3/4 adverse events (grade 3 = 21%, grade 4 = 7%; Table 3). Of the per-protocol population, 88% (161/183) of patients completed all six cycles of treatment. Twelve percent (22/183) discontinued treatment prematurely: 4.4% (8/183) because of progressive disease, 6.0% (11/183) because of toxicity, 1.6% (3/183) because of other reasons. No treatment-related deaths were reported.

Discussion

In this study, we demonstrate that carboplatin plus docetaxel NAC regimen yields a high pathologic response rate (55%), which translates to encouraging 3-year RFS and OS. Recent randomized trials demonstrate that the addition of carboplatin to anthracycline and taxane-based NAC improves pathologic response from 37%–41% to 50%–58% in TNBC (11, 19, 21, 22, 27). The pCR rate of 55% with this carboplatin plus docetaxel regimen appears to be comparable with the pCR rate noted when carboplatin is added to anthracycline-taxane chemotherapy and numerically higher than classical neoadjuvant anthracycline–taxane combinations, where 28% to 40% of TNBC patients achieved pCR (11, 21, 33). Long-term benefits from the addition of neoadjuvant

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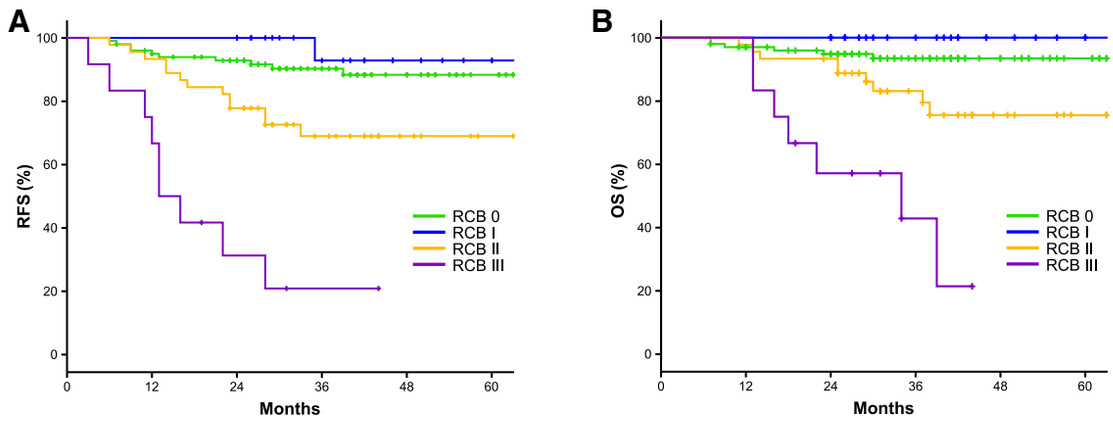

No. at risk[a]

RCB 0	100	91	80	51	29	19
RCB I	23	23	20	12	6	1
RCB II	45	42	34	18	8	4
RCB III	12	8	3	1	0	0

No. at risk[a]

RCB 0	100	93	82	53	30	20
RCB I	23	23	20	13	6	1
RCB II	45	44	41	23	10	5
RCB III	12	12	6	2	0	0

Figure 3.

A, RFS by RCB class; **B,** OS by RCB class. [a]RCB unavailable for 3 patients.

