Neoadjuvant, Anthracycline-Free Chemotherapy with Carboplatin and Docetaxel in Triple-Negative, Early-Stage Breast Cancer: A Multicentric Analysis of Feasibility and Rates of Pathologic Complete Response

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Key Words

Triple-negative breast cancer · Neoadjuvant chemotherapy · Carboplatin · Pathologic complete response

Abstract

Background: Triple-negative breast cancer (TNBC) attracts a disproportionate share of intensive research because of its poor prognosis. Standard anthracycline- and taxane-based regimens still yield an unsatisfactorily low rate of pathologic complete response (pCR). The pCR rate is a recognized surrogate marker for good long-term survival. **Methods:** A multicentric, retrospective study was conducted including all patients not willing to undergo or not suitable for an anthracycline-based regimen. Six cycles of docetaxel 75 mg/m² and carboplatin AUC 6 q3w were administered. The primary endpoint was pCR (ypT0/ypTis + ypN0) and near-pCR (≤5 mm residual disease). The secondary endpoint was feasibility (CTCAE version 4.03 criteria) and adherence to treatment. **Results:** Six cycles of carboplatin AUC 6 and docetaxel 75

mg/m² resulted in a high pCR rate of 50% and a combined pCR/near-pCR rate of 70%. Grade 3 and 4 toxicities were rare events and 28 of 30 (93%) patients completed all 6 cycles. No toxicity-related treatment discontinuation and no febrile neutropenia were registered. **Conclusion:** This chemotherapy regimen provides a highly effective and feasible strategy for patients not willing to receive or not suitable for an anthracycline-based treatment (cardiac ejection fraction <65% or age >65 years). Combinations of platinum compounds with taxanes and anthracyclines may be also desirable in TNBC.

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Introduction

Among human breast cancer subtypes, triple-negative breast cancer (TNBC) is a particularly heterogeneous group defined solely by the absence of expression of estrogen (ER) and progesterone receptors (PR) and HER2/

neu amplification [1, 2]. It has a prevalence of 11–20% in unselected cohorts of breast cancer patients [3–5] and has attracted a disproportionate share of intensive research because of its poor prognosis due to typical features like aggressive growth, rapid progression after recurrence [5, 6], and early metastatic spread [7, 8].

Although TNBC displays a greater chemosensitivity than other subtypes, reflected in higher pathologic complete response (pCR) rates to neoadjuvant chemotherapy, its recurrence rates are still the highest of all tumor biologies [6, 9–11] (triple-negative paradox) [12]. The current neoadjuvant or adjuvant treatment for TNBC is a combination or sequence of anthracycline- and taxane-based regimens [13]; the responses to other chemotherapeutic agents and combinations in patients who fail to respond to or relapse after treatment with these agents tend to be very brief. Multiple targeted therapies have been evaluated in preclinical and early-phase clinical studies in TNBC with controversially discussed efficacy.

The majority of breast cancers that develop in BRCA1 mutation carriers are triple negative [6, 14, 15]. Sensitivity to platinum-based agents has been demonstrated in pilot studies in BRCA1-positive patients [16]. While BRCA1 mutations are uncommon in so-called sporadic TNBC, these cancers may exhibit a dysfunctional BRCA pathway with deficient DNA mismatch repair and genomic instability [17, 18]. Given the similarities between sporadic TNBC and BRCA-associated tumors in the gene expression array, platinum analogues would seem to be a suitable addition to the standard chemotherapy approach [16, 19, 20].

The data of BCIRG 006 showed that omission of anthracyclines with a platinum- and taxane-based backbone is feasible in HER-2/neu-positive tumors [21]; this was previously reported in the 2nd interim analysis of the trial in 2006 [22]. The combination of docetaxel and carboplatin as neoadjuvant therapy has been evaluated in analyses of only small TNBC subgroups in other trials [23–25]. Because TNBC is associated with a poor prognosis unless a pCR is achieved [9], this case-cohort trial assesses the pCR rate associated with this combination in patients who were not suitable for or not willing to receive an anthracycline-based treatment.

