

# Extended Adjuvant Chemotherapy in Triple-Negative Breast Cancer

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## Keywords

Triple-negative breast cancer · Adjuvant chemotherapy · Duration of adjuvant therapy · Metronomic chemotherapy · Biologic agents

## Summary

Triple-negative breast cancer (TNBC) represents a heterogeneous breast cancer subtype with a poor prognosis. The optimal adjuvant chemotherapy regimen is still unknown. Although numerous large randomized trials have established the benefit of adjuvant anthracyclines and/or taxanes in TNBC, there is no preferred regimen for these patients. There is currently no guideline. Moreover, without knowing the optimal treatment backbone, it will not be possible to evaluate whether adding agents such as platinum or other novel therapies is beneficial for TNBC patients. Furthermore, the best duration of adjuvant treatment in TNBC is still unknown. This review will focus on results of clinical trials that analyzed the benefits of extending the duration of adjuvant treatment in TNBCs with maintenance treatments. We will further discuss promising results in favor of other new agents including capecitabine, metronomic treatment, and biological drugs.

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## Introduction

Triple-negative breast cancer (TNBC) is defined by  $\leq 1\%$  expression of the estrogen receptor (ER) and progesterone receptor, and normal human epidermal growth factor receptor 2 (HER2) gene copy number and expression. TNBC accounts for 12–17% of all breast cancers (BC). TNBC has shown an increased rate of BC-

related deaths within the first 5 years. Additionally, once metastatic, patients with TNBC have shorter overall survival (OS) in comparison to those with other subtypes. TNBC patients are prone to developing visceral metastases more often than bone metastases when compared to other subtypes. Generally, TNBC occurs in younger women. Despite the greater relative benefit of chemotherapy (CT) in this patient population and a large number of clinical trials in the last decade, no optimal neo/adjuvant CT regimen has been identified [1–4].

## Heterogeneity in TNBC

TNBC has a significant variability in pathological and morphological features with many potential molecular targets. Lehmann et al. [5] have proposed one of the most frequently used subclassifications, which includes 4 subtypes: 2 basal-like (BL1 and BL2), a mesenchymal, and a luminal androgen receptor subtype.

Approximately 70% of TNBCs contain 20% or more tumor-infiltrating lymphocytes (TILs) in the tumor stroma [6]. The generally higher level of TILs and the higher expression of immune checkpoint molecules in TNBC compared with ER-positive (ER+) BCs also makes TNBC an attractive target for immunotherapy. Immune-rich TNBC has a more favorable prognosis.

Androgen receptor-positive TNBC accounts for approximately 10% of all TNBCs and tends to have a more indolent course and share certain features with ER+ BCs, including expression of several estrogen-regulated genes and frequent PIK3CA mutations. Anti-androgens are being investigated as a potential treatment in this subset.

Germline *BRCA*-mutant TNBCs represent another potential therapeutically relevant subtype. Germline *BRCA1* and *BRCA2* mutations are more frequent in TNBC than in other BC subtypes. There is increasing evidence that germline *BRCA*-mutant BCs have above-average platinum sensitivity and increased sensitivity to poly(ADP-ribose) polymerase (PARP) inhibitors.

