The Impact of Taxotere on Adjuvant Breast Cancer

a report by
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Introduction

Adjuvant chemotherapy for breast cancer has undergone a major change over the past two decades. Results from the published update of the overview analysis indicate that administration of adjuvant chemotherapy significantly reduced the risk of recurrence by 23.5% and the risk of death by 15.3%. According to the same overview, the 10-year recurrence-free survival for node-positive patients treated with adjuvant chemotherapy was 47.6% for patients younger than 50 years and 43.6% for those 50 to 69 years old. The 10-year overall survival (OS) was 53.8% and 48.6% respectively.

The recent overview analysis found overall a moderate but highly significant advantage of anthracycline over cyclophosphamide/methotrexate/5-fluorouracil (CMF) (recurrence rate ratio 0.89 (SE 0.03); breast cancer death rate 0.84 (SE 0.03)). In addition, the allocation of about six months of anthracycline-based polychemotherapy (e.g. with 5-FL, doxorubicin and cyclophosphamide (FAC) or 5-FL, epirubicin and cyclophosphamide (FEC)) reduces the annual breast cancer death rate by about 38% for women younger than 50 years old when diagnosed and by about 20% for those aged 50 to 69 years old when diagnosed. This is largely irrespective of the use of tamoxifen and of oestrogen receptor status, nodal status or other tumour characteristics. Such regimens are significantly (2p=0.0001 for recurrence, 2p<0.00001 for breast cancer mortality) more effective than CMF chemotherapy.

Two trials provide important confirmatory information regarding the benefit of incorporating four courses of a taxane (paclitaxel) sequentially after four cycles of adjuvant chemotherapy in the adjuvant setting in node-positive patients. Mature results from Cancer and Leukemia Group B (CALGB) 9344 with 69 months of median follow-up demonstrated that the addition of four cycles of paclitaxel given at the dose of 175mg/m² every three weeks improved recurrence-free survival (reduction in the hazard rate of recurrence, 17%, p=0.0023) and OS (reduction in the hazard rate of death, 18%, p=0.0064). The results of the second trial (National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28) have been published very recently. Results with 65 months of median follow-up demonstrated that the addition of four cycles of paclitaxel given at the dose of 225mg/m² every three weeks improved disease-free survival (reduction in the hazard rate of recurrence, 17%, p=0.006) without significant improvement in OS (reduction in the hazard rate of death, 7%, p=0.46).

In these CALGB 9344 and NSABP B-28 trials it is possible to argue that the benefits observed where taxanes are added in sequence to an anthracycline-based regimen might be due in part to the administration of more cycles of chemotherapy in the experimental arm (eight cycles) in comparison with the standard arm (four cycles).

Taxotere (Docetaxel)

Docetaxel is an active agent in the treatment of breast cancer, particularly in chemotherapy-naive metastatic breast cancer patients. This activity is reported using docetaxel alone or in combination with anthracyclines. Three large randomised studies demonstrated that regimens combining doxorubicin and docetaxel (AT) or docetaxel, doxorubicin and cyclophosphamide (TAC) have antitumour activity superior, in terms of response rate, to that of doxorubicin and cyclophosphamide (AC) or fluorouracil, doxorubicin and cyclophosphamide (FAC).

In addition, docetaxel is not cross-resistant with anthracyclines and does not interfere with the pharmacokinetics of doxorubicin. So, there is a strong rationale for incorporating docetaxel and developing new more active adjuvant chemotherapy regimens.

Taxotere on Adjuvant Breast Cancer

Two trials, Breast Cancer International Research Group (BCIRG) 01 and Programme Adjuvant...
cancer du Sein (PACS) 01, provide important confirmatory information regarding the benefit of incorporating docetaxel, concomitantly or sequentially, respectively, in the adjuvant setting in node-positive patients.

Study Design

The Standard Arms, the Comparators

At the time of initiation of the BCIRG 01 study, six cycles of FAC (fluorouracil 500mg/m², doxorubicin 50mg/m² and cyclophosphamide 500mg/m²) every three weeks were generally accepted as appropriate adjuvant regimens for the treatment of early breast cancer. Epirubicin is less cardiotoxic than doxorubicin at an equimolar dose (recommended cumulative doses of doxorubicin and epirubicin are 550mg/m² and 1,000mg/m², respectively).

