The role of carboplatin in the neoadjuvant chemotherapy treatment of triple negative breast cancer

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Abstract

Triple negative breast (TNBC) cancer constitutes a heterogeneous group of disease with histologic and molecular differences. Complete pathologic response to neoadjuvant chemotherapy (NACT) in TNBC is associated with improved outcomes. Efforts have been made in identifying drug combinations that will increase the response rate to preoperative chemotherapy. In this review we present recent studies that have incorporated carboplatin (Cb) in the NACT of TNBC. We discuss the homologous recombination deficiency score and the somatic or germline mutation for BRCA as potential biomarkers for future selection of patients that could benefit from the addition of Cb to NACT.

Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 20 percent of breast cancers (BC) diagnosed worldwide, representing almost 200,000 cases each year.[1] Epidemiologic studies illustrate a high prevalence of TNBC among younger women, when compared to the other BC subtypes. These patients are also at higher risk to develop brain or visceral metastasis.[2-5] In addition, it appears to be more common among black woman than whites, and is associated with the BRCA1 genetic mutation.[6,7] TNBC is characterized by the absence of expression of the estrogen (ER), progesterone receptors (PR) and lack of amplification of the human epidermal growth factor receptor 2 (HER2)/Neu gene.[8]

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Unlike hormonal receptor positive (HR+) and HER2 overexpressing breast cancers, TNBC is unresponsive to endocrine therapy and HER2-targeted agents and treatment options are limited to conventional cytotoxic chemotherapy.[9] Chemotherapy has been effective in the treatment of early-stage disease, with pathologic complete response (pCR) rates exceeding those of HR+ subtypes.[10,11] Patients with metastatic disease however experience rapid progression through several lines of chemotherapy, and overall survival (OS) in the metastatic setting is usually poor with reports being between 9 and 13 months.[12] Pathologic complete response rates to neoadjuvant chemotherapy (NACT) among patients with TNBC range from 27-45%, while pCR rate for patients with HER2 negative/HR+ breast cancer is generally around 10-20%.[13,14] Pathological complete response has been proposed as a surrogate endpoint for prediction of long-term clinical benefit, such as disease free survival (DFS) and OS.[14,15] However, while patients with TNBC who achieve a pCR appear to have a good DFS, patients with TNBC who have more than minimal residual disease at surgery have a much higher risk of early distant disease recurrence.[16-18]

Based on the fact that currently there are no approved targeted therapies for the neoadjuvant or palliative treatment of TNBC, identifying potential targets and developing effective targeted agents is greatly needed.

Heterogeneity of TNBC

It is well recognized that there are histologic and molecular differences in TNBC.[19] From the histology point of view, the majority of TNBC corresponds to the invasive ductal carcinoma type (IDC). Other less commonly seen histologies include: Medullary carcinoma, metaplastic carcinoma, adenoid cystic carcinoma and apocrine carcinoma.[20] The prognosis varies greatly among these different histology groups. Patients with metaplastic carcinoma have been identified to have higher relapse rates; a retrospective study by Bae and colleagues, demonstrated an inferior 3 year DFS in patients with lymph node metastasis who underwent adjuvant chemotherapy of 44.4% *vs* 72.5% when compared to TNBC-IDC (P=0.025).[21] Medullary carcinomas on the other hand, are believed to have a better prognosis. This was demonstrated in an analysis of 13 International Breast Cancer Study Group (IBCSG) trials, where the 14 year DFS was 89% for patients with medullary carcinoma (ER negative and high grade tumors) *vs* 63% for patients with TNBC-IDC (HR 0.24, P=0.002).[22] Adenoid cystic carcinomas have also been found to have a good prognosis with 5 year DFS typically above 90%.[23]

