The evidence for adjuvant taxanes in early breast cancer

Sanraj Basi, John R. Mackey
Department of Oncology, University of Alberta Cross Cancer Institute, Edmonton, Canada

Summary: Adjuvant chemotherapy plays an important role in improving disease free and overall survival in women with high-risk early stage breast cancer. While more than seventy thousand women have enrolled in taxane-based adjuvant chemotherapy studies, interim and final results are available from several of these randomized phase III adjuvant studies. In this review, we will summarize the design and outcomes from the reported trials, and draw conclusions about the role adjuvant taxanes now play in the standard management of operable breast cancer. In aggregate, these studies show that adjuvant taxanes can improve important clinical outcomes beyond those achieved with anthracycline-based chemotherapy, without imparting prohibitive acute or chronic toxicities. Important questions are being addressed in ongoing adjuvant trials, including comparisons of combination to sequential therapy, direct comparisons between paclitaxel and docetaxel, and how to safely integrate targeted therapies into these highly active adjuvant regimens.

Key Words: Breast Cancer, Chemotherapy, Taxane

INTRODUCTION

Adjuvant chemotherapy is now firmly established as a routine component of the management of early breast cancer. Chemotherapy is offered to the majority of women at high risk of breast cancer relapse after surgical therapy, with the aim of preventing recurrence of distant metastases and ultimately prolonging survival. (1-3) Among cytotoxic drugs, two taxanes, paclitaxel and docetaxel, have proven to be active drugs in the metastatic setting (4, 5) where they lack cross resistance with anthracyclines. In an attempt to further improve outcomes, breast cancer trialists launched a number of studies to evaluate the efficacy and long-term toxicities of adjuvant taxanes (Tables 1, 2, 3). To date, several taxane-based chemotherapy trials have reported the critical outcomes of disease free and overall survival. The majority of these trials belong to the first generation where the comparator arm was non-taxane based. However, some recent results from second generation trials, where taxanes are incorporated in all arms of the study, are further refining our understanding of these issues. This report will review the reported...
studies in detail, with reference to both the sequential anthracycline - taxane trials, and then the concurrent anthracycline - taxane studies. Finally, we will attempt to provide an integration of the signals we are obtaining from these trials.

MAIN DISCUSSION

SEQUENTIAL ANTHRACYLINE → TAXANE ADJUVANT STUDIES

CALGB-9344

This study (6) was designed to determine if i) increasing the dose of doxorubicin in standard adjuvant chemotherapy or ii) adding paclitaxel would prolong time to recurrence or survival. A total of 3121 women with node positive breast cancer were randomized to cyclophosphamide (600mg/m²) with one of three doses of doxorubicin (60, 75, 90mg/m²) for 4 cycles every three weeks followed by no further therapy, or an additional 4 cycles of paclitaxel (175mg/m²) given every three weeks. Tamoxifen was given to hormone receptor positive patients.

CALGB-9744 reported that the addition of 4 cycles of paclitaxel after the completion of a standard course of cyclophosphamide and doxorubicin, when compared to cyclophosphamide and doxorubicin alone, improved both five-year disease free survival (70 ± 1% vs. 65 ± 1%, p=0.0023 adjusted) and overall survival (80 ± 1% vs. 77 ± 1%, p=0.0064 adjusted) in women with lymph node positive early breast cancer. Although increasing the doxorubicin dose failed to improve disease free or overall survival, higher dose doxorubicin did confer increased hematologic toxicity and stomatitis.

NSABPB-28

NSABPB-28 was a study quite similar in design to CALGB-9744, in that the standard AC was compared to an additional four cycles of paclitaxel every three weeks, although the paclitaxel dose in NSABPB B-28 was higher (225 mg/m²). The addition of paclitaxel improved disease free survival, however, in contrast to the CALGB-9744 study, overall survival was not improved in women with lymph node posi-

tive early breast cancer. The most likely explanation for this effect was that the protocol called for concurrent administration of tamoxifen with chemotherapy in those women over 50 or premenopausal and ER positive. Recent reports from the Southwest Oncology Group (SWOG) 8814 trial (7) show that concurrent administration of chemotherapy and tamoxifen in postmenopausal ER positive patients is substantially less effective than chemotherapy followed by tamoxifen. Based on these data, future NSABPB neoadjuvant and adjuvant trials will require that tamoxifen be delayed until after the completion of chemotherapy.