**Table 1.** Duration of adjuvant chemotherapy in triple-negative breast cancer (TNBC)

Study	Design	Patients, n	Endpoints	Results	Conclusion	Comments
EBCTCG (Early Breast Cancer Trialists' Collaborative Group) [10] overview	meta-analysis of data from 47 randomized controlled trials of prolonged poly-CT vs. no CT that started before 1990; 1 of the 2 types of comparison between different poly-CT regimens reviewed in this report was different durations of the same regimen	18,000 women in 47 trials of prolonged poly-CT vs. no CT 6,000 in 11 trials of longer vs. shorter poly-CT	comparison of longer vs. at least 6 months of poly-CT and longer vs. less than 6 months	a number of months of adjuvant poly-CT (e.g. with CMF or an anthracycline-containing regimen) typically produces an absolute improvement in 10-year survival of about 7–11% for women aged < 50 years at presentation with early BC, and of about 2–3% for those aged 50–69 years (unless their prognosis is likely to be extremely good even without such treatment)	overall, there were a non-significant 7% further reduction in recurrence with longer therapy and no difference in OS (1% increase)	no advantage in extending therapy beyond about 6 months; restriction to women aged < 50 years did not modify the findings; paper based on data collected and finalized between 1995 and 1997; for the analyses presented here, data were sought for all randomized trials that started before 1990
IBCSG (International Breast Cancer Study Group) Trial V [29, 30]	randomized trial: first group received a single perioperative course of adjuvant combination CT starting within 36 h of mastectomy; second group received 6 cycles of conventionally timed adjuvant CT starting 25–32 days after surgery; third group received both the perioperative cycle and the conventionally timed regimen	1,229 divided into 3 treatment groups	investigated the role of a single cycle of CMF immediately after surgery as compared with 6 or 7 cycles of the same treatment for patients with node-positive disease	median F/U 42 months; estimated 4-year DFS 40% for the single perioperative cycle, 62% for the longer conventionally timed regimen, and 60% for the combined program (p < 0.0001); OS differences also in favor of the longer treatments (p = 0.011).	although a single cycle of perioperative CT improved outcome compared with no adjuvant CT in node-negative disease, such treatment was found to be less effective than a longer duration of CMF in node-positive disease	without considering subgroups, these results suggest that optimal duration of adjuvant CMF therapy is more than 1 but not more than 6 28-day cycles
Colleoni et al. [31]	joint analysis of 2 trials: first study was a randomized trial of the German Breast Cancer Study Group (GBSG) [32]; second study was the IBCSG Trial VI [33]	481 node-positive BC patients (GBSG) 1,554 patients node-positive BC (IBCSG)	GBSG compared 3 vs. 6 cycles of days 1 and 8 iv CMF (modified Bona-donna regimen) with or without tamoxifen IBCSG compared 3 vs. 6 cycles of initial classical CMF (oral cyclophosphamide) with or without 3 additional single cycles of reintroduction CMF	GBSG: median F/U 10 years; IBSG: median F/U 7.9 years; results for all ER- tumors (n = 302) also showed a possible increased risk for the CMF ×3 group (RR 1.15, 95% CI 0.85–1.57; p = 0.37); 5-year DFS Kaplan-Meier: 48 ± 4% for 3 cycles vs. 54 ± 4% for 6 cycles of CMF; 5-year OS Kaplan-Meier: 60 ± 4% for 3 cycles vs. 71 ± 4% for 6 cycles of CMF; RR for patients aged < 40 years with ER- tumors was 1.57 and for those aged < 40 with ER+ tumors 1.54	both the IBCSG and the GBSG study showed that CMF ×3 may not be sufficient for ER- BC (RR 1.18 and 1.08, respectively), although the results were not statistically significant; the increased risk of relapse in the CMF ×3 group for patients aged < 40 years was observed for both ER+ and ER- BC patients	joint analysis considered ER values of ≥ 10 fmol/mg to be ER+; majority of patients in both the GBSG and the IBCSG trial had ER+ tumors (69–70%); results of subgroup analyses especially because some of the subgroups had small sample sizes; however, there is some biological rationale for expecting benefit from longer-duration therapy in the sub-population of patients with ER- tumors

**Table 1.** Continued on next page

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Study	Design	Patients, n	Endpoints	Results	Conclusion	Comments
Fisher et al. [34]	prospective trial	2,194 with BC non-responsive to tamoxifen	direct comparison, 6 courses of classical CMF (154 days) and 4 courses of AC combination (63 days)	median F/U 3 years	6 courses of classical CMF (154 days) and 4 courses of AC combination (63 days) yielded similar results despite the different durations	none
Clahsen et al. [35]	prospective randomized trial	452 node-positive BC	compared 24 months of low-dose CMF iv vs. no adjuvant treatment	median F/U 10 years; OS was significantly prolonged in the CT arm (HR 0.75, 95% CI 0.56–0.99; p = 0.04); 10-year OS (+/- SE) was 59% (+/- 3.6%) for the CT arm and 50% (+/- 3.7%) for the control arm; time to local relapse was significantly prolonged in the CT arm (HR 0.63, 95% CI 0.42–0.94; p = 0.02)	significantly prolonged OS in the low-dose CT arm was observed	patients with 1–3 positive axillary nodes and those with ER- tumors especially benefited from CT