The triple negative clinical subtype comprises mainly the

basal-like molecular subtype, but caution should be used when referring to TNBC in general as "basal like" tumors. As an example, 172 triple-negative tumors based on IHC staining were correlated with gene expression profiles that defined the basal subtype and only 71 % of TNBC were consistent with the basal subtype.[24] At the molecular level, gene expression (GE) profiles from 587 TNBC cases by cluster analysis identified 6 TNBC types displaying unique GE and ontologies, including 2 basal-like (BL 1 and BL 2), an immunomodulatory (IM), a mesenchimal (M), a mesenchimal stem-like (MSL), and a luminal androgen receptor (LAR) subtype.[25] BL 1 and BL 2 subtypes have higher expression of cell cycle and DNA damage response genes, and representative cell lines that preferentially respond to platinum agents. The IM subtype is enriched for immune cell processes. M and MSL subtypes are enriched in GE for epithelial-mesenchymal transition and growth factor pathways, cell models of this the subtype responded to NVP-BEZ235 (a PI3K/mTOR inhibitor) and dasatinib (an abl/scr inhibitor). The LAR subtype includes patients with decreased relapse-free survival and is characterized by androgen receptor (AR) signaling. LAR cell lines were uniquely sensitive to bicalutamide (an AR antagonist).[25]

Recent NACT trials with Cb in TNBC

There is a large body of literature indicating that patients with aggressive breast cancer subtypes who obtain a pCR to NACT have a better prognosis; this is especially true for the hormonal receptor negative (HR-) BC subtypes.[17,18] Currently pCR is considered a surrogate endpoint for OS in patients receiving NACT for TNBC. The optimal chemotherapy regimen however remains to be determined. TNBC demonstrates sensitivity to DNA-damaging agents like platinum.[10] Based on this finding a number of clinical trials have sought to determine if adding Cb to anthracycline-taxane based or simply taxane NACT would increase the pCR rates (Table 1[26-34]).

In the phase II GeparSixto trial 315 patients with stage II to III TNBC were treated for 18 weeks with weekly paclitaxel (wP) 80 mg/m^2 and non-pegylated-liposomal doxorubicin 20 mg/m^2. Bevacizumab 15 mg/kg every 2 weeks (q 2w) was given concomitantly. All patients were randomized 1:1 to receive concurrently Cb AUC 2 but later on reduced to 1.5 secondary to toxicity. Primary outcome of the study was pCR rates.[26] The addition of Cb increased pCR from 37% in the control group to 53% in patients that received Cb (P=0.005). Hematological side effects were more common in the Cb group and included grade ≥ 3 neutropenia 65% *vs* 27%, grade ≥ 3 anemia 15% *vs* <1% and grade ≥ 3 thrombocytopenia 14% *vs* 1%. Cb was more often associated with dose discontinuation, in 48% with Cb and 39% without Cb (P=0.031).[26] The 3 year analysis shows that 85.8% of the patients treated with Cb were without evidence of disease *vs* 76.1% in the control group (HR 0.56, 95% CI 0.33-0.96, P=0.0350).[27]

In the randomized phase II trial conducted by the Cancer Leukemia Group (CALGB 40603), 443 patients with stage II to III TNBC received a backbone chemotherapy of wP 80 mg/m^2 for 12 weeks, followed by doxorubicin plus cyclophosphamide q 2w (ddAC) for four cycles and were randomly assigned to concurrent Cb AUC 6 every 3 weeks (q 3 w) for four cycles and/or bevacizumab 10 mg/kg q 2 w for nine cycles.[28] Employing one-sided P values, addition of either Cb (60% *vs* 44%; P=0.0018) or bevacizumab (59% *vs* 48%; P=0.0089) significantly increased pCR in the breast, whereas only Cb (54% *vs* 41%; P=0.0029) significantly raised pCR in the breast and axilla. Patients assigned to either Cb or bevacizumab were less likely to complete wP and ddAC without skipped doses, dose modification, or early discontinuation resulting from toxicity. Grade ≥ 3 neutropenia and thrombocytopenia were more common with Cb, as were hypertension, infection, thromboembolic events, bleeding, and postoperative complications with bevacizumab.[28] The analysis of event free survival (EFS) and OS with a median follow-up duration of 39 months, showed that treatment with Cb or bevacizumab did not significantly affect either outcome. The addition of Cb was associated with an EFS hazard ratio (HR) of 0.84 (95% CI 0.58-1.22, P=0.36) and a survival HR of 1.15 (95% CI 0.74-1.79, P=0.53). Outcomes were similar with the addition of bevacizumab.[29]