PACS 01 study

The PACS 01 study was the strategically logical follow-up to the FASG-05 trial, which demonstrated that six cycles of FE100C were superior to six cycles of VE50C. (8) The primary objective of the PACS 01 trial was to compare disease-free survival in node positive breast cancer after adjuvant treatment with six cycles of FE100C, or with 3 cycles of FE100C followed by 3 cycles of docetaxel 100 mg/m², all at three week intervals (see Tables 1). Secondary endpoints were overall survival, safety, cost effectiveness and quality of life, and assessment of prognostic and predictive factors of treatment efficacy. This study was reported in abstract form and as an oral presentation at the 2004 San Antonio Breast Cancer Symposium. (9)

Eligible patients were between 18 and 65 years, had T1-T3 breast cancer, axillary node positive disease with at least 5 removed axillary nodes, no distant metastases, and adequate end organ function. Patients were stratified according to centre, age, and number of involved lymph nodes (1-3 vs. ≥3). The median age was 50 years, 60% were premenopausal, and breast conservation was achieved in 52%. Randomization led to more estrogen receptor positive patients (76.3% vs. 71.1%) assigned to receive FE100C followed by docetaxel.

The sequential schedule produced fewer cardiac events, fewer cycle delays and required less G-CSF
<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample Size</th>
<th>Patient population</th>
<th>Randomization</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCIRG 001</td>
<td>1491</td>
<td>Node-positive</td>
<td>TAC × 6</td>
<td>Reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FAC × 6</td>
<td></td>
</tr>
<tr>
<td>PACS 01</td>
<td>1999</td>
<td>Pre- and postmenopausal; node-positive</td>
<td>FEC × 6</td>
<td>Reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FEC × 3 → T × 3</td>
<td></td>
</tr>
<tr>
<td>NSABP B-27</td>
<td>2411</td>
<td>Operable patients</td>
<td>AC × 4 → surgery</td>
<td>Reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AC × 4 → surgery → T × 4</td>
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<td></td>
<td></td>
<td></td>
<td>AC × 4 → surgery → T × 4 → surgery</td>
<td></td>
</tr>
<tr>
<td>US Oncology 9735</td>
<td>1016</td>
<td>Operable disease (stages III)</td>
<td>TC × 4</td>
<td>Reported</td>
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<td></td>
<td></td>
<td></td>
<td>AC × 4</td>
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<tr>
<td>ECOG2197</td>
<td>2889</td>
<td>Node-positive; high-risk node-negative</td>
<td>AT × 4</td>
<td>Reported</td>
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<td></td>
<td></td>
<td></td>
<td>AC × 4</td>
<td></td>
</tr>
<tr>
<td>BIG 02-98</td>
<td>2900</td>
<td>Node-positive</td>
<td>AT × 4 → CMF × 3</td>
<td>Closed</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>AC × 4 → CMF × 3</td>
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<td>A × 3 → T × 3 → CMF × 3</td>
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<td></td>
<td></td>
<td></td>
<td>A × 3 → CMF × 3</td>
<td></td>
</tr>
<tr>
<td>PACS 04</td>
<td>2600</td>
<td>Node-positive</td>
<td>FEC × 6 ± H</td>
<td>Closed</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ET × 6 ± H</td>
<td></td>
</tr>
<tr>
<td>Italian trial</td>
<td>800</td>
<td>Pre- and postmenopausal; node-positive</td>
<td>E × 4 → CMF × 4</td>
<td>Closed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E × 4 → T × 4 → CMF × 4</td>
<td></td>
</tr>
<tr>
<td>ICCG</td>
<td>800</td>
<td>Postmenopausal; node-positive and node-negative</td>
<td>E (days 1 and 8) × 6</td>
<td>Open</td>
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<td></td>
<td></td>
<td></td>
<td>E (days 1 and 8) × 3 → T × 3</td>
<td></td>
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<tr>
<td>UK TACT</td>
<td>3340</td>
<td>Operable, invasive disease</td>
<td>FEC × 8 or E × 4 → CMF × 4</td>
<td>Open</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FEC × 4 → T × 4</td>
<td></td>
</tr>
<tr>
<td>AGO Study Group</td>
<td>1900</td>
<td>Node-positive (1?3)</td>
<td>EC × 4 → T × 4</td>
<td>Open</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FEC × 6 or CMF × 6</td>
<td></td>
</tr>
<tr>
<td>GEICAM 9906</td>
<td>1248</td>
<td>Node-positive</td>
<td>FE90Cx6</td>
<td>Reported</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>FE90Cx4 → Pq1x8</td>
<td></td>
</tr>
<tr>
<td>CALGB 9344</td>
<td>3121</td>
<td>Node-Positive</td>
<td>A(60/75/90)Cx4 → PqX4</td>
<td>Reported</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>A(60/75/90)Cx4</td>
<td></td>
</tr>
<tr>
<td>CALGB 40101</td>
<td></td>
<td>4646 target</td>
<td>ddACx4</td>
<td>Open</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ddACx6</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ddPxx4</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ddPxx6</td>
<td></td>
</tr>
<tr>
<td>NCIC MA-21</td>
<td>2,100 target</td>
<td>node positive and negative</td>
<td>CEFq4x6</td>
<td>Open</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ddEXx6 → PqX3x4</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>ACx4 → PqX3x4</td>
<td></td>
</tr>
<tr>
<td>ICCG-C14/96</td>
<td>800 target</td>
<td></td>
<td>EqX6</td>
<td>Open</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EqX6 → Tq3x4</td>
<td></td>
</tr>
<tr>
<td>LMU-ADEBAR</td>
<td>446 target</td>
<td></td>
<td>FEOqX6</td>
<td>Open</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EC (d1,21,42,63) → T(d84,105,126,147)</td>
<td></td>
</tr>
</tbody>
</table>