CT = Chemotherapy; F/U = follow up; DFS = disease free survival; RR = relative risk; CI = confidence interval; HR = hazard ratio; ER = estrogen receptor; OS = overall survival; BC = breast cancer; CMF = cyclophosphamide, methotrexate, fluorouracil; AC = doxorubicin and cyclophosphamide; SE = standard error.

## Adjuvant Therapies for Early-Stage TNBC

The optimal adjuvant CT regimen is still unknown. A 6–9 times higher risk for relapse has been reported for patients with TNBC who do not achieve a pathologic complete response (pCR) with neoadjuvant treatment. Because of this strong prognostic effect, pCR was proposed as a surrogate for OS in these 2 BC subtypes [7–9]. Numerous clinical trials have been designed to test the value of further adjuvant therapy in TNBC patients with no pCR. Although numerous large randomized trials have established the benefit of adjuvant anthracyclines and/or taxanes in TNBC, there is no preferred regimen for these patients, unlike for those with other BC subtypes. There is currently no guideline. Moreover, without knowing the optimal treatment backbone, it will not be possible to evaluate whether adding agents such as platinum or other novel therapies is beneficial for TNBC patients. There are promising results in favor of other new agents including capecitabine (X), platinum-based agents, and ixabepilone.

### Duration of Adjuvant Chemotherapy in TNBC

Several trials have addressed the question of the optimal duration of adjuvant CT for BC patients. Duration of CT might be best tested in patients with ER-negative (ER-) tumors, where cytotoxic rather than endocrine effects of CT might prevail. Although this is a small subset compared with the entire BC population, it might represent a group with particular relevance for specific treatment analysis pertaining to questions of adjuvant CT.

Several trials are examining regimens that differ in duration of therapy but also in the drugs given. In these trials, the effects of treatment duration and drug choice are inextricably confounded. Differing conclusions about treatment duration are being reached.

CMF (cyclophosphamide, methotrexate, and fluorouracil) regimens were widely used in the 1990s, and were followed by the introduction of anthracycline-containing regimens and anthracycline/taxane regimens as suitable options for TNBC patients. In 1998, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [10] presented a meta-analysis of data from 47 randomized controlled trials of prolonged poly-CT versus no CT that started before 1990. 1 of the 2 types of comparison between different poly-CT regimens reviewed in this report was different durations of the same regimen. The analysis involved 6,104 women in 11 trials and evaluated the comparison of longer versus at least 6 months of poly-CT and longer versus less than 6 months. Overall, there were a non-significant 7% further reduction in recurrence with longer therapy and no difference in OS (1% increase). The restriction to women aged < 50 years did not modify these findings.

Table 1 summarizes the results of the most significant trials which addressed the question of the optimal duration of adjuvant CT.

The US Intergroup trial investigating the addition of 4 cycles of paclitaxel following 4 cycles of AC (cyclophosphamide, doxorubicin) demonstrated a small but significant improvement in disease-free survival (DFS) and OS for the longer adjusted regimen [11]. This improvement was observed almost exclusively among patients with ER- tumors who did not receive tamoxifen.