A National Cancer Institute of Canada (NCIC) study showed that six cycles of cyclophosphamide, epirubicin, fluorouracil (CEF) were superior to six cycles of CMF. The Groupe Français d’Etudes Adjuvantes (GFEA; The French Adjuvant Trial Group) has studied epirubicin in the treatment of breast cancer for several years. The FEC regimen has also evaluated in the trial setting lymph node-positive patients. Six cycles of adjuvant FEC 50 (epirubicin 50mg/m²) are better than three cycles. Subsequently, a trial in patients who were less than 65 years old, with node-positive operable breast cancer, compared FEC 50 versus FEC 100 (epirubicin 100 mg/m²). Six cycles of FEC 100 were associated with improved relapse rates and better survival. This last regimen was chosen as the reference arm in the PACS01 trial.

The Docetaxel Arms

In the BCIRG01 study, docetaxel 75mg/m² was administered in combination with doxorubicin 50mg/m² and cyclophosphamide 500mg/m², called a three-weekly ‘TAC’ regimen. All patients were to receive a prophylactic antibiotic, but prophylaxis with granulocyte colony-stimulating factor (G-CSF) was not permitted. In the PACS01 Study, the patients randomised to arm B received three cycles of FEC 100 (fluorouracil 500mg/m², epirubicin 100mg/m² and cyclophosphamide 500mg/m² every three weeks) followed by three-weekly cycles of docetaxel at dose of 100mg/m². Prophylaxis with granulocyte colony-stimulating factor (G-CSF) was also not permitted.

Stratification

In the BCIRG01 study, randomisation was stratified according to institution and number of involved nodes (one to three versus four or more). The same criteria for stratification were designed in the PACS01 trial with the addition of the age (≥ or ≤ 50 years).

End-points, Statistical Analysis

The primary end-point, five-year disease-free survival (DFS) was assessed on the intent-to-treat (ITT) population in the two studies. Secondary end-points were safety, OS, and quality of life.

Table 1: Characteristics of the Patients and the Tumours at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BCIRG01 6 TAC</th>
<th>BCIRG01 6 FAC</th>
<th>BCIRG01 p</th>
<th>PACS01 3 FEC 100 followed by 3 docetaxel</th>
<th>PACS01 6 FEC100</th>
<th>PACS01 Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age–year, Median</td>
<td>49</td>
<td>49</td>
<td>50</td>
<td>49</td>
<td>60.4</td>
<td>62.3</td>
</tr>
<tr>
<td>Age &lt;50 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopausal status %</td>
<td>56.5</td>
<td>54.8</td>
<td>49.8</td>
<td>50.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥50 years %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary tumour size T2–T3 %</td>
<td>59.6</td>
<td>57.1</td>
<td>51</td>
<td>52.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal status N+ 1–3 %</td>
<td>62.7</td>
<td>61.5</td>
<td>62.4</td>
<td>61.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive oestrogen-receptor status</td>
<td>76.1</td>
<td>75.7</td>
<td>80.9</td>
<td>77.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast-conserving surgery %</td>
<td>40.3</td>
<td>41.2</td>
<td>52.9</td>
<td>51.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Overall Efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BCIRG01 6 TAC</th>
<th>BCIRG01 6 FAC</th>
<th>BCIRG01 p</th>
<th>PACS01 3 FEC 100 followed by 3 docetaxel</th>
<th>PACS01 6 FEC100</th>
<th>PACS01 Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS at five years %</td>
<td>75</td>
<td>68</td>
<td>0.001</td>
<td>78.2</td>
<td>73.2</td>
<td>0.01</td>
</tr>
<tr>
<td>OS at five years %</td>
<td>87</td>
<td>81</td>
<td>0.008</td>
<td>90.7</td>
<td>86.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>
The BCIRG01 trial was designed to have an overall power of 97% to detect a 27% reduction in the risk of relapse among patients treated with TAC compared with those treated with FAC, regardless of nodal status. A sample size of 1,491 was planned. In the PACS01 study, to show a gain of 7.5% in the five-year DFS (65% in the reference arm versus 72.5%, corresponding to a relative risk of 0.75), the protocol originally stated that 1,600 patients were needed to ensure that the power of the test was at least 90% ($\beta = 10\%$), assuming a two-coded situation and accepting a significance level of 5%. However, following a successful recruitment rate and to ensure a higher statistical power, a protocol amendment extended the study population to 2,000 patients.

