TRIPLE NEGATIVE BREAST CANCER: NEOADJUVANT AND ADJUVANT TREATMENT

ESMO PRECEPTORSHIP ON BREAST CANCER

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BACKGROUND

- Triple negative breast cancers (TNBC) comprise 12-20% of all breast cancer and are a heterogenous group of tumors, both clinically and pathologically.
- These cancers are characterized by the lack of expression of the hormone receptors, oestrogen receptor (ER) and progesterone receptor (PR) combined with the lack of either overexpression or amplification of the human epidermal growth factor receptor 2 (HER2) gene.
- The majority (around 70%) are basal-like breast cancers, and this subtype is defined by an overexpression of Epidermal Growth Factor Receptor 1 (EGFR-1) and basal cytokeratins, particularly the cytokeratin 5/6 (CK5/6) as well as cytokeratins 14 and 17.
- These pathological basal cell type TNBC have a typical histopathological appearance, most being poorly differentiated, grade three carcinomas, with some or all of the following microscopic features:
  - a solid growth pattern
  - a prominent lympho-plasmacytic infiltrate
  - a medullary-like growth pattern.
- Tumour cells are characteristically markedly pleomorphic with pleomorphic nuclei, prominent mitotic activity and well-marked cellular apoptosis.
• There is often quite extensive geographic tumor necrosis which can be associated with the exceptionally high proliferative rate of these tumors. Some exhibit prominent stromal fibrosis. Characteristically these tumors have a “pushing” rather than an infiltrative border.

• While most of these tumors show the basal-like molecular characteristics some may show squamous differentiation and even spindle cell morphology (metaplastic carcinomas). These last two histologic variants have been regarded to be basal-like variants.

• Other types of tumors classified as TNBC include some carcinomas morphologically designated as of no specific type (NST), salivary gland like carcinomas (particularly the adenoid cystic carcinomas and myoepithelial carcinomas), occasional examples with lobular, and/or mixed features, whilst some papillary and secretory-like carcinomas may also be triple negative.
Gene expression array analysis has identified six different groups of TNBC including:
- two basal-like subtypes
- an immune-modulatory variant
- a mesenchymal subtype
- a mesenchymal stem-like variant
- a luminal androgen receptor subtype.

Up to 70% of patients with BRCA1 mutations develop tumors that are morphologically identical to the basal cell-like carcinomas and are often triple negative. These probably form a further subset of the basal-type carcinomas, but not all BRCA1-associated tumors are TNBC.
NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC
Treatment of LABC

- Multimodality treatment strongly indicated in almost all cases
- Initial therapy should be systemic
- Initial therapy depends on tumour and patient characteristics

**HR+ HER2- LABC**
- Non-inflammatory
  - Endocrine therapy
  - Operable tumour
    - Non-inflammatory
      - BCS if appropriate
      - RT (if not given previously)
    - Inflammatory
      - Mastectomy
      - RT (if given previously)

**Triple-negative LABC**
- Inflammatory
  - ChT
  - Operable tumour
    - Non-inflammatory
      - BCS if appropriate
      - RT (if not given previously)
    - Inflammatory
      - Mastectomy
      - RT (if given previously)

**HER2+ LABC**
- ChT + anti-HER2 therapy
- Operable tumour
  - Further systemic treatment (if appropriate)
  - Tumour remains inoperable
    - RT
    - Palliative care
  - Inflammatory
    - Mastectomy
    - Adjuvant endocrine therapy/continuation of anti-HER2 (if appropriate)
NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC

- The lack of a predictive marker in identifying potential targets for the treatment of TNBC leaves a gap in the advancement of the neoadjuvant treatment for this subgroup of between 11 to 20% of breast cancer patients.
- Conventional cytotoxic chemotherapy and DNA damaging agents continue to be the mainstay for treatment of this disease.
- Platinum agents have seen renewed interest in TNBC based on an increasing body of preclinical and clinical data suggesting encouraging activity.
- Several studies have now demonstrated that TNBC has significantly higher pathologic complete response (pCR) rates compared to hormone receptor positive breast cancer when treated with neoadjuvant chemotherapy and pCR correlates well with improved outcomes.
NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC

- A large retrospective study from the MD Anderson Cancer Center compared the response to neoadjuvant therapy in TNBC compared to non-TNBC.
- The study consisted of 1,118 patients treated between 1985 and 2004. Analysis of a prospectively collected clinical database was performed. Two hundred fifty-five patients (23%) had TNBC.
- Patients with TNBC compared with non-TNBC had significantly higher pCR rates (22% v 11%; P = .034), but decreased 3-year progression-free survival (PFS) rates (P < .0001) and 3-year overall survival (OS) rates (P < .0001).
- TNBC was associated with increased risk for visceral metastases (P = .0005), lower risk for bone recurrence (P = .027), and shorter post recurrence survival (P < .0001).
Recurrence and death rates were higher for TNBC only in the first three years.

If pCR was achieved, patients with TNBC and non-TNBC had similar survival ((94% and 98%, P = 0.24). In contrast, patients with residual disease following neoadjuvant chemotherapy had worse OS if they had TNBC compared with non-TNBC (68% vs. 88%, p=.0001).

Thus patients with TNBC have increased pCR rates compared with non-TNBC, and those with pCR have a good survival. On the other side of the spectrum, patients with residual disease following neoadjuvant chemotherapy have significantly worse survival if they have TNBC compared with non-TNBC, particularly in the first three-years.


Another retrospective study was conducted in 435 patients between 1985 and 2003 on patients treated with neoadjuvant therapy for breast cancer. The ER negative tumors were more likely to achieve a pCR than ER positive (21.6% vs. 8.1%). OS at five years was significantly higher in the ER negative subgroup, which achieved a pCR (TNBC 90% vs. Non-TNBC 52%) in agreement with previous observations.
NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC
AC TO TAXANE PRE OP

- The NSABP B-27 trial randomized 2,411 women to one of three treatment arms to evaluate the response to neoadjuvant therapy and long-term outcomes.
- Patients received either four cycles of standard AC every three weeks followed by surgery, four cycles of AC followed by four cycles of docetaxel and afterwards surgery, or four cycles of AC followed by surgery and then four cycles of adjuvant docetaxel.
- The addition of preoperative docetaxel almost doubled the pCR rate from 12.9% and 14.4% in each of the two AC arms, to 26.1% in the AC-D arm.
- Determination of hormone receptor status was not required for study entry, however subgroup analysis showed that the pCR rate almost doubled with the addition of docetaxel for both the ER positive and ER negative tumors, from 5.7% to 14.1% and 13.6% to 22.8%, respectively.
- The pCR rate of the ER negative subset itself was nearly double that of the ER positive subset in each treatment group (5.7% vs. 13.6% for AC, and 14.1% vs. 22.8% for AC-D).
- Patients who achieved a pCR had significantly better DFS and OS outcomes compared with patients who did not.
NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC AC TO TAXANE

- The GEPAR DUO trial also evaluated the pCR rate in 913 women randomized to receive preoperative doxorubicin and docetaxel for four cycles or doxorubicin and cyclophosphamide for four cycles followed by docetaxel for four cycles.
- Overall pCR rate was 10.6% in the entire study population. There was an improvement from 7.0% for patients treated with doxorubicin and docetaxel to 14.3% with the three-drug regimen.
- In this study, the ER negative subgroup was three times more likely to achieve a pCR compared with the ER positive subgroup (22.8% vs. 6.2%).
- Triple-negative tumors could be divided into subgroups with different pCR rates according to their Ki-67 proliferation rate. Responses were more likely if the Ki-67 level was greater than 20% (P < 0.0001).
NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC TAC

In GEPAR-TRIO 2,072 women with operable breast cancer, tumor size of 2 cm or locally advanced disease (T4 or N3)

- All treated with 2 cycles of neoadjuvant TAC
- If tumor reduction was >50% according to breast ultrasound, pts were randomized to receive either 4 or 6 additional cycles of TAC.
- Non-responders randomized to either an additional 4 cycles of TAC or 4 cycles of Vinorelbine and Capecitabine.