platinum to anthracycline/taxane regimens in TNBC are not yet clear. The Cancer and Leukemia Group B (CALGB) 40603 randomized phase II trial evaluated the addition of carboplatin and/or bevacizumab to a standard chemotherapy regimen of weekly paclitaxel followed by AC in TNBC and demonstrated improvement in pCR rates with the addition of carboplatin (41% vs. 54%; $P = 0.003$). In this trial, however, the addition of carboplatin did not lead to improvement in 3-year event-free survival (71% vs. 76%, $P = 0.36$; ref. 11). The GeparSixto randomized phase II trial reported that addition of weekly carboplatin to the combination of paclitaxel, nonpegylated liposomal doxorubicin, and bevacizumab improved pCR rate (37% vs. 53%, $P = 0.005$), and unlike CALGB 40603, at a median follow-up of 3 years demonstrated a 44% improvement in 3-year disease-free survival (DFS; 76% vs 85%, $P = 0.0325$) in patients with TNBC (21, 34). It is possible that differences in the chemotherapy backbones of the control arm between CALGB 40603 and GeparSixto (i.e., absence of the alkylating agent cyclophosphamide in the control arm of GeparSixto) could have contributed to the differences in the long-term outcomes noted in the two studies. However, it is noteworthy that neither CALGB 40603 nor GeparSixto were sufficiently powered for DFS and OS endpoints; several ongoing, adequately powered, randomized phase III trials are evaluating the efficacy of adjuvant platinums in the context of AC-plus-taxane chemotherapy in TNBC (NCT02488967, NCT02455141, NCT02441933). In our study, where more than half of patients had node-positive disease and a third had stage III disease, we reported a 3-year RFS and OS of 79% and 87%, respectively. These findings are in line with 3-year outcomes reported from GeparSixto (48% node-positive) and CALGB 40603 (58% node-positive) and also compare favorably with outcomes noted in contemporary adjuvant trials of AC plus taxane in TNBC (35, 36).

In a recently reported germline *BRCA*-focused subgroup analysis of GeparSixto, pCR and DFS benefit from the addition of carboplatin was observed primarily in patients without germline *BRCA* mutation (37). *BRCA* mutation carriers experienced a high pCR rate of 66.7% with the anthracycline + taxane + bevacizumab regimen, and this rate was not increased further by addition of carboplatin. In contrast, in patients with *BRCA* wild type TNBC, the addition of carboplatin increased pCR from 36% to 55%. Regardless of the treatment regimen, DFS was generally high in *BRCA* mutation carriers, with no significant difference separated by study arms, whereas in patients with *BRCA* wild type TNBC, better DFS was noted in the carboplatin arm (HR = 0.53; 95% CI, 0.29–0.96; $P = 0.04$). These findings suggest that the substantial homologous recombination deficiency induced by germline *BRCA* mutation may be therapeutically responsive to most types of DNA-damaging chemotherapy, including anthracyclines, and that this responsiveness is not improved further by addition of a platinum agent. However, the homologous recombination deficiency brought about by mechanisms other than germline *BRCA* mutation may not be as robust, and could therapeutically respond to targeting by platinum agents, even in the presence of anthracyclines. Further translational research is needed to understand mechanisms of homologous recombination deficiency in *BRCA* wild type TNBC and their relationship to platinum response.

Previous studies and meta-analyses have demonstrated that pCR is a robust surrogate for improved long-term outcomes in aggressive breast cancer subtypes like TNBC (3, 38). The positive impact of pCR on long-term outcomes (event/disease-free and OS) was also observed in both GeparSixto and CALGB 40603 trials. Hazard ratios for the prognostic impact of pCR on RFS and OS noted with the current carboplatin plus docetaxel regimen overlap with hazard ratios noted in the meta-analysis by Cortazar et al and those from both GeparSixto and CALGB 40603. It is noteworthy that for patients with pCR, where only 5% received adjuvant anthracycline-based chemotherapy, we demonstrate 3-year RFS and OS of 90% and 94%, respectively. These findings suggest that the favorable prognostic impact of pCR in TNBC is probably independent of the chemotherapy regimen leading to pCR, a finding which has also recently been noted by the I-SPY 2 investigators (39). An interesting finding of our trial is the excellent outcome of patients who achieved RCB class I pathologic response, which was as good as the outcome of those achieving pCR. A similar finding has recently been reported for TNBC patients treated with neoadjuvant anthracycline and taxane-based

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Table 2. Univariate and multivariate analysis of RFS and OS

