



American Society of Breast Disease

Taxane Use and Dose-Dense Scheduling May Benefit Patients with Early Stage Breast Cancer

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The Consensus Committee of the American Society of Breast Disease agrees that the use of taxanes and dose-dense scheduling may both benefit patients with early stage breast cancer. Although the widespread use of adjuvant chemotherapy prescribed for early-stage breast cancer has contributed to an improvement in overall survival, the optimal chemotherapeutic regimen is still unknown.

Conclusions

1. The addition of a taxane to adjuvant therapy may offer an advantage over a non-taxane-containing regimen.
2. The optimal taxane has not been determined (paclitaxel vs. docetaxel).
3. The use of the albumin-bound paclitaxel remains investigational in the adjuvant setting.
4. A dose-dense schedule may benefit patients with lymph node positive disease, especially hormone-insensitive disease.
5. Cytokine support is often required to reduce toxicity with dose-dense therapy, or with higher-dose docetaxel regimens.

The Committee considered multiple clinical trials and publications to reach the above conclusions. Background information leading to the Committee's conclusions is available online at the Society's web site at www.asbd.org. The statement was written by Committee member, Beth Overmoyer, MD, Connecticut Oncology, Torrington, Connecticut.

About the American Society of Breast Disease

The American Society of Breast Disease is the leading professional medical society in the United States to bring together physicians and allied professionals committed to an *interdisciplinary* team approach to breast disease management, prevention, early detection, treatment, and research. The Society advocates for improvements in breast healthcare. For information about the ASBD, visit the Society at www.asbd.org.

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Background

Although the widespread use of adjuvant chemotherapy prescribed for early-stage breast cancer has contributed to an improvement in overall survival [1, 2], the optimal chemotherapeutic regimen is still unknown. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) presented an overview meta-analysis of adjuvant therapy trials after a 15-year follow-up with the following conclusions:

1. The use of adjuvant polychemotherapy reduces the risk of recurrence from 53.5% to 41.1% and reduces the absolute risk of breast cancer mortality by 10% ($P < 0.00001$) among women under the age of 50 years. These reductions in risk were also statistically significant among women aged 50-69 years, though to a smaller degree. These results were seen regardless of nodal status, and hormonal status.
2. There is a slight benefit with anthracycline-containing regimens compared with non-anthracycline-containing regimens, with a ratio of annual recurrence rate = 0.89 ($P = 0.001$), and the breast cancer death ratio = 0.84 ($P < 0.00001$), regardless of age or nodal status.

There has been insufficient follow-up for the EBCTCG to assess the impact of taxanes on adjuvant therapy, nor to comment on optimal dosing, i.e., dose-dense vs. standard schedules. This document attempts to provide some guidelines and a review of the recent data on adjuvant chemotherapy as it pertains to non-trastuzumab containing regimens.

Taxane Therapy for Adjuvant Disease

Several randomized trials have been published that support a superiority of chemotherapeutic regimens that contain a taxane. To date, no study has demonstrated superiority with a specific taxane (paclitaxel vs. docetaxel vs. albumin-bound paclitaxel); therefore this characteristic will not be used to differentiate the trials.

- A. Four randomized trials support an additional efficacy with the use of a taxane-containing regimen vs. a non-taxane containing regimen. Three randomized trials evaluate the addition of paclitaxel (Taxol) to a constant anthracycline-containing regimen; a fourth trial uses docetaxel (Taxotere) as its additional taxane.
1. National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28 [3]: Patients with node-positive disease were randomized to 4 cycles of Adriamycin and Cytosan (AC) or 4 cycles of AC followed by paclitaxel (Taxol). The dose of AC was standard (A=60mg/m²; C=600mg/m²) and given every 3 weeks. The dose of paclitaxel was higher than currently used (Taxol=225mg/m²), and concurrent tamoxifen was administered for hormone-sensitive disease.
 - a. The addition of paclitaxel resulted in a 17% reduction in risk of recurrence ($P = 0.006$), but no impact on survival (85% for both groups).
 - b. The concurrent administration of tamoxifen may have confounded these results.



2. Cancer and Leukemia Group B (CALGB) 9344 [4]: Node-positive patients were randomized to 4 cycles of Adriamycin and Cytosin (AC) to 4 cycles of AC followed by paclitaxel (Taxol). The dose of Cytosin was standard (C=600mg/m²), however three different doses of Adriamycin were studied: (60mg/m², 75mg/m², 90mg/m²). The dose of paclitaxel (Taxol=175mg/m²) was standard. The dosing schedule was every 3 weeks, and tamoxifen was administered to hormone-sensitive disease following the completion of chemotherapy.
 - a. The addition of paclitaxel resulted in a 17% reduction in recurrence (P=0.002) and an 18% reduction in risk of death (P=0.006).

The results of these 2 trials are confounded by differences in duration of chemotherapy (4 vs. 8 cycles of treatment). However 2 further studies that do not differ in total number of cycles administered also support an added benefit with the use of a taxane-containing regimen.