1390 (66.5%) were randomly assigned as responders after two initial TAC cycles to receive an additional four (n = 704) or six (n = 686) TAC cycles.

- Rates of pathological complete response were not statistically significantly different between the arms (21.0% with 6 TAC cycles and 23.5% with 8 TAC cycles; difference = 2.5%, 95% confidence interval [CI] = -1.8% to 6.8%; P = .27).
- Grade 3 or 4 leukopenia and oedema and various grade 1 or 2 adverse events were more frequent in patients receiving 8 TAC cycles than in those receiving 6 cycles.
- The rate of breast-conserving surgery was similar in both arms (67.5% vs 68.5%, respectively, P 0.68).
- Eight cycles of TAC cannot be recommended.
Studies suggest that the sequential use of an anthracycline with a taxane is associated with better results than their concurrent use.

It is impossible to determine whether the observed benefit is a result of the sequential use or because of differences in total delivered dose of chemotherapy (higher in the sequential arm) or treatment duration (longer in the sequential arm).
Anti-angiogenesis therapy was evaluated TNBC in the GeparQuinto (GBG 44) study.

This trial assessed the pCR rate after neoadjuvant epirubicin, cyclophosphamide and docetaxel containing chemotherapy with and without bevacizumab in patients with TNBC.

The study included patients with untreated T1c-4d TNBC and represented a stratified subset of the 1948 participants of the HER2-negative part of the GeparQuinto trial.

Randomized patients received four cycles of epirubicin at a dose of 90mg/m2 and cyclophosphamide 600 mg/m2 every three weeks followed by four cycles docetaxel at a dose of 100 mg/m2 every three weeks each with or without bevacizumab at a dose of 15 mg/kg, every three weeks added to backbone chemotherapy treatment.

A total of 340 TNBC patients were randomized to chemotherapy without and 323 with bevacizumab respectively. The primary end point was pCR (pT0 pN0).

pCR rates were 27.9% without and 39.3% with bevacizumab (P = 0.003). Bevacizumab treatment was confirmed as independent predictors of higher pCR in multivariate logistic regression analysis.

The German group concluded that the addition of bevacizumab significantly increases pCR rates compared to chemotherapy without bevacizumab in TNBC…. However
These findings were not confirmed in NSABP B-40 neoadjuvant trial of 1206 patients.

Women were randomly assigned to receive neoadjuvant chemotherapy consisting of docetaxel at a dose of 100 mg/m\(^2\) on day 1, or docetaxel 75 mg/m\(^2\) plus capecitabine 825 mg/m\(^2\) twice a day on days 1 to 14, or docetaxel 75 mg/m\(^2\) on day 1 plus gemcitabine 1000 mg/m\(^2\) on days 1 and 8 for a total of four cycles.

All regimens followed by treatment with doxorubicin and cyclophosphamide at standard doses for four cycles.

Patients were also randomly assigned to receive or not to receive bevacizumab at a dose of 15 mg/kg of body weight for the first six cycles of chemotherapy.

Although there was a numerically higher pCR rate in patients with TNBC that received bevacizumab this was not clinically significant. The addition of bevacizumab increased the rate of pCR in the breast, from 28.2% to 34.5% (P=0.02).

When the rate of pathological complete response was examined according to hormone-receptor status, the effect of bevacizumab was more pronounced in the hormone receptor positive subset (15.1% without bevacizumab vs. 23.2% with bevacizumab, P=0.007), with a weaker effect in the hormone receptor negative subset (47.1% without bevacizumab vs. 51.5% with bevacizumab, P=0.34).

Bevacizumab plus chemotherapy led to an increase in toxicity in both clinical trials, particularly hypertension, cardiac dysfunction and mucositis and can not be recommended as a standard of care.
NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC
TIL IMPLICATIONS

- Tumor-infiltrated lymphocytes (TILs) have been identified in both tumor and stromal tissues. Intratumoral TILs (It-TILs) are lymphocytes that have a direct interaction with cancer cells, whereas stromal TILs (Str-TILs) are lymphocytes localized in the peripheral stromal area. Considering BC subtypes, TNBCs have the highest tumor TIL expression (~20%) compared to other BC subtypes.