	Univariate analysis			
	RFS		OS	
Variable	**HR (95% CI)**	***P***	**HR (95 % CI)**	***P***
Age				
≤50	1		1	
>50	0.90 (0.47–1.73)	0.75	0.60 (0.27–1.33)	0.20
Lymph node status				
Negative	1		1	
Positive	4.47 (1.96–10.21)	<0.0001	5.40 (1.85–15.74)	0.001
T stage				
1/2	1		1	
3/4	4.56 (2.30–9.02)	<0.0001	6.11 (2.55–14.65)	<0.0001
Histologic grade				
1/2	1		1	
3	1.18 (0.57–2.46)	0.66	0.56 (0.19–1.64)	0.26
Germline *BRCA* mutation				
Negative/unknown	1		1	
Positive	0.69 (0.24–2.00)	0.49	0.51 (0.12–2.21)	0.29
pCR				
No	1		1	
Yes	0.30 CI (0.14–0.61)	0.0005	0.25 (0.10–0.63)	0.001
RCB				
II/III	1		1	
0/I	0.20 (0.10–0.41)	<0.0001	0.16 (0.06–0.42)	<0.0001
RCB				
II/III	1		1	
I	0.09 (0.01–0.67)	0.003	0.027 (0.00–2.16)	0.006
Adjuvant chemotherapy (in patients with RCB II/III)				
Yes	1		1	
No	1.30 (0.56–3.03)	0.54	0.75 (0.27–2.08)	0.58
	Multivariate analysis[a]			
	RFS		OS	
Variable	**HR (95% CI)**	***P***	**HR (95 % CI)**	***P***
RCB				
II/III	1		1	
0/I	0.30 (0.14–0.63)	0.002	0.26 (0.10–0.70)	0.008
T stage				
1/2	1		1	
3/4	2.28 (1.07–4.86)	0.032	2.79 (1.06–7.36)	0.038
Lymph node status				
Negative	1		1	
Positive	2.51 (1.04–6.03)	0.040	2.47 (0.79–7.74)	0.12

[a]Variables included age, lymph node status, T stage, pathologic response, RCB class, germline mutation status, adjuvant chemotherapy.

NAC (40). If confirmed in additional studies, a composite of pCR plus RCB class I pathologic response could be more suitable than pCR alone for identification of TNBC patients destined for excellent prognosis following NAC. Two thirds of patients (68%) in this study demonstrated pCR or RCB I with this carboplatin plus docetaxel regimen, and these patients enjoyed very robust 3-year RFS (≥90%) and OS (≥93%) without adjuvant anthracycline treatment. These data indicate that adjuvant anthracycline can be avoided for patients achieving pCR or RCB with carboplatin plus docetaxel.

Table 3. Grade 3 to 4 treatment-related toxicities

***N* = 190**	**Grade 3/4 *n* (%)**	**Grade 3 *n* (%)**	**Grade 4 *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 ($n = 1$).

Poor outcomes were noted in patients with RCB II and III, particularly so in patients with RCB III, where the 3-year RFS was only 21%. In our study, a modest proportion (58%) of patients with RCB II or III received adjuvant anthracycline-based chemotherapy; however, adjuvant chemotherapy use did not impact outcomes in these patients. These findings highlight the need for and support the ongoing investigations of novel therapies in TNBC patients who have significant residual disease.

Anthracyclines and cyclophosphamide, although very active for treatment of breast cancer, carry established small but serious long-term risks (secondary leukemia/myelodysplastic syndrome, cardiomyopathy; refs. 41, 42). Anthracycline-free platinum–taxane chemotherapy regimen is associated with lower incidence of secondary leukemia/myelodysplastic syndrome and cardiomyopathy compared with anthracyclines-cyclophosphamide-taxane regimen when given concurrent with trastuzumab in HER2-positive