A = doxorubicin; AGO = Arbeitsgemeinschaft für Gynäkologische Onkologie; BCIRG = Breast Cancer International Research Group; BIG = Breast International Group; C = cyclophosphamide; ECOG = Eastern Cooperative Oncology Group; E = epirubicin; F = fluorouracil; GEICAM = Gruppo Esperienza per l’Investigazione en Cancer de Mama; H = trastuzumab; ICGG = International Cancer Collaborative Group; M = methotrexate; NSABP = National Surgical Adjuvant Breast and Bowel Project; T = docetaxel; P = paclitaxel; INT = Intergroup; CALGB = Cancer and Leukemia Group B; q = every; w = week(s); dd = dose dense with q 2 week administration; NCIC = National Cancer Institute of Canada; ICGG = International Collaborative Cancer Group; LMU-ADEBAR = Ludwig-Maximilians-Universität-Adjuvant-Docetaxel-vs-Epirubicin-Based-Regimen-Trial.
Table 2. Selected second generation randomized clinical trials of docetaxel or paclitaxel in the adjuvant setting

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample Size</th>
<th>Patient population</th>
<th>Randomization</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCIRG005</td>
<td>3301</td>
<td>Node-positive; HER2-negative (FISH)</td>
<td>AC×4→T×4, TAC×6</td>
<td>Closed</td>
</tr>
<tr>
<td>BCIRG006</td>
<td>3204</td>
<td>Node-positive and high-risk node-negative; HER2 positive (FISH)</td>
<td>AC×4→T×4, AC×4→T×4 + H×1 year T-Carbo + H×1 ×6</td>
<td>Closed</td>
</tr>
<tr>
<td>NSABP B-30</td>
<td>5400</td>
<td>Node-positive</td>
<td>AC×4→T×4, AT×4, TAC×4</td>
<td>Closed</td>
</tr>
<tr>
<td>NSABP B-38</td>
<td>4800</td>
<td>Node-positive and high-risk node-negative</td>
<td>TAC×6, ddAC×4→ddP×4, ddAC×4→ddP×4</td>
<td>Open</td>
</tr>
<tr>
<td>E1199</td>
<td>4988</td>
<td>Node positive, high risk node-negative</td>
<td>AC×4→Pq3×4, AC×4→Pq3×4, AC×4→Tq3×4, AC×4→Tq3×4</td>
<td>Reported</td>
</tr>
<tr>
<td>INT C9741</td>
<td>1972</td>
<td>Node-Positive</td>
<td>ACPq2×4, ACpQ2×4, ACpQ2×4, ACpQ2×4, ACpQ2×4, ACpQ2×4</td>
<td>Reported</td>
</tr>
<tr>
<td>US09 99016</td>
<td>1830</td>
<td>Stage I/II</td>
<td>AC×4→Pq3×4, AP×4→Pq1×4</td>
<td>Reported</td>
</tr>
<tr>
<td>SWOG-0221</td>
<td>4,646 (target)</td>
<td></td>
<td>ACq2x6→Pq2x6, ACq1x5→Pq2x6, ACq2x6→Pq1x2, ACq1x5→Pq1x2</td>
<td>Open</td>
</tr>
</tbody>
</table>

A = doxorubicin; BCIRG = Breast Cancer International Research Group; C = cyclophosphamide; dd = dose dense with q2 week administration; E = epirubicin; G = gemcitabine; H = trastuzumab; NSABP = National Surgical Adjuvant Breast and Bowel Project; P = paclitaxel; T = docetaxel; INT = Intergroup; SWOG = Southwest Oncology Group; q = every; w = week(s).

usage, but produced a higher rate of febrile neutropenia on the fourth cycle. Significantly more cardiac events occurred in women randomized to 6 cycles of F100C (13 vs. 4 patients, p < 0.027). Radiotherapy was to start within 4 weeks of the last chemotherapy. Hormone therapy with tamoxifen was mandated for all patients with hormone receptor positive breast cancer, beginning after chemotherapy.