- A subsequent analysis of the GeparQuinto trial by the same German group prospectively validated that an increased lymphocytic infiltrate in breast tumor tissue is predictive for a response to anthracycline and taxane based neoadjuvant chemotherapy, and associated with a significantly improvement in pCR rates.

- A prospective evaluation of TILs in the GeparSixto trial found that lymphocyte-predominant (LP) BC, defined as tumors with lymphocytic infiltrate greater than 50%, were more likely to achieve pCR as compared to non-LP BCs (59.9% vs 33.8%; p < 0.001). The addition of carboplatin to anthracycline and taxane in LPBCs further increased the pCR rate up to 75% (p = 0.002).

- The predictive role of TILs primarily suggested by some small retrospective data was confirmed by the large meta-analysis present at the SABCS 2016, where a total of 3,771 tumors from the clinical Gepar studies (Gepar-Duo, GeparTrio, GeparQuattro, GeparQuinto, GeparSixto, and GeparSepto) were evaluated for the presence of TIL. These results suggest TILs are a strong predictive marker for response to NST in all BC subtypes. This predictive value was translated into a survival benefit in the TNBCs group.
The GeparSixto study is researching the addition of carboplatin to neoadjuvant therapy for patients with early-stage TNBC as well as HER2-positive disease.

Patients were treated for 18 weeks with paclitaxel (80 mg/m\(^2\) once a week) and non-pegylated liposomal doxorubicin (20 mg/m\(^2\) once a week). Patients with triple-negative breast cancer received simultaneous bevacizumab (15 mg/kg intravenously every 3 weeks).

The primary endpoint the proportion of patients who achieved a pathological complete response

Of the patients with triple-negative breast cancer, 84 (53·2%, 54·4–60·9) of 158 patients achieved a pathological complete response with carboplatin, compared with 58 (36·9%, 29·4–44·5) of 157 without (p=0·005)

Haematological and non-haematological toxic effects that were significantly more common in the carboplatin group than in the no-carboplatin group included grade 3 or 4 neutropenia (192 [65%] vs 79 [27%]), grade 3 or 4 anaemia (45 [15%] vs one [<1%]), grade 3 or 4 thrombocytopenia (42 [14%] vs one [<1%]), and grade 3 or 4 diarrhoea (51 [17%] vs 32 [11%]); carboplatin was more often associated with dose discontinuations

The addition of neoadjuvant carboplatin to a regimen of a taxane, an anthracycline, and targeted therapy significantly increases the proportion of patients achieving a pathological complete response in patients with triple-negative breast cancer.
NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC PLATINUM ADDITION

- In 2018 the GeparSixto survival data and the potential prognostic and predictive role of homologous recombination deficiency (HRD) was publish in Annals of Oncology.
- The secondary study end points disease-free survival (DFS) and overall survival (OS) were analyzed. Median follow-up was 47.3 months. HRD was among the exploratory analyses in GeparSixto and was successfully measured in formalin-fixed, paraffin-embedded tumor samples of 193/315 (61.3%) participants with TNBC. Homologous recombination (HR) deficiency was defined as HRD score ≥42 and/or presence of tumor BRCA mutations (tmBRCA).
- A significantly better DFS (hazard ratio 0.56, 95% CI 0.34-0.93; P = 0.022) was observed in patients with TNBC when treated with PMCb.
- The improvement of OS with PMCb was not statistically significant. Additional carboplatin did not improve DFS or OS in patients with HER2-positive tumors.
- HR deficiency was detected in 136 (70.5%) of 193 triple-negative tumors, of which 82 (60.3%) showed high HRD score without tmBRCA. HR deficiency independently predicted pCR as adding carboplatin to PM significantly increased the pCR rate from 33.9% to 63.5% in HR deficient tumors (P = 0.001), but only marginally in HR nondeficient tumors (from 20.0% to 29.6%, P = 0.540).
NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC PLATINUM ADDITION

- The Cancer and Leukemia Group B (CALGB) 40603 also evaluated the addition of carboplatin and or bevacizumab to standard chemotherapy in the neoadjuvant setting for TNBC.