Patients and Methods

Eligibility Criteria

Patients with histologically confirmed, primary, unilateral, nonmetastasized TNBC were eligible for this retrospective analysis if they were unsuitable for or had refused standard anthracycline-

based neoadjuvant chemotherapy. All patients were offered standard anthracycline-taxane-based treatment first. Patients refusing to take the risk of an anthracycline-containing regimen with views to its well-known cardiotoxic potential and opting for an alternative treatment schedule of taxane- and carboplatin-based therapy were included in our study. Patients considered not eligible for an anthracycline-taxane-based combination were patients with a reduced cardiac output with an ejection fraction <60% or patients aged >65 years.

Other inclusion criteria were: age ≥ 18 years, adequate baseline hematologic values (absolute neutrophil count $\geq 1.5 \times 10^9/l$, platelet count $\geq 100 \times 10^9/l$, and hemoglobin level ≥ 100 g/l), and normal hepatic and renal functions. Pregnancy or breast-feeding and prior chemotherapy for this cancer were exclusion criteria. This study complies with the principles of the Declaration of Helsinki and was approved by the institutional review board.

Immunohistochemical Evaluation

Core needle biopsies (≥ 3 representative samples) were used for immunohistochemical determination of HER-2/neu and hormone receptors (HR). All tests (IHC and FISH) were performed according to each of the institution's standards. HER2-negative disease was defined as IHC 0/1+ or a FISH ratio (HER2 gene copy/chromosome 17) <2.0 according to ASCO-CAP guideline recommendations [26]. Tumors with <1% positive cancer cells by IHC were classified as ER negative and PR negative [27]; 3 patients were included according to the older definition of $\leq 10\%$ positive cancer cells [28]. CK 5/6, CK14, CK17, and/or EGFR were utilized as markers for the basal-like subtype (basal-like breast cancer; BLBC). Patients in this cohort had not been tested for BRCA mutational status, and thus we expected a normal representation of the BRCA-subtype proportion of patients in our cohort and could not differentiate between potentially BRCA-mutated and wild-type-BRCA patients.

Response and Toxicity Assessment

The primary objective was to assess the pCR rate, defined as an absence of invasive tumor cells in the breast and axilla, with residual ductal carcinoma in situ (DCIS) allowed (ypT0/is + ypN0). Near-pCR was defined as residual disease (RD) ≤ 5 mm. The secondary objective was the feasibility of this drug combination in TNBC with regard to treatment-related toxicity. Side effects were classified according to CTCAE v4.03 [29] based on blood examinations and standardized patient questionnaires.

Treatment

All eligible patients were treated with 6 cycles of carboplatin AUC 6 and docetaxel 75 mg/m², both given intravenously as a 1-hour infusion every 21 days. Glucocorticoids and 5-HT₃ antagonists were administered as antiemetics. Granulocyte colony-stimulating factor and other supportive medications between cycles were permitted at the investigator's discretion. Patients with clinically negative axillary lymph nodes underwent a sentinel lymph node (SLN) biopsy before chemotherapy. After completion of the chemotherapy, all patients underwent breast conservation or mastectomy. Axillary lymph node dissection was performed in patients with clinically positive lymph nodes or if the pretherapeutic SLN biopsy showed lymph node involvement.

Statistics

The patient and tumor characteristics before the start of chemotherapy were summarized. Continuous data were expressed as medians, ranges, or means and categorical data as frequency percentages. A nonparametric Spearman's correlation test (two-tailed Spearman's rank correlation coefficient, r) was used to evaluate the bivariate relationship between ordinal data. Associations between basal-like status and pCR were correlated using a two-tailed Fisher's exact test. $p < 0.05$ was considered statistically significant.

Results

Patient and Tumor Characteristics

From January 2007 to December 2011, thirty patients with primary TNBC from 3 breast units were analyzed. Table 1 summarizes the patient and tumor characteristics. The mean age was 56.3 years (range 28–76). The majority of tumors were high-grade (G3: 77%), invasive ductal carcinomas NOS (90%).

Fifteen patients were clinically T1 and 13 were T2, whereas 2 were considered T4. Nineteen patients were pathologically node negative (pN0) and 7 were node positive (pN+) on pretreatment SLN sampling. Four patients with clinically positive axillary nodes (cN+) did not undergo SLN sampling. Thus, UICC stages were predominantly stage I and IIA (73%) at diagnosis.