The interim analysis was triggered by the prespecified 482 relapses, which occurred after a median follow of 59.7 months. Disease free survival for the sequential regimen was increased, with the adjusted log rank hazard ratio of 0.80 (95% CI 0.67-0.96, p=0.014; 5 year absolute disease free survival of 78.3% vs. 73.2%). Overall survival was also prolonged, with the adjusted log rank hazard ratio of 0.73 (95% CI 0.56-0.94, p value of 0.017; 5 year absolute overall survival of 90.7% vs. 86.7%). Surprisingly, there was a clear interaction between age of the patient and disease free survival effects, with those women older than 50 markedly benefiting from randomization to sequential docetaxel (hazard ratio 0.67, p=0.001), while younger women showed no clear benefit (hazard ratio 0.98, p = 0.7, multivariate interaction test positive p = 0.026). There is no obvious mechanistic explanation for this effect, as the minor preponderance of ER positive disease in the experimental arm would be unlikely to produce such a strong signal. This report provides another example of modern chemotherapy providing substantial benefit to postmenopausal...
Table 3. Outcomes of reported phase III docetaxel or paclitaxel adjuvant studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median follow up</th>
<th>Regimen</th>
<th>DFS HR (p value)</th>
<th>5 year absolute</th>
<th>OS HR (p value)</th>
<th>5 year absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCIRG 001</td>
<td>55 months</td>
<td>TAC×6, FAC×6</td>
<td>0.72 (0.001)</td>
<td>75% 68%</td>
<td>0.70 (0.008)</td>
<td>87% 81%</td>
</tr>
<tr>
<td>PACS 01</td>
<td>59.7 months</td>
<td>FEC×3—T×3, FEC×6</td>
<td>0.80 (0.014)</td>
<td>78.3% 75.3%</td>
<td>0.73 (0.017)</td>
<td>90.7% 86.7%</td>
</tr>
<tr>
<td>US Oncology 9735</td>
<td>43 months</td>
<td>TC×4, AC×4</td>
<td>0.70 (0.13)</td>
<td>86% 81%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NSABP B-27</td>
<td>68.8 months</td>
<td>AC×4—surgery</td>
<td>0.86 (0.10)</td>
<td>NR</td>
<td>0.94 (0.57)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC×4—T×4—surgery</td>
<td>0.91 (0.27)</td>
<td>NR</td>
<td>1.07 (0.53)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC×4—surgery—T×4</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>E2197</td>
<td>53 months</td>
<td>AT×4, AC×4</td>
<td>1.08 (0.43)</td>
<td>87% (4 yr) 87%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.09 (0.48)</td>
<td>92.8% 92.2%</td>
</tr>
<tr>
<td>GEICAM 9906</td>
<td>47 months</td>
<td>FE90Cx6, FE90Cx4—P qx8</td>
<td>NR</td>
<td>86.9% 79.2%</td>
<td>NR</td>
<td>94.5% 91.8%</td>
</tr>
<tr>
<td>ECOG1999</td>
<td>46.5 months</td>
<td>AC×4—Pq3x4, AC×4—P qx12, AC×4—Tq3x4</td>
<td>1.20 (0.06), 1.13 (0.20), 1.03 (0.78)</td>
<td>NR, NR, NR</td>
<td>NR, NR, NR</td>
<td>NR, NR, NR</td>
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<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>CALGB 9344</td>
<td>69 months</td>
<td>A(60/75/90)Cx4—P x4, A(60/75/90)Cx4</td>
<td>0.83 (0.013), 0.82 (0.0061)</td>
<td>70% (±1), 65% (±1)</td>
<td>80% (±1), 77% (±1)</td>
<td>NR, NR</td>
</tr>
<tr>
<td>USO 9906</td>
<td>3 years</td>
<td>AC×4—Pq3x4, APx4—P qx12</td>
<td>0.69 (0.02)</td>
<td>86.1% 90.3%</td>
<td>0.57 (0.02)</td>
<td>92.1% 95.5%</td>
</tr>
<tr>
<td>INT C9741</td>
<td>36 months</td>
<td>ACPq2x4, ACPq3x4, ACq2x4—Pq2x4, ACq3x4—Pq3x4</td>
<td></td>
<td></td>
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</tbody>
</table>

A = doxorubicin; BCIRG = Breast Cancer International Research Group; C = cyclophosphamide; E = epirubicin; F = fluorouracil; M = methotrexate; NSABP = National Surgical Adjuvant Breast and Bowel Project; NR = not reported; T = docetaxel; P = paclitaxel; GEICAM = Grupo Español de Investigação en Cancer de Mama; INT = Intergroup.