- Patients (N = 443) with stage II to III TNBC received paclitaxel 80 mg/m$^2$ once per week (wP) for 12 weeks, followed by doxorubicin plus cyclophosphamide once every 2 weeks (ddAC) for four cycles, and were randomly assigned to concurrent carboplatin (area under curve 6) once every 3 weeks for four cycles and/or bevacizumab 10 mg/kg once every 2 weeks for nine cycles.

- Patients assigned to either carboplatin 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 carboplatin, as were hypertension, infection, thromboembolic events, bleeding, and postoperative complications with bevacizumab.

- Employing one-sided $P$ values, addition of either carboplatin (60% v 44%; $P = .0018$) or bevacizumab (59% v 48%; $P = .0089$) significantly increased pCR breast, whereas only carboplatin (54% v 41%; $P = .0029$) significantly raised pCR breast/axilla. More-than-additive interactions between the two agents could not be demonstrated.

- The addition of Cb or Bev to standard NACT for TNBC did not improve Long Term Treatment Outcomes (LTOs) in this trial, although it should be noted that the trial was not powered for this endpoint.
NeoAdjuvant Chemotherapy in the Treatment TNBC Nab-Paclitaxel

- In the phase III GeparSepto study, pCR was reached in 48% of TNBC patients treated with weekly nab-paclitaxel 150 mg/m² versus 26% of patients treated with weekly paclitaxel 80 mg/m² ($p = 0.00027$).
- Of note, the dose of nab-paclitaxel was reduced from 150 to 125 mg/m² due to the higher incidence of severe sensory neuropathy, without affecting the treatment efficacy.
- A phase III trial (ETNA study) first presented at the American Society of Clinical Oncology (ASCO) 2016 showed a higher rate of response in the nab-paclitaxel arm compared to the paclitaxel one (41.3% vs 35.5%; $p$-value not statistically significant).
- Similar pCR rates have been reported by Kuwayama et al in a subgroup of TNBC patients treated with four cycles of weekly nab-paclitaxel 100 mg/m².
- Moreover, early results from the WSG-ADAPT trial showed a possible advantage in terms of pCR by adding nab-paclitaxel, rather than gemcitabine, to carboplatin (44.5 vs 28.4, $p = 0.004$).
NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC

CONCLUSIONS

- Neoadjuvant chemotherapy studies have reported higher response rates in TNBC than non-TNBC. Pathologic complete response has been shown to predict improved long-term outcomes for TNBC.
- Conventional cytotoxic chemotherapy and DNA damaging agents continue to be the mainstay for treatment of this disease.
- HR deficiency independently predicts for pCR when carboplatin was added to conventional chemotherapy.
ADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC
ADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC

- Adjuvant chemotherapy decreases risk of recurrence and improves survival, but the absolute benefits in patients with a low risk of recurrence may be small. Therefore, the decision to offer chemotherapy must take into account risk factors of the disease as well as patient age and comorbidities.

- Adjuvant chemotherapy is standard for patients with triple-negative breast cancer (TNBC) and either a tumor size >0.5 cm or pathologically involved lymph nodes (regardless of tumor size).

- Patients with tumors that do not express hormone receptors (ie, ER- and PR-negative) are not candidates for endocrine therapy, and as the tumor is HER2 negative, they are not candidates for anti-HER2 therapy, either. Therefore, our threshold for the use of chemotherapy in these patients is low because this is the only form of adjuvant treatment available to them, and because studies have suggested a significant risk of recurrence if left untreated.

- The prognosis of small (<0.5 cm), node-negative TNBC is generally favorable. For that reason, the benefits of adjuvant chemotherapy are very small, and must be weighed against the chances of serious side effects of chemotherapy. Patients with microinvasive or very small (1 to 3 mm) tumors generally do not need chemotherapy.
ADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC

- The data to support adjuvant chemotherapy (versus no treatment) and specifically, the administration of anthracycline and taxane therapy in the adjuvant setting come from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The EBCTCG performs a meta-analysis every five years to review the data on adjuvant treatment of breast cancer.