**Table 2.** Metronomics in adjuvant treatment of triple-negative breast cancer (TNBC)

Study	Design	Patients, n	Endpoints	Results	Conclusion	Comments
Nasr et al. [36]	prospective randomized trial: 78 patients were assigned to either 3 cycles of FEC100 and 3 cycles of docetaxel, carboplatin, followed by maintenance metronomic CM (C 50 mg oral daily, and M 2.5 mg oral BID days 1,2 of each week) for 1 year; 80 patients were assigned to 3 cycles of FEC100 and 3 cycles of docetaxel alone	158 TNBC patients TNM stages II–III	investigating the role of a metronomic approach as a maintenance treatment vs. no maintenance after standard adjuvant CT comparing DFS and OS	median F/U 52 months (95% CI 46–60 months) median DFS for maintenance group 28 months vs. 24 months for no maintenance (95% CI 9–36 and 8–34 months, respectively) (p = 0.05) median OS 37 and 29 months, respectively (95% CI 12–40 and 10–38 months) (p = 0.04) 4-year DFS 63 and 42%, while 4-year OS was 74 and 55% for maintenance vs. no maintenance (p = 0.05 and 0.04, respectively)	extended adjuvant metronomic CM showed improvement in the outcome parameters and was well tolerated	small sample size
IBCSG (International Breast Cancer Study Group) Trial 22-00 [37]	randomized, open-label, 2-arm, phase III trial	between 23 January 2001 and 27 December 2012, 1,086 patients were enrolled, and 1,081 patients (n = 542 in CM maintenance; n = 359 in no CM) were included in the intent-to-treat population	evaluation of efficacy and safety of 12-month CM maintenance regimen for 1 year vs. no CM after standard adjuvant CT; primary endpoint was DFS	for the pre-specified secondary analysis of the triple-negative cohort, at a median of 6.9 years F/U, the estimated 5-year DFS was 78.7% among patients assigned CM maintenance vs. 74.6% among those with no CM reduction in HR with CM maintenance vs. no CM was consistently observed for the primary endpoint of DFS (HR 0.80, 95% CI 0.60–1.06) no HR was observed for patients who received < 75% of the CM maintenance dose compared to those with no CM	addition of low-dose maintenance cytotoxic drugs after completion of standard adjuvant CT does not significantly improve DFS despite the low event rate and high non-adherence, patients with triple-negative node-positive disease assigned to CM maintenance had relative and absolute reductions in DFS events of 24 and 7.9%, respectively authors concluded that addition of CM maintenance treatment should not be recommended for women with hormone receptor-negative early BC	456 patients had fully reported dose information trend suggests a positive effect on selected subpopulations (node-positive TNBC, no pCR after neoadjuvant CT) good low-dose maintenance tolerability profile; incidence of grades 3/4 adverse events only 14% potential limitation of the trial is prolonged accrual period selection bias and type of adjuvant treatments used during more than a decade of accrual might have influenced the results observed; indeed, a shift toward anthracycline- and taxane-containing regimens was noted, and fewer patients received CMF-like adjuvant CT; treatment non-adherence was the second limitation for Trial 22-00

CT = Chemotherapy; F/U = follow up; DFS = disease free survival; RR = relative risk; CI = confidence interval; HR = hazard ratio; OS = overall survival; pCR = pathologic complete response; BC = breast cancer; FEC100 = fluorouracil, epirubicin, cyclophosphamide; CM = cyclophosphamide and methotrexate; CMF = cyclophosphamide, methotrexate, fluorouracil.

Hence, there are conflicting results on antitumor activity for CT administered for a prolonged time.

#### *Metronomics in the Adjuvant Treatment of TNBC*

The term metronomic CT was first introduced almost 20 years ago by Douglas Hanahan following the results of a preclinical study published by Jutah Folkman and Nob Kerbel [12, 13].

Chronically administered low-dose cyclophosphamide produces apoptosis of endothelial cells in the tumor microvasculature with a compromised repair process, which induces a prolonged antiangiogenic effect [12]. Low-dose methotrexate (M) inhibits endothelial cell proliferation in vitro and blocks endothelial cell growth factor-induced neovascularization in the rabbit cornea assay [14].