GEICAM 9906

This phase III multicentre randomized trial of adjuvant chemotherapy for node positive women was presented in oral and abstract form at the 2005 San Antonio Breast Symposium. A total of 1,238 were randomized to either FE90C or FE90C followed by sequential weekly paclitaxel. Women were stratified based on menopausal status and number of affected lymph nodes (1-3, or more than 4). A total of 634 patients received FE90C (Fluorouracil 600mg/m², Epirubicin 90mg/m², cyclophosphamide 600mg/m²) every three weeks for 6 cycles and another 614 patients received FE90C every three weeks for 4 cycles followed by 8 weekly doses of paclitaxel (100mg/m²). Tamoxifen was given for five years to those with hormone receptor positive disease.

The main patient characteristics were well balanced between both arms. Analysis was performed at a follow up of 47 months and found a significant increase in disease free survival favoring the paclitaxel arm (86.9% vs. 79.2%, p = 0.0009). No statistically significant differences in overall survival have yet been achieved (94.5% for paclitaxel arm vs. 91.8% control arm, p = 0.1375). Thus, this trial demonstrates that sequential FE90C followed by weekly paclitaxel improved disease free survival for node positive operable breast cancer patients compared to FE90C alone. The two regimens differed in toxicity, in that febrile neutropenia rates were higher in the control arm (9.3% vs. 5.1%, p = 0.004), while mod-
erate neuropathy and mild asthenia was more common in the paclitaxel arm.

Although the dose of epirubicin varied slightly between the PACS 01 and GEICAM 9906 trials, these studies support the use of either docetaxel or paclitaxel sequentially after FEC in node positive breast cancer. Both PACS 01 and GEICAM 9906 have shown improvements in disease free survival when a taxane is given sequentially following an FEC combination. Similarly, both CALGB 0344 and NSABP-B28 report improved DFS for the addition of paclitaxel after four cycles of AC, while only the former study improved overall survival.

NSABP-B27

This study was an important attempt to explore the effect of adding docetaxel to neoadjuvant therapy of early stage breast cancer. Preliminary results of this three arm trial were presented (14) and the final study results are now published. (15) Comparison was made between two neoadjuvant chemotherapy regimens - namely AC×4 or AC×4 followed by docetaxel 100mg/m^2×4 - and a third regimen of preoperative AC×4 followed by postoperative docetaxel ×4. On the first day of administration of chemotherapy, all three groups, regardless of hormone receptor status, received tamoxifen daily for five years.

Fifty six percent of women were under 50, the mean clinical tumor size was 4.5 cm, and 70% had negative axillary nodes on clinical examination. The initial surgical findings were reported, with pooling of arms 1 and 3 which both gave only four cycles of neoadjuvant AC. A higher rate of pathological complete response within the breast (26.1% vs. 13.6%) and improved downstaging of axillary nodes was observed with sequential AC followed by docetaxel given preoperatively. However, despite mature followup of 68.8 months and an analysis triggered by exceeding 430 deaths, this result has not translated into improvement in disease free survival or overall survival (Table 3).

One of the most interesting results of this trial is the apparent disconnect between improvements in pathological complete response (pCR) and disease free survival. While the disease free survival of women who achieved pCR was substantially better than those who did not achieve pCR (hazard ration 0.45, p < 0.0001), in absolute terms, only an additional 13% of patients achieved in breast pathologic complete response by the addition of 4 cycles of preoperative docetaxel. Thus, although the docetaxel / concurrent tamoxifen regimen appears to have improved prognosis in this small subgroup, the absolute numbers of patients who benefited appear to be insufficient to shift overall outcomes.

What remains unexplained, however, is how the addition of a powerful cytotoxic such as docetaxel did not improve DFS and OS. The universal requirement for concurrent administration of chemotherapy and tamoxifen in this trial may provide part of the explanation. Recent reports from the Southwest Oncology Group (SWOG) 8814 trial (7) show that concurrent administration of chemotherapy and tamoxifen in postmenopausal ER positive patients is substantially less effective than chemotherapy followed by tamoxifen. Based on these data, future NSABP neoadjuvant and adjuvant trials will require that tamoxifen be delayed until after the completion of chemotherapy.

