

Phase III Trial Evaluating Weekly Paclitaxel Versus Docetaxel in Combination With Capecitabine in Operable Breast Cancer

BACKGROUND

- Combo chemotherapy with an anthracycline and taxane has shown significant survival advantages for all stages of operable breast cancer (BC), however regimens differ greatly
- Docetaxel should upregulate the enzyme thymidine phosphorylase that converts capecitabine to FU, its active metabolite, and increase delivery of FU to tumor cells, enhancing the antitumor effect of docetaxel. This has already been proven through improvements in survival in the metastatic setting. This starting combination, followed by fluorouracil, epirubicin, and cyclophosphamide (FEC), could be more effective than the current standard adjuvant breast cancer regimen (weekly paclitaxel (WP) followed by FEC).

OBJECTIVE

- To determine whether capecitabine with docetaxel (XT) followed by FEC or weekly paclitaxel (WP) followed by FEC would improve relapse-free survival (RFS) in operable BC.

METHODS

- **Design:** Single site, open-label, randomized, phase III trial; **Duration:** Ongoing, but study reports results at median follow-up of 50 months and 64 relapse-free survival (RFS) events
- **Inclusion criteria:** Histologic confirmation of invasive carcinoma of the breast; LVEF > 50%, ANC > 1,500/ μ L, platelet count > 100,000/ μ L, normal bilirubin, transaminases up to 2.5 times the upper limit of normal [ULN], or alkaline phosphatase up to 4 times ULN if transaminases were less than or equal to ULN, serum creatinine < 2.5 mg/dL and/or creatinine clearance > 51 mL/min; To be eligible for preoperative therapy → clinically palpable disease in the breast and/or axilla measurable by ultrasound;
 - Any one of the following criteria would be allowed under the trial criteria: High risk, as defined by any one of the following: Ki-67 > 35%, poorly differentiated tumors [Black's modified grade 310], ER-negative/PR-negative, or lymphovascular invasion; Patients with bilateral disease and those with pN2a and pN3a; Prior diagnosis of breast cancer if it was not of higher stage than the current breast cancer plus no prior exposure to study agents; LVEF > 50%
- **Exclusion criteria:** Inflammatory carcinoma of the breast; T1N0 portion of the trial excluded patients from preoperative portion of the trial; patients with pN2b (metastasis in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis), clinically staged N2 or N3 nodal disease, T4 lesions, or metastatic breast cancer; HER-2 positive disease; LVEF < 50%
- **Primary outcome measure:** RFS
- **Secondary outcome measures:** Overall survival (OS), ability of pre-op XT to enhance breast-conserving surgery (BCS) vs WP, and assessment of each regimen's safety profile
- 603 patients (302 assigned to WP, 301 assigned to XT) received:
 - Paclitaxel 80 mg/m² intravenously (IV) weekly for 12 weeks
 - OR Docetaxel 75 mg/m² IV over 1 hour on day 1 and capecitabine 1,500 mg/m² daily in two divided doses 12 hours apart on days 1 to 14, every 21 days
 - If a patient discontinued capecitabine for any reason, the remaining cycles of docetaxel were given at a dose of 100 mg/m² every 3 weeks.
 - THEN Four cycles of FU 500 mg/m² IV, epirubicin 100 mg/m² IV, and cyclophosphamide 500 mg/m² IV (FEC) on day 1 every 21 days.
- Planned to accrue 930 patients to give 80% power with an alpha level of 0.05 to detect a 7% difference in RFS between the 2 groups; Data handling method was intent-to-treat

RESULTS

- Two patients were found ineligible after randomization; In XT and WP arms, 90% and 86% received all preplanned # of treatment cycles. In the XT group, 148 (50.5%) patients required ≥ 1 dose reduction or discontinuation of capecitabine alone or in addition to docetaxel; 7 of these (2.4% of total) stopped both drugs before four cycles were completed
- **Primary outcome measure:** No significant improvement in RFS for XT (87.5%; 95% CI, 82.7% to 91.1%) compared with WP (90.7%; 95% CI, 86.4% to 93.7%; $P = .51$). No significant improvement in RFS in patients who received pre-op therapy with XT (81.5%; 95% CI, 71.8% to 88.2%) versus WP (85.5%; 95% CI, 76.0% to 91.4%; $P = .65$) or adjuvant XT (90.9%; 95% CI, 85.1% to 94.4%) versus WP (93.5%; 95% CI, 88.6% to 96.4%; $P = .66$). Multivariate Cox proportional hazards model showed no significant improvement in RFS for XT compared with WP (hazard ratio, 1.02; 95% CI, 0.62 to 1.69; $P = .93$)
- **Secondary outcome measures:** No significant difference in OS (92.2% v. 95.0%; 95% CI, 88.0% to 95.0% and 91.3% to 97.2%; $P = .39$), rate of pCR (19.8% v 16.4%; $P = .48$) or the rate of BCS (45% v 40%; $P = .45$) in the XT and WP arms, respectively. Significant increase in hematologic, mucosal, and skin toxicity including N/V/D, neutropenia, stomatitis, hand-foot syndrome, myalgias, arthralgias, and constipation in XT arm versus WP arm.
- **Author's conclusion:** No difference in efficacy between WP and XT as used in this trial. The use of XT was associated with higher GI, skin, and neutropenic-related toxicities.

STRENGTHS

- Random assignment with a distribution of approx. half post- and half pre-menopausal
- Inclusion and exclusion criteria were ethical and appropriate for target population

LIMITATIONS

- Single institution; stopped early before full accrual and prespecified # of events reached
- Futility analysis at 35 events \rightarrow predictive prob. of concluding in favor of either was low
- Unblinded (Open-label)
- Protocol specified capecitabine dose of 2,000 mg/m²/d. Because of toxicity in first 10 patients, starting dose was reduced to 1,500 mg/m²/d.
- No data provided to account for adherence; Non-study drugs taken by patients not reported

CONCLUSION

- In spite of promising evidence in favor of XT over WP for the treatment of breast cancer in the preoperative and adjuvant setting, the lack of significant difference in RFS between the two in non-metastatic breast cancer seems to favor WP due to significantly less hematologic, skin, and mucosal toxicity.
 - Although both XT and WP are equally efficacious in the primary outcome measure of RFS, WP should be clinically preferred considering the drastic difference in the secondary outcome measure of safety between the adverse events of the two arms.
 - Although QOL was not evaluated, the use of WP instead of XT may potentially result in an improvement in QOL due to the reasons stated above.
- Future research:
 - Conflicting evidence in use of capecitabine in breast cancer in the adjuvant setting indicates the need for additional research in order to find its true value, perhaps studying XT in patients refractory to WP in the adjuvant treatment of breast cancer

Reference: Kelly CM, Green MC, Broglio K, Thomas ES, Brewster AM, et al. Phase III trial evaluating weekly paclitaxel versus docetaxel in combination with capecitabine in operable breast cancer. *J Clin Oncol.* 2012 Mar;30(9):930-5.

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