The ISPY-2, randomized 60 women whose tumors had a genomic signature consistent with TNBC to receive wP 80 mg/m^2 for 12 weeks, followed by ddAC for four cycles, with or without an experimental regimen consisting of Cb AUC 6 q 3 w for four cycles and the oral poly-ADP ribose polymerase (PARP) inhibitor, veliparib (50 mg twice daily by mouth).[30] The study demonstrated a pCR of 51% in the veliparib-Cb containing arm [95% probability interval (PI) 36-66%] compared to 26% in the control arm (95% PI 9-43%). Given the design of the study, it is difficult to determine how much the addition of the PARP-inhibitor added to the effect of Cb. Early detection of therapy response or resistance in the neoadjuvant setting may help to optimize the chemotherapy strategy. In the phase II Adjuvant Dynamic Marker-Adjusted Personalized Therapy (ADAPT) triple negative trial, 336 patients with centrally confirmed TNBC were randomized to receive nab-paclitaxel at 125 mg/m^2 either with Cb AUC 2 or Gemcitabine 1000 mg/m^2.[31] The study reported pCR of 45.9% *vs* 28.7 %, favoring the Cb containing arm. Early response was predictive of pCR regardless of the treatment arm. The observed efficacy in this study seems com-

Table 1. Selected Cb NACT trials in TNBC.

Study [reference]	Study design	Chemotherapy regimen	N	PCR definition used	PCR (%) Control	PCR (%) Platinum
GeparSixto[26]	Randomized phase II	wP + nPLD 20 mg/m^2 qw + B 15 mg/kg q 3w ± Cb AUC 1.5-2 qw x 18 w	315	ypT0 ypN0	37	53
CALGB 40603[28]	Randomized phase II	wP x 12 ± Cb AUC 6 q 3w x 4 → ddAC x 4 ± B 10 mg/kg q 2w x 9	433	ypT0/is ypN0	41	54
ISPY-2[30]	Randomized phase II	wP x 12 ± Cb AUC 6 q 3w x 4 + veliparib → ddAC x 4	60	ypT0/is ypN0	26	51
ADAPT[31]	Randomized phase II	weekly nap-paclitaxel 125 mg/m^2 + Cb AUC 2 or gemcitabine 1, 000 mg/m^2 on day 1 and 8 q 3w x 4	336	ypT0/is ypN0	28.7	45.9
Sharma *et al.*[34]	Observational	Cb AUC 6 + Docetaxel 75 mg/m^2 3w x 4-6 cycles	76	ypT0/is ypN0	na	66

Abbreviations: AC, doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2; ddAC, dose dense AC; Cb, carboplatin; AUC, area under the curve; B, Bevacizumab; wP, weekly paclitaxel 80 mg/m^2; nPLD, non-pegylated-liposomal doxorubicin; pCR, complete pathologic response; na, not available; qw, every week; q 2w, every 2 weeks; q 3w, every 3 weeks; ypT0 ypN0, absence of invasive cancer and *in situ* cancer in the breast and axillary nodes; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes, irrespective of carcinoma *in situ*.

parable to longer and less tolerable anthracycline-taxane containing regimens. Patients that did not achieve a pCR in the study were offered standard post-operative chemotherapy with epirubicin and cyclophosphamide for 4 cycles. It is unknown if outcome is affected by the type of chemotherapy administered in order to obtain a pCR. Anthracyclines are associated with long-term worrisome side effects, especially cardiotoxicity and leukemia.[32] There have been studies looking at omitting these agents in the adjuvant treatment of TNBC, but so far it has been demonstrated that 6 cycles of docetaxel in combination with cyclophosphamide is associated with a higher breast cancer recurrence, when compared to standard anthracycline-taxane based regimens.[33] This raises the question if results could be improved by combining docetaxel with Cb instead. A prospective multisite registry study evaluated Docetaxel in combination with Cb and included 76 patients with ≥ T1c to Stage III TNBC. Patients received 4-6 cycles of docetaxel 75 mg/m2 in combination with Cb AUC 6 given q 3 w. This regimen produced pCR in 66% of the patients. With a median follow up of 2.3 years the cohort of patients that achieve a pCR demonstrated a 95% recurrence free survival.[34]

Can we select patients that benefit from the addition of Cb to NACT?