ECOG 1199 - a comparison of taxanes and schedules

Although sharing similarities with the prototype taxane paclitaxel, there are several differences between docetaxel and paclitaxel: docetaxel has more potent cytotoxic anti-tumor effects than paclitaxel on an equimolar basis. (16) achieves higher intracellular drug concentration with less cellular efflux, (17) and has a higher affinity for microtubules. (18) These differences were also apparent in the clinic, with differences in activity and tolerability when administered in the metastatic setting at the FDA mandated doses. (19) In addition, several reports suggested retained or enhanced activity, and different toxicity profiles, when the taxanes were
administered in weekly schedules. These findings provided the rationale for the E1199 trial. In this phase III study presented at the San Antonio Breast Cancer Symposium 2005, a comparison was made between two taxanes (paclitaxel and docetaxel) and schedule (every 21 days vs weekly) in high risk node-negative breast cancer patients and node positive patients. The 4988 eligible patients were randomized to one of four treatment arms. All patients received four cycles of AC (doxorubicin 60mg/m² and cyclophosphamide 600mg/m²) every three weeks followed by either: i) paclitaxel 175mg/m² every three weeks for four cycles or ii) paclitaxel 80mg/m² weekly for twelve cycles or iii) docetaxel 100mg/m² every three weeks for four cycles or iv) docetaxel 35mg/m² weekly for twelve cycles. All patients who were hormone receptor positive received a 5 year or longer course of adjuvant hormonal therapy with tamoxifen, an aromatase inhibitor or tamoxifen followed by an aromatase inhibitor.

Event rates were lower than anticipated for the study, and although the protocol specified number of events had not yet been reached to report the trial, a ‘futility’ analysis suggested the results were unlikely to change dramatically. At a median follow up of 46.5 months there was no significant difference in disease free survival in the hazard ratios comparing taxane (HR 0.985, p = 0.83) or schedule (1.043, p = 0.54). Although not statistically significant, weekly paclitaxel and q21 day docetaxel had numerically improved DFS and OS over standard schedule paclitaxel. The attempt to deliver weekly docetaxel every week for 12 weeks was compromised, as expected, by the requirement for frequent treatment breaks. Febrile neutropenia rates were highest with every 21 day docetaxel. The worst grade 3 toxicity of any kind was highest in the arm 4 (docetaxel 35mg/m²) and grade 4 toxicity was highest in arm 3 (docetaxel 100mg/m²).

**CALGB 9741 - dose-dense paclitaxel**

The efficacy of adjuvant chemotherapy can be compromised by administration delays, which raises the question whether administering treatment over a shorter time period might similarly improve outcomes. In the CALGB 9741 study, originally reported after three years of follow-up, dose-dense therapy was shown to be safe and effective. A comparison was made between dose dense chemotherapy (every two weeks) compared to standard (every three weeks) and concurrent to sequential paclitaxel. In this trial 1972 patients were randomized to one of four possible treatment arms, however the dose for doxorubicin (A), paclitaxel (P), and cyclophosphamide (C) were constant (A=60mg/m², P=175mg/m², C=600mg/m²).

At a median follow up of 36 months there was no difference between concurrent or sequential chemotherapy administration. There was however an improvement in disease free survival (HR 0.80, p = 0.018) and a trend towards and improvement in overall survival (HR 0.85, p = 0.12) in the dose dense (every two week) therapy. The benefits were most striking in the first 3 years of follow up, and appear to be largely confined to the population with estrogen receptor negative breast cancer. The long-term results of this study were recently updated in a published abstract at the 2005 San Antonio Breast Cancer Symposium, which showed a continued disease free survival benefit to dose-dense therapy, although overall survival was not significantly improved. A further updated analysis, representing a median followup of 6.8 years, was given during the oral presentation of this study, and reports an overall survival advantage (absolute benefit - 2.5%) of borderline statistical significant (p=0.049). Cardiac toxicity and leukemogenicity, two long-term complications of adjuvant chemotherapy, were not increased in those receiving q2 weekly therapy.