Twenty-three samples were completely negative for HER2 (score 0); 6 were scored as 1+. One case had an IHC score of 2+ but was classified as HER2 negative by FISH analysis. Twenty-seven tumors were diagnosed as HR negative with less than 1% positive cancer cells by IHC. As noted above, 3 patients were considered HR negative with $\leq 10\%$ staining of cancer cells based on an older definition (PR 1%, $n = 1$; PR 4%, $n = 1$, and ER $\leq 10\%$, $n = 1$, not specified). Information on the BLBC immunophenotype was available in 21 out of 30 core needle biopsies, 12 of which were scored as BLBC. There was no significant correlation between patient age and the prevalence of BLBC.

Response to Neoadjuvant Chemotherapy

After completion of the chemotherapy, all patients underwent surgery (breast-conserving surgery, $n = 25$, and mastectomy, $n = 5$), yielding a breast conservation rate of 83.3%. Fifteen out of 30 patients (50.0%) achieved a pCR (ypT0/is + ypN0), including 4 patients with residual DCIS only. A near-pCR was found in 6 patients (20.0%) (ypT1mic, $n = 2$, and ypT1a, $n = 4$). Thus, a pCR or near-pCR was achieved in 70% of cases (fig. 1).

Table 1. Patient and tumor characteristics before chemotherapy

Age at diagnosis, years	
Mean	56.3
Range	28–76
Median	57
Age distribution, n (%)	
≤50 years	12 (40)
>50 years	18 (60)
Menopausal status, n (%)	
Premenopausal	12 (41.4)
Postmenopausal	17 (58.6)
Missing	1
Tumor size, mm	
Mean	25.5
Range	8.4–93
Median	20.2
Tumor stage, n (%)	
cT1a	0
cT1b	3 (10.0)
cT1c	12 (40.0)
cT2	13 (43.3)
cT3	0
cT4a	1 (3.3)
cT4b	1 (3.3)
Lymph node stage, n (%)	
pN0	19 (63.3)
pN1	6 (20.0)
pN2	1 (3.3)
pN3	0
no SLNB (cN1)	
(clinically positive lymph node)	4 (13.3)
UICC stage, n (%)	
I	11 (36.7)
IIA	11 (36.7)
IIB	5 (16.7)
IIIA	1 (3.3)
IIIB	2 (6.7)
IIIC	0
IV	0
Histological subtype, n (%)	
Invasive ductal (NOS)	27 (90.0)
+DCIS	2
Partial mucinous	1
Apocrine	2 (6.7)
Medullary	1 (3.3)
Grading, n (%)	
G1	1 (3.3)
G2	5 (16.7)
G2–3	1 (3.3)
G3	23 (76.7)
Basal-like phenotype, n (%)	
Basal-like	12 (57.1)
Non-basal-like	9 (42.9)
Missing	9

Fig. 1. pCR and near-pCR rates of 6 cycles of docetaxel 70 mg/m² and carboplatin AUC 6 in TNBC.

Fig. 2. Correlation of age with pCR/non-pCR.

Fig. 3. UICC stages before and after neoadjuvant chemotherapy.

A pCR or near-pCR was achieved in 83.3% (10/12) of patients aged ≤ 50 years versus 61.1% (11/18) in patients aged > 50 years, but there was no significant correlation between age and pCR ($r_{\text{Spearman's } \rho} = -0.12$; $p = 0.54$) (fig. 2). Patients with BLBC by IHC criteria were no more likely to achieve a pCR with this neoadjuvant regimen than those who were not (two-tailed $p_{\text{Fisher's exact test}} = 1.00$).

Of the 9 patients who did not achieve a pCR or near-pCR, 8 still had limited RD (ypT1); only 1 patient, who had T4b disease at diagnosis, still had locally advanced disease at surgery. Twelve patients underwent axillary lymph node dissection, and only 2 of them had positive

lymph nodes (ypN0, $n = 10$; ypN1a, $n = 1$, and ypN2a, $n = 1$). Five out of 7 patients with pretherapeutic positive sentinel nodes had no additional positive nodes in their axillae and all 4 patients with clinically positive axillae (cN1) converted to ypN0. Figure 3 displays the UICC stages before and after neoadjuvant chemotherapy.