Gene defects in the homologous recombination (HR) pathway are of potential therapeutic relevance in a variety of cancers. Clinical studies have demonstrated that BRCA1/2-deficient tumors are sensitive to both platinum salts and PARP-inhibitors.[35,36] The three DNA-based homologous recombination deficiency (HRD) scores: HRD-loss of heterozygosity score (LOH), HRD-telomeric allelic imbalance score (TAI), and HRD-large-scale state transition score (LST) are highly correlated with defects in BRCA1/2, and are associated with response to platinum therapy in triple negative breast and ovarian cancer.[37-40]

Analysis of triple negative tumors in the GeparSixto clinical trial found HR deficiency in 136 (70.5%) tumors; 82 (60%) of them showed high HRD score (LOH score + TAI score + LST score ≥ 42) without BRCA mutation. The study utilized the HRD assay developed by Myriad Genetics Inc. (Salt lake City, UT, https://www.myriad.com). HR deficiency was associated with a higher rate of pCR 55.9% *vs* 29.8% (P=0.001). Adding carboplatin (Cb) to the paclitaxel, non-pegylated-liposomal doxorubicin and bevacizumab combination increased the pCR rate from 45.2% to 64.9% in HR deficient tumors (P=0.025). This effect was also seen in patients with somatic BRCA mutations, where the pCR rate was increased from 38.1% to 69.7% with the addition of Cb (P=0.022). The pCR rate in the HR non-deficient patients was 20% without Cb and 40.7% with Cb, but did not reach statistical significance (P=0.146).[41]

Pooled analysis of six phase II clinical trials (including GeparSixto), in which patients with TNBC received a platinum agent, demonstrated that patients with high HRD score were significantly more likely to achieve a pCR than those with HR-non-deficient tumors: 53% *vs* 18% (adjusted odds ratio = 4.64; P<0.0001), regardless of BRCA1/2 mutation status.[42] To further support the fact that the presence of a BRCA-1 mutation confers high sensitivity to platinum agents, Byrski and colleagues treated 107 patients with BRCA-1 associated breast cancer with single agent cisplatin 75 mg/m^2 every 3 weeks for 4 cycles. The study demonstrated a very significant pCR rate of 61%, considering anthracyclines and taxanes were not given.[43]

Masuda and colleagues evaluated clinical outcomes in 130 patients based on subtypes of TNBC.[16] They found that patients with the basal-like 1 subtype had the highest pCR rate (52%). In contrast, those with the LAR subtype had one of the lowest pCR rates (10%). However, despite their low pCR rate, OS was better in patients with the LAR subtype.[16] These findings indicate that perhaps the LAR molecular subtype of TNBC may not benefit from more intense NACT protocols that add Cb.

Although specific tests are not approved or commercially available at the moment, it is possible that in the future, the NACT agents could be tailored according to the molecular subtype of TNBC. Adding Cb could be more beneficial in subtypes other than the LAR. It is also possible that addition of Cb could at some point be selected based on high HRD scores or the presence of a somatic or germline mutation for BRCA.

Prognostic significance of pCR in TNBC

Evidence from accumulated neoadjuvant studies reveals that pCR provides a surrogate marker that is predictive of long-term clinical response and survival in TNBC patients.[14,15] Despite its widespread use, there is still no uniform definition of pCR. Three definitions have been traditionally used by different investigators: i) ypT0 ypN0: absence of invasive cancer and in situ cancer in the breast and axillary nodes; ii) ypT0/is ypN0: absence of invasive cancer in the breast and axillary nodes, irrespective of carcinoma in situ; iii) ypT0/is: absence of invasive cancer in the breast, irrespective of ductal carcinoma in situ or nodal involvement.