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breast cancer (43). The efficacy of anthracycline-free neoadjuvant combinations in sporadic and *BRCA*-associated TNBC has not been adequately explored so far. Taxanes are important components of neo/adjuvant chemotherapy regimens for breast cancer treatment and appear to contribute particularly among patients with TNBC (23, 44). Platinum and taxanes are mechanistically distinct, and preclinical and clinical data demonstrate synergy between platinum compounds and taxanes in several solid tumor types, including metastatic TNBC (24–26, 28). In the metastatic setting, the randomized TNT trial demonstrated superior efficacy of single-agent carboplatin over single-agent docetaxel in the presence of germline *BRCA* mutation but equal efficacy of either agent in the absence of germline *BRCA* mutation. Furthermore, the TNT trial noted no cross-resistance between the two drugs, with equal response rates noted for both agents upon cross-over (45). The promising efficacy of the neoadjuvant carboplatin plus docetaxel regimen noted in the current study might also be explained by the notion that the combination of docetaxel and carboplatin offers robust antitumor coverage for both basal and nonbasal TNBC (45).The encouraging outcomes noted with this carboplatin plus docetaxel regimen provide further evidence for the clinical efficacy of platinum-taxane combination in TNBC. Together, these data provide clinical and biological rationale for further investigation of anthracycline-free, platinum–taxane chemotherapy for early-stage TNBC.

Tolerance of the carboplatin plus docetaxel regimen used in this study was good, with only 6% of patients discontinuing 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-positive breast cancer and is likewise associated with a favorable toxicity profile.

Sixteen percent of the current study population carried a deleterious germline *BRCA1/2* mutation, which is consistent with expected prevalence of germline *BRCA1/2* mutation in TNBC (14, 15). We noted a pCR rate of 59% in *BRCA* mutation carriers, which is in line with previously reported pCR rates with single-agent platinum chemotherapy in *BRCA1* mutation carriers (46). In our study, deleterious *BRCA* mutation was not associated with 3-year DFS or OS, a finding that is also consistent with previous reports (47, 48). Furthermore, it is becoming increasingly evident that 40% to 50% of *BRCA* wild type TNBC may harbor homologous recombination deficiency (as identified by genomic mutational and transcriptional signatures), and that the benefit of platinum agents may extend beyond *BRCA* mutation–associated breast cancers (12, 16, 17, 49, 50). Several homologous recombination deficiency assays are being evaluated in clinical and translational research studies; however, assays with demonstrable clinical utility in selecting *BRCA* wild type TNBC patients likely to derive preferential benefit from platinum agents are not yet available.

Our study has limitations. First, the decision to combine the two patient cohorts for the purpose of reporting pCR and survival outcomes was made *post hoc* and was not preplanned. However, this report includes almost 200 patients with TNBC treated uniformly across three different continents. In this combined analysis, more than half of the patients had node-positive disease, and a third had stage III disease. These patient characteristics are very similar to contemporary neo/adjuvant randomized clinical trials for TNBC (11, 36).

Second, we acknowledge the lack of a control arm, a deficit that can only be addressed in the setting of a randomized trial. In fact, an ongoing randomized phase II study is currently comparing neoadjuvant carboplatin plus docetaxel regimen to an anthracycline-taxane-carboplatin regimen (NCT02413320). While we await data from ongoing trials, this regimen may provide an alternative for patients who desire treatment with a platinum regimen but are not candidates for anthracycline. We also acknowledge the modest follow-up of 3 years; however, given the natural history of TNBC, where the majority of recurrence events occur in the first 3 years, longer follow-up is unlikely to significantly change our results (2, 3).

In conclusion, the combination of carboplatin plus docetaxel yielded significant antitumor activity in stage I–III TNBC, with a favorable toxicity profile.

Disclosure of Potential Conflicts of Interest

F. Moreno is a consultant/advisory board member for Pfizer and Roche. J. Cortés is a consultant/advisory board member for AstraZeneca, Biothera, Celgene, Cellestia Biotech, Eisai, Merus, Novartis, Pfizer, Roche, and Seattle Genetics. I. Márquez-Rodas is a consultant/advisory board member for Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, and Roche. C.M. Perou is an employee of and holds ownership interest (including patents) in Bioclassifier LLC. M. Martín is a consultant/advisory board member for AstraZeneca, Lilly, Novartis, Pfizer, and Roche. No potential conflicts of interest were disclosed by the other authors.

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