Toxicity

Treatment was well tolerated. The only common grade 3 and 4 toxicities were leukopenia (CTCAE grade 3: 53.6%, grade 4: 7.1%) and neutropenia (CTCAE grade 3: 46.4%, grade 4: 28.6%); despite this incidence of grade

Table 2. Reported toxicities

Toxicities, n (%)	NCI-CTCAE		
	grade 1 or 2	grade 3	grade 4
Leukopenia	24 (85.7)	15 (53.6)	2 (7.1)
Neutropenia	15 (53.6)	13 (46.4)	8 (28.6)
Anemia	27 (96.4)	2 (7.1)	0
Thrombopenia	22 (78.6)	3 (10.7)	0
Febrile neutropenia	0	0	0
Infection	7 (24.1)	0	0
Allergy	4 (13.8)	2 (6.9)	0
Nausea	16 (55.2)	2 (6.9)	0
Emesis	2 (6.9)	1 (3.4)	0
Diarrhea	5 (17.2)	1 (3.4)	0
Mucositis	13 (44.8)	0	0
Fatigue	5 (17.2)	1 (3.4)	0
Joint pain	10 (34.5)	0	1 (3.4)
Edema	4 (13.8)	0	1 (3.4)
Dysesthesia	12 (41.4)	1 (3.4)	–
Skin toxicity	9 (31.0)	1 (3.4)	0
Liver values ↑	23 (76.7)	2 (6.7)	0
Creatinine ↑	20 (66.7)	0	0
Alopecia	29 (100)	–	–

3–4 neutropenia, no episodes of febrile neutropenia were reported and only 7 cases of grade 1 and 2 infection occurred. Grade 3 thrombocytopenia or anemia developed in 3 and 2 cases, respectively. While 41.4% of patients developed grade 2 dysesthesia, only 1 instance of grade 3 peripheral neuropathy was recorded. The more common grade 1 and 2 toxicities were hematologic, increased creatinine and liver values, mucositis, dysesthesia, and fatigue. Alopecia occurred in all documented patients. No fatal (CTCAE grade 5) toxicities were registered. We observed no correlation between age at diagnosis and the frequency or severity of toxicity events ($r_{\text{Spearman's } \rho} = -0.08$; $p = 0.70$). The toxicities reported during neoadjuvant chemotherapy are listed in table 2.

Dose Reduction and Interval Modification

Carboplatin dose reduction (to AUC 5) was required in 6 out of 30 cases (because of impairment of renal function, the patient's age, or hematologic side effects, especially thrombopenia and anemia); 3 of them received AUC 5 at baseline at the physician's discretion. Intercycle delays during chemotherapy for more than 3 days were required in 8 patients, on average for 7 days (primary cause: platelet count $<100/\text{nl}$). Of these patients, 8 experienced a treatment delay in more than 2 cycles; however, the delay exceeded 1 week only in 1 case.

Discussion

Neoadjuvant chemotherapy for TNBC is essentially limited to standard chemotherapeutic agents, with non-responding patients experiencing high rates of relapse and predilection for visceral metastasis [7, 8, 30, 31]. Our study population achieved a high pCR or near-pCR rate (70%) with neoadjuvant carboplatin (AUC 6) and docetaxel (75 mg/m^2), which exceeds most of the results reported with even anthracycline-taxane-containing regimens. We used carboplatin at the dosage of AUC 6 with docetaxel at 75 mg/m^2 because there is good evidence of its feasibility from BCIRG 006 in the Her2-positive early breast cancer setting [21, 22] as well as from treatment schedules in the first-line setting of ovarian cancer [32] and also non-small cell lung cancer [33].

The results were superior for younger patients, though this did not reach statistical significance, probably due to the sample size. Loibl et al. [34] also reported age as a predictive factor for achieving pCR in triple-negative patients (pCR rate 45% in patients aged ≤ 35 years vs. 31% in patients aged >35 years).

There was no apparent increment in the response for patients with BLBC as defined by immunohistochemical stains for cytokeratins and/or EGFR. BLBC patients and non-BLBC patients both derived equal benefits from our taxane-platinum-protocol, unlike in the GEICAM/2006-03 trial in which this effect could not be shown for the BLBC cohort [35]. However, the categorization of TNBC is almost certainly more complex than BLBC versus non-BLBC; Lehmann et al. [36] identified 6 TNBC subtypes in a cluster analysis of the gene expression profiles of 587 TNBC cases, each of which may have different response and resistance characteristics.