Two large meta-analyses have looked at the long-term outcomes of patients achieving pCR after NACT. Both studies have demonstrated a major benefit in the long-term outcome from achieving a pCR in patients with aggressive BC subtypes (triple-negative; HR-/HER2-positive and high-grade HR+/HER2-negative).[17,18]

In the German Breast Group (GBG) and the *Arbeitsgemeinschaft Gynäkologische Onkologie* Breast (AGO-B) study groups, seven prospective clinical trials with a total of 6377 patients receiving neoadjuvant anthracycline-taxane-based chemotherapy were analyzed during a median follow up of 46.3 months. Prognostic impact of pCR on DFS was demonstrated in 4193 patients according to the breast cancer intrinsic subtype. The eradication of tumor from both breast and lymph nodes (ypT0/is ypN0 and ypT0 ypN0) compared to the absence of tumor in breast only (ypT0/is) revealed a stronger association with improved EFS and OS. TNBC represented 15% of the study group and demonstrated a pCR (ypT0 ypN0) of 44%. Progression free survival in this subgroup of patients with pCR was over 90% at 5 years (P<0.001).[17]

The US Food and Drug Administration established an international working group known as Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC). The study included 12 international neoadjuvant trials with 11,955 patients in the pooled responder analysis. Patients who achieved a pCR had longer EFS and OS than did patients with residual invasive cancer. Eradication of tumor from both the breast and axillary lymph nodes (ypT0pN0 and ypT0/is ypN0) was better associated with improved EFS and OS than was eradication of invasive tumor from the breast alone (ypT0/is). The association between pCR and long-term outcomes was strongest in patients with TNBC (EFS: HR 0.24, 95% CI 0.18–0.33; OS: 0.16, 0.11-0.25).[18] However, the trial-level association between pCR and long-term outcome by tumor subtype recorded no correlation between improvement in frequency of pCR and the treatment's effect on EFS or OS. It is possible that dif-

ferent biological subtypes of BC require a different end point definition regarding pCR to indicate a survival benefit and the inclusion of heterogeneous populations may have obscured the association. It has also been indicated that large increases in pCR between the control group and investigation arm will be needed in NACT studies to demonstrate a statistically significant change in survival.[44,45] This maybe the reason behind the fact that improvement in pCR by 20% in the case of the Neo-ALLTO trial, narrowly missed statistical significance in the ALLTO trial (HR 0.84, 97.5 % CI 0.70-1.02).[46,47]

Selected ongoing Cb NACT studies in TNBC

There are several studies evaluating various schedules and combinations of Cb in the NACT of TNBC (Table 2). The phase II NeoStop clinical trial determines the need for anthracyclines in the NACT setting by randomizing patients to a non-anthracycline containing arm of Docetaxel and Cb in standard dose and frequency given for six cycles vs. weekly paclitaxel in combination with Cb followed by ddAC. The study's primary endpoint is pCR rates (NCT02413320). The phase III PEARLY clinical trial is randomizing patients to receive a taxane-anthracycline chemotherapy plus or minus Cb, in either the neoadjuvant or adjuvant setting. The primary outcome of the study is five-year EFS, secondary outcomes include pCR rates and long-term effects of Cb (NCT02441933).

The 50-gene qPCR assay (PAM50) can identify the intrinsic biological BC subtypes using RNA isolated from more readily available formalin-fixed, paraffin-embedded (FFPE) tissue. These subtypes can also be assessed using a multiplexed gene-expression profiling technology (NanoString Technologies; Seattle, WA, USA). The PAM50 gene set provides a risk of relapse score not only in ER-positive, node negative patients (similarly to the Oncotype Dx Recurrence Score) but also in the ER negative disease. Additionally, the PAM50 assay is highly predictive of neoadjuvant response when considering all BC subtypes.[48] This test is being used to identify predictors of response to NACT with docetaxel and Cb (NCT01560663). The GeparOla multicenter, prospective, randomized, open-label phase II clinical trial, is testing the effect of adding olaparib to weekly paclitaxel and Cb followed by epirubin and cyclophosphamide (NCT02789332). Patients will have centrally confirmed tumor high HRD score and known germline BRCA and/or tumor BRCA mutation. The study is looking at pCR rates and assessing the effect of olaparib in this population of patients. Immune checkpoint inhibitors have demonstrated activity as single agents in the treatment of advanced TNBC.[49] The effect is potentiated by the addition of nab-paclitaxel.[50] To explore this effect in NACT of TNBC, the randomized clinical trial NeoTRIPaPDL1aims to evaluate the addition of atezolizumab to Cb and nab-paclitaxel in patients with locally advanced TNBC (NCT02620280).