**NON-ANTHRACCYLINE TAXANE COMBINATIONS**

**USON 9735 AC vs. TC**

The final reported adjuvant docetaxel trial, US Oncology Network 9735, assessed the substitution
of a taxane for all cycles of an anthracycline, again
with an equal number of cycles in each group. In the
USON 9735 study, 1016 women with stage I-III
operable breast cancer were stratified by nodal status
and age and randomized to either four cycles of AC
(doxorubicin 60 mg/m² with cyclophosphamide 600
mg/m²) or to four cycles of docetaxel 75 mg/m² with
cyclophosphamide 600 mg/m² (TC). (25) Courses
were repeated every 3 weeks and completed prior to
adjuvant radiation therapy and/or tamoxifen, which
was used for hormone receptor- positive disease.
Treatment groups were well balanced, with 48% of
patients having node-negative disease and 41% hav-
ing 1-3 positive nodes and 11% having more than 4
nodes. At a median follow-up of 5 years 165 events
occurred. In the taxane-containing group 68
women relapsed and 50 deaths occurred whereas in
the control group there were 87 relapses and 66
deaths. There was a significant improvement in dis-
ease-free survival at 5 years in the taxane-containing
group (86% vs. 81% p = 0.027) but overall survival
was not improved (89% vs. 88% p = 0.188). (26) In
practice, this study does provide good evidence that a
non-anthracycline regimen might outperform four
cycles of AC. The TC regimen might therefore be
reserved for those women who have contraindi-
cations to anthracycline chemotherapy.

Concurrent anthracycline-taxane regimens

Given the successes achieved in many malignan-
cies by the concurrent use of highly active agents in
combination, it is not surprising that investigators
have explored combining taxanes with anthracy-
clines. Due to a direct pharmacokinetic interaction
of paclitaxel preparations that reduce the elimin-
ation of anthracyclines, however, cardiotoxicity has
been prohibitive for many schedules of paclitaxel-antha-
cycline combinations. In contrast, docetaxel does
not change anthracycline metabolism, and studies in
the adjuvant and metastatic settings have not shown
cardiotoxicity concerns when docetaxel is combined
with anthracycline chemotherapy. To date, whether
sequential or combination anthracycline-taxane
strategies differ in efficacy is unknown - the trials to
address this issue have not yet been reported.

BCIRG 001

Combination anthracycline/docetaxel regimens
are well-studied the setting of advanced disease:
although they are highly myelosuppressive, they pro-
duce acceptable levels of cardiotoxicity and are high-
ly active. (27-30) These favorable results provided
the rationale to launch a number of docetaxel-
anthracycline combination adjuvant studies (Table
1). The first such study to report was the BCIRG
001, a comparison of six cycles of TAC (docetaxel 75
mg/m², doxorubicin 50 mg/m², cyclophosphamide
500 mg/m²) to six cycles of FAC (fluorouracil 500
mg/m², doxorubicin 50 mg/m², cyclophosphamide
500 mg/m²) all at three weekly intervals. In this
study, 1491 women with axillary node positive dis-
ease were accrued between June 1997 and June
1999. Eligible patients were between 18 and 70
years, had T1-T3 breast cancer, axillary node posi-
tive disease with at least 6 removed axillary nodes, no
distant metastases, and adequate end organ function.
Patients were stratified according to centre and num-
ber of involved lymph nodes (1-3 vs. >3). The med-
ian age was 49 years, 49% were premenopausal, and
38% of women had more than 4 involved nodes.
Randomization produced no imbalances in prog-
nostic factors, and tamoxifen was given after chem-
otherapy for those with hormone receptor pos-
tive disease.

With a median follow-up of 55 months, 400 DFS
events triggered the prespecified interim analysis.
The primary endpoint of disease free survival was
improved by TAC, with a hazard ratio of 0.72 (p =
0.001). The benefit in disease free survival was seen
in all subsets of patients (hormone receptor positive
and negative, HER-2 amplified and non-amplified),
and no interactions were identified with the number
of involved axillary nodes, or with menopausal sta-
tus. Overall survival was prolonged by TAC, with a
hazard ratio of 0.70 (p = 0.008). Primary prophylax-
is with G-CSF was not allowed, and febrile neu-
tropenia (24% vs. 2%) and grade 3/4 infection (2.8% vs. 1.3%) were higher with TAC, but no septic deaths occurred. Other toxicities were expected and manageable, and quality of life returned to baseline after completion of either chemotherapy regimen.([31], [32])

In contrast to some adjuvant paclitaxel studies ([6], [33]), disease-free survival was clearly improved in the subset of women with estrogen receptor positive disease. The major toxicity of TAC may be largely preventable, when delivered with primary prophylactic G-CSF febrile neutropenia can be reduced to the range of 4-7% of patients patients.([34], [35])

**E2197 AC vs. AT**

Preliminary results from this phase III Intergroup trial was presented at ASCO 2005.([36]) This trial tested adjuvant AT versus AC in high risk node negative and node positive women. Patients were randomized to receive either 4 cycles of AT (doxorubicin 60mg/m² and docetaxel 60mg/m²) or 4 cycles of AC (doxorubicin 60mg/m² and cyclophosphamide 600mg/m²) every three weeks. Patients who were also estrogen or progesterone receptor positive went on to receive tamoxifen upon completion of chemotherapy.