The addition of platinum analogues to standard chemotherapy in the neoadjuvant setting has been reported only in small cohorts in the treatment of TNBC. Cisplatin monotherapy showed higher response rates in BRCA1-mutated TNBC (pCR: 83%) [16]; however, a lower response rate of 21% in a non-BRCA-screened triple-negative cohort was reported earlier by Silver et al. [19]. Chen et al. [24] (carboplatin AUC 2 + paclitaxel 80 mg/m^2 q1w, 4 cycles) and Roy et al. [25] (carboplatin AUC 6 + docetaxel 75 mg/m^2 q2w + G-CSF, 4 cycles) reported pCR-rates of 33.3 and 44.4%, respectively, in triple-negative cohorts; however, the doses of carboplatin were lower than those used in this study. In studies utilizing similar carboplatin dosing, Chang et al. [23] (carboplatin AUC 6 + docetaxel 75 mg/m^2 q3w, 4 cycles) and Sikov et al. [37] (carboplatin AUC 6 q4w + paclitaxel 80

mg/m² weekly, 4 cycles) reported pCR rates of 54.5 and 66.6%, respectively, in TNBC. The pCR/near-pCR rate of 70.0% in this study is high in a relatively large cohort of patients (n = 30) receiving an anthracycline-free regimen. However, the cohort of patients treated in this study had an earlier stage of disease than patients included in some neoadjuvant trials, with 73% having stage I–IIA disease and only 13% having a clinically node-positive status, which likely contributed to the pathologic response results.

It may also be difficult to compare results across trials due to the different definitions of pCR used by various study groups [38–41]. Minimal RD, residual DCIS, and axillary lymph node involvement after chemotherapy are not consistently defined as RD or pCR. von Minckwitz et al. [40] compared the different definitions of pCR and their impact on prognosis. Patients with pCR, defined as no invasive and no in situ RD in the breast and axilla, showed the most favorable relapse-free survival and overall survival, while the inclusion of patients with RD reduced the prognostic significance of achieving a pCR [40]. However, a more extensive meta-analysis performed by Cortazar et al. [41] demonstrated that the inclusion of DCIS in the definition of pCR (like in our study) does not essentially change the survival outcomes of neoadjuvant-treated patients [41].

The use of platinum analogues also seems to have an impact on the overall survival in retrospective studies of locally advanced breast cancer. Hurley et al. [42] explored in their retrospective analysis different settings of anthracycline, taxane, and platinum combinations. Anthracyclines were applied before and after surgery, and thus this study is classified not as a pure neoadjuvant study. Furthermore, this trial did not include an anthracycline-free case cohort, which renders the impact of taxanes and platinum compounds unclear. Moreover, platinum-containing regimens show a high efficacy and tolerability in combination with taxanes in metastatic breast cancer [43].

Previous analyses have reported the pCR rates achieved using standard anthracycline- and taxane-based protocols in TNBC, such as the retrospective analysis of the MD Anderson Cancer Center with pCR rates of 11.8% for taxane monotherapies, 20.0% for FAC/FEC/AC regimens, and 28.0% for TFAC/TFEC protocols [9]. The highest pCR rates reported in TNBC from large, multicenter, prospectively randomized phase III trials have been with anthracycline- and taxane-based regimens, with rates of 34.9–38.9% in the GeparTrio trial (TAC) [44], with patients under 40 years of age achieving a pCR rate of 57% [45]. The results of retrospective analyses like

the MA5 trial [46] have been attributed to low levels of topoisomerase II α gene amplification. This is being analyzed further in several studies [6, 47, 48]. In exploratory analyses of the FINXX trial, the integration of capecitabine into an adjuvant regimen that also contains anthracyclines, taxanes, and cyclophosphamide has improved breast cancer-specific survival in TNBC (HR 0.64; 95% CI 0.44–0.95; p = 0.027) and also recurrence-free survival in women with more than 3 positive axillary lymph nodes [49]; however, recent studies of metastatic TNBC have shown that capecitabine-containing doublets like TX or NX have limited potency in the TNBC subtype [50].