Conclusions

The long-term survival effect of the addition of Cb to standard NACT regimens remains unclear. The 3 year follow up of the GeparSixto clinical trial demonstrated an EFS advantage favoring the Cb containing arm, while the CALGB40603 39 month median follow up report did not show a statistical difference in EFS or OS with the addition of Cb. It is important to understand that neither one of these two studies were powered to demonstrate EFS differences. Since there are no targeted therapies currently approved for the NACT of TNBC, we need to continue to rely on chemotherapies with the goal of increasing pCR rates. Based on the fact that pCR confers a good prognosis, it seems reasonable to continue to seek this outcome. The improvement in pCR seen in these trials however, comes at the cost of increased toxicity, dose reductions and omissions, which were needed in up to 40-50% of the patients. Ongoing randomized phase III clinical trials will hopefully provide more information on the survival effect, as well as on long-term toxicity with the addition of Cb to adjuvant chemotherapy (NCT02488967, NCT02441933).

Based on the fact that TNBC constitutes a heterogeneous group of disease, it is important to point out that future studies will need to individualize therapies according to the different subgroups of TNBC. Current studies have started to evaluate the addition of Cb to NACT based on high HRD scores. Other studies test its addition to patients with molecular profiling consistent with the basal subtype. Once the patients that are likely to benefit from the addition of Cb to NACT are identified, this may result in improved response to treatment demonstrated by higher rates of pCR. Most importantly, patients that are not likely to benefit will be spared from the additional toxicity of Cb.

Until more information is available, the addition of Cb to standard NACT for TNBC should be individualized. Currently it is acceptable to add it in the following cases: BRCA-associated BC, patients with inflammatory BC or for those who present with locally advanced disease. Patients should be healthy enough and clinically fit to tolerate the increased toxic effect of adding Cb to standard NACT. At this time, treating TNBC patients with NACT, which does not incorporates anthracyclines, remains investigation-

Table 2. Selected active NACT evaluating the addition of carboplatin in TNBC.

NCT Identifier (Acronym)	Phase	Study design	Chemotherapy regimen
NCT02413320 NeoSTOP	II	Randomized, open-label	wP x 12 + Cb AUC 6 q 3w x 4 → ddAC x 4 vs Docetaxel 75 mg/m^2 + Cb AUC 6 q 3w x 6
NCT02441933 PEARLY	III	Randomized, open-label	AC x 4 q 3 w → taxane (Docetaxel 75 mg/m^2 q 3w x 4 or wP x 12) ± Cb AUC 5 q 3w x 4
NCT02789332 GeparOla	II	Randomized, open-label	wP + olaparib 100 mg bid x 12 w or Cb AUC 2 q w x 12 → EC q 2-3w x 4
NCT01560663	II	Observational, case control	Docetaxel 75 mg/m^2 + Cb AUC 6 q 3w x 6
NCT02620280 NeoTRIPaPDL1	II	Randomized, open- label	Cb AUC 2 + nab-paclitaxel 125 mg/m^2 on day 1 and 8 q 3 w x 8 ± atezolizumab 1200 mg i.v. on day 1 q 3 w x 8

Abbreviations: AC, doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2; ddAC, dose dense AC; Cb, carboplatin; AUC, area under the curve; wP, paclitaxel 80 mg/m2 weekly; i.v, intravenous; bid, twice a day; qw, every week; q 2w, every 2 weeks; q 3w, every 3 weeks.

al. If possible, patients should be enrolled in ongoing Cb NACT studies looking to answer the questions raised above.

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