Hormonotherapy and Radiotherapy

On completion of chemotherapy, tamoxifen (20mg daily for five years) was administered to patients enrolled in the BCIRG01 trial with oestrogen-receptor (OR)-positive, progesterone-receptor (PR)-positive, or both. In the PACS01 study, hormonotherapy was administered after the end of cytotoxic therapy, and all post-menopausal patients with OR/PR positive tumours received tamoxifen (20mg/day) for five years. Hormone therapy for post-menopausal patients with receptor-negative tumours was left to the clinician’s discretion, but the chosen option was applied to both treatment arms and to all patients throughout the trial. It was not allowed for pre-menopausal patients with receptor-negative tumours.

In October 1998, a protocol amendment called for tamoxifen administration in pre-menopausal ER-/PR-positive patients. Post-menopausal status was that which had been observed before the start of chemotherapy. In the two studies radiotherapy was mandatory after breast conserving surgery and was administered after mastectomy according to each institution’s guidelines.

Characteristics of the Patients and the Tumours at Baseline

These characteristics are summarised in Table 1. Some criteria such as age and nodal status are similar between the two studies. However, the characteristics are different regarding menopausal status, primary tumour size and breast-conserving surgery.

Efficacy

Overall (Table 2)

In the BCIRG01 study, at a median follow-up period of 55 months, adjuvant chemotherapy with TAC improved recurrence-free survival (reduction in the hazard rate of recurrence, 28%, $p=0.001$) and OS (reduction in the hazard rate of death, 30%, $p=0.008$). In the PACS01 trial, at a median follow-up period of 60 months, adjuvant chemotherapy with three cycles of FEC100 followed by three cycles of docetaxel improved recurrence-free survival (reduction in the hazard rate of recurrence, 17%, $p=0.04$) and OS (reduction in the hazard rate of death, 23%, $p=0.005$).

Subgroup Analyses

The superiority of TAC over FAC was observed in all subgroup analyses that included the number of involved axillary lymph nodes, HER-2 status and hormonal-receptor status, and was independent of menopausal status. Analysis of Cox model did not detect any difference in the treatment effect between the two nodal-status strata (one to three positive nodes versus $\geq$ four positive nodes), ratio of hazard ratios 1.34; $p=0.17$. In the PACS01, the superiority of the sequential-docetaxel treatment over six FEC100 was observed in subgroup analyses that included the number of involved axillary lymph nodes and hormonal-receptor status. However, analysis of Cox model detects difference in the treatment effect between the two age strata (<50 years versus $\geq$50 years).

### Table 3: Adverse Events

<table>
<thead>
<tr>
<th>Toxic Effects</th>
<th>BCIRG01 6 TAC grade 3 or 4 or severe</th>
<th>BCIRG01 6 FAC grade 3 or 4 or severe</th>
<th>BCIRG01 6 FAC grade 3 or 4 or severe</th>
<th>BCIRG01 6 FAC grade 3 or 4 or severe</th>
<th>PACS01 3 FEC 100 grade 3 or 4 or severe</th>
<th>PACS01 6 FEC100 grade 3 or 4 or severe</th>
<th>PACS01 6 FEC100 grade 3 or 4 or severe</th>
<th>PACS01 6 FEC100 grade 3 or 4 or severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia %</td>
<td>65.5</td>
<td>49.3</td>
<td>&lt;0.001</td>
<td>7.3</td>
<td>9.4</td>
<td>&lt;0.001</td>
<td>9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Febrile neutropenia %</td>
<td>28.8</td>
<td>4.4</td>
<td>&lt;0.001</td>
<td>2.9</td>
<td>1.6</td>
<td>&lt;0.001</td>
<td>1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea %</td>
<td>5.1</td>
<td>9.5</td>
<td>0.001</td>
<td>3.3</td>
<td>6.6</td>
<td>&lt;0.001</td>
<td>6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mucositis %</td>
<td>7.1</td>
<td>2.0</td>
<td>&lt;0.001</td>
<td>1.3</td>
<td>0.8</td>
<td>0.03</td>
<td>0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Oedema %</td>
<td>0.5</td>
<td>0.1</td>
<td>0.37</td>
<td>2.4</td>
<td>0.1</td>
<td>&lt;0.001</td>
<td>0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nail changes</td>
<td>0.4</td>
<td>0.1</td>
<td>0.62</td>
<td>5.8</td>
<td>0.6</td>
<td>&lt;0.001</td>
<td>0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>Overall 61.7</td>
<td>Overall 52.4</td>
<td>0.007</td>
<td>Overall 68.4</td>
<td>Overall 72.4</td>
<td>0.13</td>
<td>Overall 72.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Chronic heart failure (CHF)</td>
<td>1.6</td>
<td>0.7</td>
<td>0.09</td>
<td>0.4</td>
<td>0.09</td>
<td>0.001</td>
<td>0.09</td>
<td>0.001</td>
</tr>
</tbody>
</table>
years), ratio of hazard ratios 0.66; p=0.026. The benefit of the incorporation of docetaxel is mainly reported for the older group of patients.