Some patients in our study refused to take the risk of an anthracycline-containing regimen with the well-known increased probability of congestive heart failure earlier described by Von Hoff et al. [51]. A reduced cardiac output or an age >65 years are being associated with a higher risk of mortality. As Pinder et al. [52] published earlier, women aged 66–70 years who received adjuvant treatment with anthracyclines had a significantly higher risk of developing congestive heart failure. This effect continued to increase throughout more than 10 years of follow-up, as the authors pointed out [52]. Swain et al. [53] also reported a greater incidence of congestive heart failure with the use of anthracyclines in 3 NSABP trials with an age cutoff of 65 years. In general, they observed estimated cumulative percentages of 5% of patients at a cumulative dose of 400 mg/m², 26% of patients at 550 mg/m², and 48% of patients at 700 mg/m², and an HR of 2.25 (p = 0.029) for patients aged >65 years versus <65 years [53]. Considering the (long-term) risk of cardiotoxicity [54] and the potential risk of leukemia and myelodysplastic syndrome [55], especially after dose-dense G-CSF-supported anthracycline-based treatment, the development of an effective, well-tolerated non-anthracycline-based regimen for TNBC may be desirable.

This trial provides valuable information on the safety, feasibility, and efficacy of this platinum-taxane-based regimen in a study population with a wide age range, i.e. from 28 to 76 years, with very few necessary dose reductions and no age-dependent increase in toxicity. Of note, a large number of patients, i.e. 28 out of 30 (93.3%), completed all 6 cycles and a dose reduction from AUC 6 to AUC 5 was performed in only 16.6% of patients and no episode of febrile neutropenia occurred. The breast conservation rate was also very high, i.e. 83.3%, in our study population. Limitations of this study include that it represents a multicentric but nonrandomized single-arm study, with the treatment selected based on patient ineligibility for or refusal of a more standard regimen, as well

as the relatively early stage of many of the included patients at diagnosis. BLBC was determined by IHC and cytokeratins and not by intrinsic subtyping. We did not explore the BRCA1/2 mutation status in this trial, which might influence the response to the platinum-containing regimen. Follow-up data will be presented in a subsequent analysis. The sensitivity to neoadjuvant chemotherapy varies in different intrinsic breast cancer subtypes [56]. Larger prospectively randomized trials are studying the value of adding platinum analogues to neoadjuvant anthracycline/taxane regimens for TNBC. The addition of carboplatin in the prospective, randomized GeparSixto trial achieved an absolute increase of more than 20% in pCR (defined as ypT0 ypN0/is), i.e. from 37.9% (paclitaxel + myocet + bevacicumb) to 58.7% ($p < 0.05$) (paclitaxel + myocet + bevacizumab + carboplatin) in TNBC, as demonstrated by von Minckwitz et al. [57] at ASCO 2013. The CALBG 40603 trial presented by Sikov et al. [58] at the San Antonio Breast Cancer Symposium 2013 showed that the addition of carboplatin to paclitaxel in a sequential dose-dense anthracycline/cyclophosphamide-containing regimen significantly increased the pCR rates

(defined as ypT0/is, N any) in stage II/III TNBC from 46 to 60% ($p = 0.0018$). Bevacizumab increased the pCR in the breast (48 vs. 59%; $p = 0.0089$) but not in the breast and axilla (44 vs. 52%; $p = 0.057$) [58].

Molecular subgroup analyses in the RD might reveal further evidence of the mechanisms of primary chemotherapy resistance and potentially define prognostic markers for the therapy response of the different TNBC subtypes. Because pCR has been confirmed as a surrogate marker for improved long-term survival in TNBC, the addition of platinum analogues to standard anthracycline-taxane-based regimens in TNBC may contribute to favorable long-term outcomes in spite of the aggressiveness of this subtype of human breast cancer.

Acknowledgement

We thank André Scherag and Hildegard Lax of the Institute for Medical Informatics, Biometry and Epidemiology (IMIBE) for statistical advice, and Isabelle Krasowski, Birgit Klopries, and Susanne Herz for their diligent work with the patients and their contribution to data collection.

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