3. MD Anderson Cancer Center (MDACC) Phase III Trial [5]: Chemotherapy was administered either adjuvantly or neo-adjuvantly. Patients receiving adjuvant treatment received either 8 cycles of a complex schedule of 5-fluorouracil (F=500mg/m² day 1), Adriamycin (A=50mg/m² IV day 1-3), Cytosin (C=500mg/m² day 1) (FAC) or 4 cycles of paclitaxel (Taxol 250mg/m² over 24hr) followed by 4 cycles of FAC. Tamoxifen was administered after chemotherapy for patients greater than 50yo with hormone sensitive disease.
 - a. There was a trend supporting an advantage in disease-free survival (DFS) with the administration of paclitaxel (DFS 86% vs. 83%; P=0.09).
 - b. This study is too small to make any further conclusions.
4. Programmes d'Actions Concertees Sein (PACS) 01 [6]: Node-positive patients were randomized to 3 cycles of 5-fluorouracil (F=500mg/m²), Epirubicin (E=100mg/m²), Cytosin (C=500mg/m²) (FEC) every 3 weeks followed by 3 cycles of docetaxel (Taxotere) (Taxotere=100mg/m²) every 3 weeks; or 6 cycles of standard dose/schedule FEC.
 - a. The regimen FEC followed by docetaxel demonstrated superiority to FEC alone in DFS (78.4% vs. 73.2%; P=0.011) and overall survival (OS) (90.7% vs. 86.7%; P=0.014).

B. Four trials replace a standard chemotherapeutic agent with a taxane, rather than adding a taxane to a standard regimen. Two of the four studies demonstrate superiority with the taxane-containing regimen for node-positive disease. The optimal taxane has not been determined, and these trials use either paclitaxel or docetaxel.

1. US Oncology Phase III Trial [7]: This trial evaluated 4 cycles of standard AC (Adriamycin=60mg/m²; Cytosin=600mg/m²) given every 21days followed by 4 cycles of standard dose paclitaxel (Taxol=175mg/m²) given every 3 weeks compared with a regimen that replaces the Cytosin with paclitaxel. The comparator regimen is: 4 cycles of Adriamycin/paclitaxel (AT) (A=50mg/m²; Taxol= 200mg/m²) followed by paclitaxel (Taxol=80mg/m²) weekly for 12 weeks.
 - a. The AT followed by Taxol demonstrated superiority to AC followed by Taxol in DFS (90.3 % vs. 86.1%; P=0.02) and OS (95.5 % vs. 92.1%; P=0.02).



2. Breast Cancer International Research Group (BCIRG) 001 [8]: Randomized node-positive patients to FAC (5-fluorouracil=500mg/m²; Adriamycin=50mg/m²; Cytoxan=500mg/m²) every 3 weeks for 6 cycles or TAC (docetaxel (Taxotere)=75mg/m²; Adriamycin=50mg/m²; Cytoxan=500mg/m²) every 3 weeks for 6 cycles. Tamoxifen was administered following chemotherapy for hormone-sensitive disease.
 - a. TAC demonstrated superiority to FAC in DFS (75% vs. 68%; P=0.001) and OS (87% vs. 81%; P=0.008).
 - b. A 25% incidence of neutropenic fever was seen among patients receiving TAC therefore cytokine support is required with this regimen. .

The data that support a clinical advantage when a taxane replaces a standard drug in a standard regimen is not as clear among studies that involve both node-positive and high-risk node-negative disease. ECOG 2197 is the only trial that did not support a clinical advantage with a taxane-containing regimen, and this was in the setting of drug replacement.

1. Eastern Cooperative Oncology Group (ECOG) 2197 [9]: Randomized patients with high-risk node-negative and node positive disease to 4 cycles of standard AC (Adriamycin=60mg/m²; Cytoxan=600mg/m²) every 3 weeks or replaced the Cytoxan with docetaxel (Taxotere (T)): AT (Adriamycin 60mg/m²; docetaxel 60mg/m²) every 3 weeks for 4 cycles. Tamoxifen, and later an aromatase inhibitor, was administered for hormone sensitive disease following completion of chemotherapy.
 - a. There was no statistically significant difference in DFS or OS between the 2 regimens.
2. US Oncology [10]: Randomized patients with high-risk node-negative and node positive disease to 4 cycles of standard AC (Adriamycin=60mg/m²; Cytoxan=600mg/m²) every 3 weeks or replaced the Adriamycin with docetaxel (Taxotere (T)): TC (docetaxel 75mg/m²; Cytoxan 600mg/m²) every 3 weeks for 4 cycles.
 - a. TC demonstrated superiority to AC in DFS (86% vs. 80%; P=0.67).
 - b. There was a trend toward a superior OS with TC compared with AC (90% vs. 87%; P=0.13).

Variations in Dosing Schedules for Adjuvant Therapy: The Role of Dose-Dense Chemotherapy

One study to date supports equivalent outcomes with the two most commonly used taxanes in the adjuvant setting: paclitaxel and docetaxel. This trial also supports equivalency in outcomes when these taxanes are administered either weekly or every 3 weeks.