**Toxic Effects (Table 3)**

In the BCIRG01 trial, the rates of febrile neutropaenia were 24.7% in the TAC arm versus 2.5% in the FAC arm (p<0.001). Grade 3 or three infections occurred in 3.9% of the patients who received TAC and 2.2% of those who received FAC (p=0.05). The overall incidence of congestive heart was 1.6% among patients treated with TAC and 0.7% for those treated with FAC (p=0.09). In comparison with the BCIRG study, the incidence of febrile neutropaenia, infection and cardiac dysfunction is lower especially in the sequential arm.

**Discussion and Conclusion**

The results of CALGB 9344 and NSABP B-28 studies provided valuable information about the role of paclitaxel in the adjuvant setting. Nevertheless, it is possible to argue that the benefits observed where taxanes are added in sequence to an anthracycline-based regimen might be due in part to the administration of more cycles of chemotherapy in the experimental arm (eight cycles) in comparison with the standard arm (four cycles).

These two trials, BCIRG01 and PACS01, provide important confirmatory information regarding the benefit of incorporating docetaxel, concomitantly or sequentially respectively, in the adjuvant setting in node-positive patients. In addition the same number of cycles was administered in the standard and experimental arms. Regarding efficacy, the standard arms and the characteristics of the patients and tumours are different impeding objective comparisons between the concomitant or sequential approaches of incorporating docetaxel. However, without granulocyte-colony stimulating factor (G-CSF) prophylaxis, the incidence of febrile neutropaenia is lower in the PACS01 trial.

Recent results from the Spanish Breast Cancer Research Group (GEICAM) 9805 Spanish trial demonstrated a significant decrease of the incidence of febrile neutropenia (<5%) giving G-CSF prophylaxis during TAC treatment. Finally, the PACS01 sequential approach allows the use of lower cumulative dose of anthracycline explaining the lower incidence of cardiac events.

In node-positive human epidermal growth factor receptor-2 (HER-2) negative early breast cancer patients, several methods could be explored. Administration of cytotoxic courses every two weeks (q2w) (so-called dose-dense therapy) is one of the ways to improve efficacy in node positive (N+) breast cancer.

Attempts to optimise the sequential anthracycline/paclitaxel regimen by administration it in a dose-dense fashion with colony-stimulating factor support have produced early promising results in terms of further improving DFS and OS. However, the report data should be viewed as immature and suffer from weakness. In addition PACS06 compared FEC 100 (5-FU 500mg/m2, epirubicin 100mg/m2, cyclophosphamide 500mg/m2) x three cycles every two weeks followed by Taxotere 100 mg/m2 x three cycles every two weeks, in association with G-CSF day three to 10, with either a two-week (arm A) or a four-week (arm B) interval between FEC and Taxotere.

The primary end-point was to define the rate of patients with any toxicity (DLT) requiring dose reduction or treatment delay by more than one week over the six courses. An interim analysis was planned after the enrolment of 30 patients in each arm. If eight (27%) or more DLTs as defined above reported, the patient recruitment should be stopped in this arm. In May 2005, the recruitment was stopped with the following conclusion, FEC 100 x three cycles every two weeks followed by Taxotere 100mg/m2 x three cycles every two weeks, with a two-week interval between FEC and Taxotere is not feasible due to an excess of skin/hand-foot syndrome severe toxicities.

The results of these or other recently or completed trials will provide valuable information about the safest and more effective way to incorporate docetaxel in an adjuvant setting.

**References**