In the past 15 years, metronomic CT demonstrated clinical activity associated with a low incidence of adverse events (AEs) in patients with metastatic BC [15]. In 2014, André et al. [16] showed that metronomic CT has an immune-stimulatory effect through different mechanisms and an effect on tumor-initiating cells and on tumor dormancy, and might finally also interfere with the clonal evolution of tumors.

The antiangiogenic and pro-immune nature of metronomic CT makes TNBC a good candidate for re-induction of tumor dormancy or eradication of residual cancer cells [17].

Table 2 summarizes the results of the principal studies that investigated the role of a metronomic approach as maintenance treatment versus no maintenance after standard adjuvant CT in TNBC patients.

#### *Capecitabine in the Adjuvant Treatment of TNBC*

Several ongoing trials are addressing the intensification of adjuvant CT in TNBC patients, either through integration of novel agents into the adjuvant setting such as platinum, X, ixabepilone, or bevacizumab, or through introduction of maintenance therapy such as X (CIBOMA and SYSUCC-001) or bevacizumab (BEATRICE).

Preliminary results of the CREATE-X (JBCRG-04) trial by the Japan Breast Cancer Research Group were presented at the 2015 San Antonio Breast Cancer Symposium [18]. The trial randomized 910 patients to observation versus 8 cycles of X therapy, and reported improved rates of 2-year DFS (87.3 vs. 80.5%;  $p = 0.001$ ) and OS (96.2 vs. 93.9%;  $p = 0.086$ ) with X. All of the observed benefit was driven by the improved outcome in the ER- subpopulation ( $n = 296$ ) of the study.

Chen et al. [19] evaluated the clinical value of X-based combination adjuvant CT in early BC (EBC). The authors analyzed 8 randomized controlled trials with 14,072 participants. X-based combination adjuvant CT demonstrated a 16% increase in BC-specific survival (BCSS) (hazard ratio (HR) 0.84, 95% confidence interval (CI) 0.71–0.98;  $p = 0.03$ ) in the OS analysis and a 22% improvement in DFS (HR 0.78, 95% CI 0.64–0.96;  $p = 0.02$ ) in the hormone receptor-negative subgroup. However, there were no significant differences in DFS (HR 0.96, 95% CI 0.89–1.05;  $p = 0.38$ ), OS (HR 0.91, 95% CI 0.82–1.00;  $p = 0.06$ ), or relapse between X-based and X-free combination adjuvant CT. Regarding safety, reduced myelosuppression and hand-foot syndrome (HFS) development were

observed in X-treated patients. X-based combination adjuvant CT might provide some BCSS benefit compared with X-free regimens in EBC, but the absolute survival gain is small, and the survival benefit appears to be restricted to patients with hormone receptor-negative EBC, which may indicate a target population for X-based combination adjuvant CT.

In 2015, Alagizy et al. [20], in a prospective phase II study, evaluated the tolerability and efficacy of metronomic X as an extended adjuvant treatment for women with TNBC. The trial enrolled 41 patients between June 2010 and December 2013. The patients received 500 mg X orally BID continuously for 6 months after 6 cycles of adjuvant CT with FEC100 (fluorouracil, epirubicin, cyclophosphamide)  $\pm$  postoperative radiotherapy. The choice of giving uniform adjuvant CT to the patients enrolled allowed better assessment of the efficacy of metronomic X. The study showed that extended adjuvant metronomic X was well tolerated with no grade 3 or 4 toxicities or life-threatening AEs at all. Only 6 (15%) relapse events occurred. The incidence of both local and distant relapses was lower in comparison to other studies, but a larger sample and longer follow-up are required for better and more mature results. The effect of lower-dose X on DFS needs to be evaluated in a larger phase III study.