1. Eastern Cooperative Oncology Group (ECOG) 1199 [11]: Enrolled patients with high-risk node negative and node positive disease to one of 4 regimens: all patients received 4 cycles of standard AC (Adriamycin=60mg/m²; Cytoxan=600mg/m²) every 3 weeks followed by a randomization to either docetaxel or paclitaxel, given either for 4 cycles every 3 weeks (docetaxel 100mg/m²; paclitaxel 175mg/m²), or weekly for 12 weeks



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(docetaxel 35mg/m²; paclitaxel 80mg/m²). Tamoxifen or an aromatase inhibitor was administered following completion of chemotherapy.

- a. There was no statistically significant difference in DFS between the 2 taxanes.
- b. Nor was there a statistically significant difference in DFS between the 2 dosing regimens (every 3 weeks vs. weekly).
- c. However there was a trend toward improved DFS with the use of weekly paclitaxel.

Based upon biological mathematical modeling, “dose-dense” chemotherapy has been explored. Two randomized trials in node positive disease support a clinical superiority when treatment is administered in a dose-dense fashion, i.e., every 2 weeks. Two studies are quite complex and may suggest a superiority with dose-dense chemotherapy; however their results were not conclusive. It is not clear whether all drugs or just taxanes should be administered dose-dense, nor has its benefit for high-risk node negative disease been established. A dose-dense schedule requires cytokine support in most instances.

1. Cancer and Leukemia Group B (CALGB) 9741 [12,13]: Patients with node positive disease were randomized to receive standard doses of Adriamycin, Cytosin, and paclitaxel given in a combined fashion: AC (Adriamycin=60mg/m²; Cytosin=600mg/m²) followed by paclitaxel (Taxol=175mg/m²), or a sequential fashion: A (Adriamycin=60mg/m²) followed by C (Cytosin=600mg/m²) followed by paclitaxel (Taxol=175mg/m²). A second randomization specified the chemotherapies to be administered either every 3 weeks or every 2 weeks (dose-dense).
 - a. There was no difference in outcome when the chemotherapies were administered in combination or in sequence.
 - b. Dose-dense administration was associated with a statistically superior DFS and OS compared with every 3 week administration: DFS (82% vs. 75%; P=0.01); OS (92% vs. 90%; P=0.01).
 - c. Cytokine support was required with the dose-dense regimens to avoid severe myelosuppression.
 - d. There may be an added benefit in dose-dense administration especially among patients with hormone-insensitive disease.
2. Arbeitsgemeinschaft Gynakologische Onkologie (AGO) Trial [14]: Patients with 4 or more positive lymph nodes were randomized to 3 cycles of dose-dense treatment with Epirubicin, paclitaxel, Cytosin (ETC) (E=150mg/m²; T=225mg/m²; C=2500mg/m²) every 2 weeks or epirubicin, Cytosin (EC) followed by paclitaxel (T) (E=90mg/m²; C=600mg/m²; T=175mg/m²) every 3 weeks.
 - a. The dose-dense ETC treatment was associated with a statistically significant benefit in DFS (70% vs. 62%; P=0.00079) and OS (82% vs. 77%; P=0.029) compared with the every 3 week regimen.
 - b. Cytokine support was needed in the dose-dense regimen.
 - c. The outcome may be confounded by differences in drug dose.
3. NCIC CTG MA.21 [15]: Patients with high-risk node-negative or node-positive disease were randomized to 6 cycles of standard every 3 week CEF (Cytosin=75mg/m² po days 1-14; epirubicin=60mg/m² and 5-fluorouracil=500mg/m² days 1 & 8) or 6 cycles of dose-dense (every 2 week) EC followed by 4 cycles of standard every 3 week paclitaxel



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- (Taxol (T)) (epirubicin=120mg/m²; Cytoxan=830mg/m²; Taxol=175mg/m²) or 4 cycles of standard every 3 week AC followed by 4 cycles of standard every 3 week paclitaxel (Taxol) (Adriamycin=60mg/m²; Cytoxan=600mg/m²; Taxol =175mg/m²).
- a. The DFS for the 3 regimens are: CEF=90.1%; EC followed by T=89.5%; AC followed by T=85%; global test of significance for the 3 arms: P=0.0009547.
 - b. AC followed by T given every 3 weeks has an inferior DFS compared with either combination CEF or dose-dense EC followed by T.
4. Hellenic Cooperative Oncology Group (HE 10/97) [16]: Patients with high-risk node negative or node positive disease were randomized to 3 cycles of epirubicin followed by 3 cycles of paclitaxel followed by 3 cycles of CMF (E=110mg/m²; taxol=250mg/m²; cytoxan=840mg/m²; methotrexate 47mg/m²; 5-flurouracil=840mg/m²) given every 2 weeks, or 4 cycles of epirubicin followed by 4 cycles of CMF (E=110mg/m²; cytoxan=840mg/m²; methotrexate 47mg/m²; 5-flurouracil=840mg/m²) given every 2 weeks.
- a. There was no difference in DFS between E/paclitaxel/CMF or E/CMF (80% vs. 77%), nor was there a difference in OS (93% vs. 90%).
 - b. Those patients with hormone-negative disease fared better with the addition of paclitaxel.

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