A total of 2889 eligible patients were randomized to either arm (AT vs. AC) and were stratified based on nodal, hormone receptor and menopausal status. At a median follow up of 53 months, there were 197 recurrences in the AT arm vs. 212 in the AC arm and 104 deaths in the AT arm vs. 113 in the AC arm. In comparison to the USON 9735 trial, the E2197 trial did not show a significant difference in disease-free survival at 4 years (87% in both arms, p=0.43). On subgroup analysis, those 35% of women were estrogen receptor negative had a non-significant improvement in 4 year disease-free survival if they received AT vs. AC (82% vs. 79%, p=0.17). Of note, there were 3 treatment related deaths in the AT arm and febrile neutropenia occurred more frequently in the AT arm (19% vs. 6%). Overall, the authors concluded that these data did not support the routine use of AT adjuvant chemotherapy. The negative results of this study may be due, in part, to the relatively low dose of docetaxel (60mg/m²) used in the study: studies in metastatic disease support a clear dose-response relationship for this agent.

**USON 99016**

This phase III randomized, multicentre trial was presented at the San Antonio Breast Cancer Symposium in 2004([37]) and compared doxorubicin and cyclophosphamide followed by paclitaxel (AC→P) vs. doxorubicin and paclitaxel followed by weekly paclitaxel (AP→P). A total of 1830 women with stage I-III breast carcinoma were randomized to either doxorubicin and cyclophosphamide (60mg/m² and 600mg/m²) every three weeks for 4 cycles followed by paclitaxel (175mg/m²) every three weeks for an additional 4 cycles (AC→P) vs. doxorubicin and paclitaxel (50mg/m² and 200mg/m²) every three weeks for 4 cycles followed by weekly paclitaxel (80mg/m²) for an additional twelve weeks (AP→P).

There was a notable improvement in three year disease-free survival rates (96.1% vs. 90.3%, p=0.02) in favour of the anthracycline paclitaxel combination followed by weekly paclitaxel (AP→P) as well as an increase in three year overall survival rates (92.1% vs. 85.5%, p=0.02). However, as this was an interim analysis for efficacy, and the pre-specified boundaries for efficacy were not crossed (p=0.001), confidence in these effects will require more followup and more events. Toxicities were comparable in both arms, but neuropathy was greater in the doxorubicin paclitaxel (AP→P) combination arm (9% vs. 4%, p=0.01).

**Conclusion**

Many of the adjuvant taxane trials described above have a non-taxane anthracycline-based control arm, which allows us to draw some general conclusions. The majority of such studies show a disease-free survival advantage, and a handful of studies (BCIRG 001, PACS 01, CALGB 9344, CALGB 9741) also give clear improvements in overall survival. To date, no prohibitive long-term toxicities have been identi-
fied neuropathy is generally low grade and reversible, leukemogenicity has not increased, and cardiotoxicity has not been worsened. Therefore, we can safely conclude that women with high risk breast operable breast cancers should be considered for adjuvant taxane-based chemotherapy, and that adjuvant taxanes are now the standard of care for women with node positive disease.

Several questions remain unanswered, however. The relative merits of sequential therapy (anthracyline followed by taxane) and combination therapy (anthracyclines given concurrently with taxane) are still unknown, and await long-term efficacy outcomes from trials such as BCIRG 005 and NSABP B-39.

Additionally, whether choice of taxane (paclitaxel vs. docetaxel), and choice of schedule (weekly vs. q3weekly) used after anthracyclines makes a meaningful difference in outcomes will also require more followup, and a mature analysis, of the E1199 study.

Finally, it must be recognized that attempting to make further therapeutic gains in the adjuvant setting with i) novel taxanes, ii) changes in chemotherapy schedule or dose, or iii) incorporation of additional standard chemotherapeutic agents, is unlikely to provide major improvements in outcomes. Currently, highly effective hormonal therapies are reducing recurrence rates, adjuvant trastuzumab is substantially reducing recurrence rates, and we have entered an era where progress in adjuvant therapy is increasingly difficult to demonstrate. Given the low event rates we are seeing in our modern adjuvant therapy trials, convincingly demonstrating further improvements with require massive international collaborative efforts with long-term followup.

Attention has understandably turned to identifying new biological targets, and developing new targeted molecular therapies. We are in the gratifying era where chemotherapy clinical trialists have become victims of our own success.

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