- The use of an anthracycline-containing regimen compared with no treatment resulted in the following outcomes:
  - Decreased risk of recurrence from 47 to 39 percent (relative risk [RR] 0.73, 95% CI 0.68-0.79)
  - Decreased breast cancer mortality from 36 to 29 percent (RR 0.79, 95% CI 0.72-0.85)
  - Decreased overall mortality from 40 to 35 percent (RR 0.84, 95% CI 0.78-0.91)

- Anthracycline-containing regimen is at least equivalent to the historical standard regimen CMF and that the addition of taxane to an anthracycline-based regimen further improves outcomes. These data come from the 2012 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, which suggested that anthracycline-based regimens had similar or better outcomes relative to CMF, historically a standard treatment.
ADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC
TAXANE ADDITION

- The addition of taxanes to anthracycline-containing chemotherapy was associated with improved recurrence risk, breast cancer mortality, and overall mortality compared with other cytotoxic regimens. In trials where the same number of cycles of anthracyclines was used in the control arm as the experimental (anthracyclines followed by taxane) arm (n = 11,167 women), incorporation of taxanes led to the following improvements in outcomes:
  - A reduction in the risk of recurrence from 35 to 30 percent (relative risk [RR] 0.84, 95% CI 0.78-0.91)
  - A reduction in the risk of breast cancer mortality from 24 to 21 percent (RR 0.86, 95% CI 0.79-0.93)
  - A reduction in overall mortality from 27 to 24 percent (RR 0.90, 95% CI 0.79-0.93)
- No regimen has proven to be superior to AC-T, thus an anthracycline plus taxane-containing regimen is recommended for high-risk patients who are candidates for an anthracycline.
- Non-anthracycline-based regimens of docetaxel and cyclophosphamide given every three weeks for four cycles (TC) may be an appropriate alternative for patients who have indications for chemotherapy but have lower-risk disease. TC may be preferable to AC-T due to the shorter duration of treatment (12 versus 16 weeks) and avoidance of the risks of congestive heart failure and secondary leukemias associated with anthracyclines.
- TC is more effective than AC alone
ADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC
TAXANE ADDITION

- Two studies demonstrated superiority of docetaxel, doxorubicin and cyclophosphamide (TAC) in the triple negative phenotype over fluorouracil, doxorubicin and cyclophosphamide (FAC).
- The GEICAM 9805 study showed that TAC is more effective than in the adjuvant treatment of high-risk node-negative breast cancer. In the TNBC subset, the HR for DFS was 0.59 (95% CI 0.32–1.07; P = 0.08) favoring TAC over FAC.
- Similarly, The Breast Cancer International Research Group (BCIRG) 001 study also demonstrated TAC to be more effective than FAC in the adjuvant treatment of node-positive TNBC. Subgroup analyses addressing 3-year DFS showed a non-significant trend (P = 0.051) in the TNBC subgroup in favor of TAC over FAC (74% versus 60%, respectively; HR 0.50; 95% CI 0.29–1.00).
- Inhibitors of DNA repair or specific tyrosine kinases have not yet been addressed in the adjuvant setting. In the absence of data from prospective trials that focus on adjuvant treatment of early TNBC, taxanes and an anthracycline-containing regimen or classical CMF may be considered reasonable choices. Conventional chemotherapy remains the basis of TNBC treatment according to the majority of national and international guidelines including the ESMO Breast Cancer guidelines.
ADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC
TAXANE TIMING