CIBOMA 2004–01/GEICAM 2003–11 [21] is a multicenter, open-label, randomized phase III trial evaluating the efficacy of maintenance treatment with X in operable TNBC node-positive patients (or node-negative with a tumor diameter of  $\geq 1$  cm) who have received standard anthracyclines and or taxane-containing CT. Patients were randomized to Arm B (8 cycles of 1,000 mg/m<sup>2</sup> X BID, days 1–14, q21d) or the observation (Arm B). The primary endpoint was DFS. The first safety data, presented at the 2010 San Antonio Cancer Symposium [22], revealed that the safety profile of adjuvant X as maintenance therapy was consistent with its known toxicity profile. More than 75% of patients were able to continue their treatment as planned with approximately 15% discontinuing due to toxicity or withdrawal. Grade 3/4 AEs were higher with maintenance X: HFS 17.4%, diarrhea 2.9%, vomiting 1.0%, and elevated bilirubin 1.0%.

SYSUCC-001 [23] is an open-label, randomized phase III trial evaluating the efficacy of adjuvant X metronomic CT in TNBC. In this study, which is still recruiting participants, patients with early TNBC are randomized to treatment with standard adjuvant CT alone or standard adjuvant CT followed by 1 year of X metronomic therapy 650 mg/m<sup>2</sup> BID. No published data are yet available.

#### *Biological Agents in the Adjuvant Treatment of TNBC*

In another effort to evaluate the benefit of maintenance treatment for TNBC patients, the BEATRICE study [24] enrolled 1,290 patients to receive CT alone and 1,301 to receive bevacizumab (B) plus CT between 3 December 2007 and 8 March 2010. Most patients received anthracycline-containing therapy; 1,638 (63%) of the 2,591 patients had node-negative BC. At the time of analysis for invasive DFS (IDFS), median follow-up was 31.5 months (interquartile range 25.6–36.8) in the CT alone group and 32.0 months (27.5–36.9) in the B group. The 3-year IDFS was 82.7% (95% CI 80.5–85.0) with CT alone and 83.7% (81.4–86.0) with B and CT.

After 200 deaths, no difference in OS was noted between the groups (HR 0.84, 95% CI 0.64–1.12;  $p = 0.23$ ). Use of B versus CT alone was associated with increased incidences of grade 3 or worse hypertension (154 (12%) vs. 8 (1%) patients), severe cardiac events occurring at any point during the 18-month safety reporting period (19 (1%) vs. 2 (< 0.5%)), and treatment (B, CT, or both) discontinuation (256 (20%) vs. 30 (2%)). B cannot be recommended as adjuvant treatment in unselected patients with TNBC. Further follow-up needs to assess the potential effect of B on OS.

Based on these data, the use of metronomic X may gain more interest due to its low toxicity profile and lower price tag.

The findings that a subset of TNBC is immunogenic and actively involves the immune system [25–28] provides a strong rationale for testing immunotherapies or drugs with an immunomodulatory mechanism of action. Different trials are ongoing to establish the role of immune checkpoint inhibitors alone or in combination, and of other immunotherapies or CT in TNBC.

Metronomic CT coupled with anticancer vaccines has also been investigated to determine whether this combination could be a promising approach.

Ongoing and planned studies in North America, such as the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) EA1131 (NCT02445391) and SWOG (Southwest Oncology Group) S1418, are trying to define the role of X, platinum CT, or immune checkpoint inhibitors in patients with no pCR after neoadjuvant treatment. The EA1131 trial is randomizing patients to either X or carboplatin for 6 cycles.

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The S1418/BR006 trial, conducted jointly by the Southwest Oncology Group (SWOG) and the National Surgical Adjuvant Breast and Bowel Project/Radiation Therapy Oncology Group/Gynecologic Oncology Group (NRG), is randomizing patients to observation or 1 year of pembrolizumab adjuvant therapy.

## Conclusion

Further progress is needed to improve the outcome of TNBC patients in the adjuvant setting. Post-neoadjuvant strategies need further proof of benefit before becoming a standard approach. Low-dose maintenance therapy remains an attractive approach for additional studies in TNBC because of its low cost and good manageability and tolerability. Future plans should include a study evaluating low-dose oral maintenance for those TNBC patients who continue to have high-risk disease in the post-adjuvant and post-neoadjuvant setting.

## Disclosure Statement

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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