- The meta-analysis also looked at the effect of sequential versus concurrent anthracycline and taxane-based chemotherapy in 11,500 women enrolled in six trials.
- Sequential versus concurrent anthracycline plus taxane chemotherapy (eg, AC then T) was associated with improvement in disease recurrence rates compared with concurrent regimens (eg, TAC. 10-year risk 28.1 versus 31.3 percent; RR 0.87, 95% CI 0.80-0.94).
- Based on these data, AC followed by sequential taxane therapy would be the standard adjuvant chemotherapy regimen.
- Sparano et al. in a randomized controlled trial (RCT) conducted by the Eastern Cooperative Oncology Group (ECOG) in the adjuvant setting demonstrated that paclitaxel is more effective when used in a lower, but dose-dense fashion compared with a higher dosage on a three-week schedule (80 mg/m² every week x 12 versus 175 mg/m² every three weeks x 4).
- Improved outcomes initially observed for weekly paclitaxel were qualitatively similar but quantitatively less pronounced with longer follow-up, although exploratory analysis suggested substantial benefit in triple-negative disease.
For most patients who receive a "standard" course of neoadjuvant chemotherapy, no further chemotherapy in the adjuvant setting is given.

However, the survival benefit for use of capecitabine in women with residual disease after standard neoadjuvant chemotherapy, particularly in those with triple-negative breast cancer (TNBC), suggests that such patients may be appropriate candidates for adjuvant capecitabine. For patients who did not complete the full course of neoadjuvant treatment, the balance of the planned course of treatment in the adjuvant setting, may be feasible.

The CREATE-X trial randomly assigned approximately 900 patients with HER2-negative breast cancer (approximately one-third of whom had TNBC) and residual disease after neoadjuvant anthracycline and/or taxane therapy to either eight cycles of adjuvant capecitabine or no further chemotherapy.

Patients receiving capecitabine had higher rates of five-year disease-free survival (DFS; 74 versus 68 percent; hazard ratio [HR] 0.70, 95% CI 0.53-0.92) and overall survival (OS; 89 versus 84 percent; HR for death 0.59, 95% CI 0.39-0.90).

Subgroup analyses suggested that the improvement in DFS with capecitabine was driven by improved outcomes among patients with TNBC (70 versus 56 percent; HR 0.58, 95% CI 0.39-0.87).

Toxicities, however, were also higher among patients receiving capecitabine.
ADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC
ANTI VEGF

• Adjuvant bevacizumab was investigated in patients with TNBC in the open-label, randomised Beatrice Phase 3 trial. The investigators recruited patients with centrally confirmed triple-negative operable primary invasive breast cancer from 360 sites in 37 countries.

• Patients were stratified by nodal status, chemotherapy (anthracycline, taxane, or both), hormone receptor status (negative vs. low), and type of surgery.

• Patients received a minimum of four cycles of chemotherapy either alone or with bevacizumab (equivalent of 5 mg/kg every week for 1 year). The primary endpoint was invasive disease-free survival (IDFS).

• There were 1290 patients to receive chemotherapy alone and 1301 to receive bevacizumab plus chemotherapy.

• At the time of analysis of IDFS, median follow-up was 31·5 months in the chemotherapy-alone group and 32·0 months in the bevacizumab group. After 200 deaths, no difference in overall survival was noted between the groups (HR 0·84, 95% CI 0·64–1·12; p=0·23).

• Addition of bevacizumab versus chemotherapy alone was associated with increased incidences of grade 3 or worse hypertension in 154 patients (12%) vs. eight patients (1%), severe cardiac events occurring at any point during the 18-month safety reporting period 19 patients (1%) vs. two (<0·5%), and treatment discontinuation of bevacizumab, chemotherapy, or both; 256 (20%) vs. 30 (2%).

• Bevacizumab cannot be recommended as adjuvant treatment in patients with TNBC.
ADJUVANT CHEMOTHERAPY IN THE TREATMENT TNBC

CONCLUSIONS:

- Conventional chemotherapy remains the backbone of adjuvant systemic treatment for most patients with early TNBC.
- A meta-analysis shows that adjuvant taxane-based chemotherapy compared with regimens without taxanes is associated with an improvement in DFS and overall survival in TNBC.
- AC followed by sequential taxane therapy would be the standard adjuvant chemotherapy regimen.
- The use of capecitabine in women with triple-negative breast cancer and residual disease after standard neoadjuvant chemotherapy may be considered.
- For patients who did not complete the full course of neoadjuvant treatment, the balance of the planned course of treatment in the adjuvant setting, may be feasible.
THANK YOU