

**REGIONAL DRUG AND THERAPEUTICS CENTRE  
(NEWCASTLE)**

**THE ADJUVANT USE OF DOCETAXEL OR  
PACLITAXEL IN THE MANAGEMENT OF  
EARLY STAGE BREAST CANCER**

**Wolfson Unit  
Claremont Place  
Newcastle upon Tyne  
NE2 4HH**

**March 2006**



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## ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre. The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rests solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

<b>Subject</b>	<b>Date issued</b>
Alglucerase for Gaucher's disease	July 1997
Taxanes in breast cancer	July 1997
Somatropin for GHD in adults	January 1998
New drugs for Alzheimer's disease	February 1998
Atypical antipsychotics	February 1998
Dornase alfa for cystic fibrosis	July 1998
Topotecan for ovarian cancer	July 1998
Irinotecan for colorectal cancer	July 1998
Interferon alfa for haematological malignancy	July 1998
Antiretroviral therapy	July 1998
Paclitaxel in ovarian cancer	December 1998 (update)
Interferon in MS	May 1999 (update)
Octreotide	July 1999
Drug treatment of obesity	July 1999
Low molecular weight heparins in venous thrombo-embolic disease	November 1999
Low molecular weight heparins in unstable coronary artery disease	November 1999
Ribavirin and interferon alfa for chronic hepatitis C	March 2000
Temozolomide for high grade gliomas	May 2000
New drugs for rheumatoid arthritis	May 2000
Verteporfin for age related macular degeneration	November 2000
Iloprost and epoprostenol in the management of pulmonary hypertension	February 2001
Atypical antipsychotics in the management of dementia	June 2001
Interferon alfa in the management of malignant melanoma	November 2001
Imatinib (Glivec <sup>®</sup> , STI-571), in the management of chronic myeloid leukaemia	November 2001
Agalsidase alfa and beta in the management of Fabry disease	July 2002
Carbaryl glutamate in the management of N-acetylglutamate synthetase deficiency	July 2002
Erythropoietin in the management of cancer related anaemia	July 2002
Drotrecogin alfa (activated) in the management of severe sepsis	December 2002
An update on newer agents for the treatment of pulmonary hypertension	February 2004
The use of adefovir dipivoxil for the treatment of chronic hepatitis B infection	May 2004
The use of teriparatide in the management of osteoporosis	July 2004
The use of ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases	August 2005
The use of pegvisomant in the management of acromegaly	January 2006
The use of pemetrexed in the management of malignant pleural mesothelioma	February 2006
The use of bortezomib second-line in the management of multiple myeloma	March 2006
The use of erlotinib in the management of non-small cell lung cancer	March 2006
The use of ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006
The use of rituximab in combination with CVP chemotherapy for the management of follicular non-Hodgkin's lymphoma	March 2006

**CONTENTS**

SUMMARY .....	4
BACKGROUND .....	5
EFFICACY .....	6
Docetaxel .....	6
Paclitaxel .....	7
ADVERSE EFFECTS .....	8
Docetaxel .....	8
Paclitaxel .....	9
DOSAGE, ADMINISTRATION AND COST .....	9
Docetaxel .....	9
Paclitaxel .....	9
Taxanes .....	10
PLACE IN TREATMENT .....	10
ARRANGEMENTS FOR PRESCRIBING .....	11
FUTURE DEVELOPMENTS.....	11
ACKNOWLEDGEMENTS.....	11
REFERENCES .....	12
APPENDICES.....	14
Appendix 1. Breast cancer stage grouping .....	14
Appendix 2. Abridged version of the American Joint Committee on Cancer Collaborative Staging Manual - Breast Cancer .....	15
Appendix 3. Summary of trials .....	16

## SUMMARY

- **Breast cancer is the most common malignancy and cause of cancer mortality in females in the UK. The annual incidence of breast cancer in females is 144 per 100,000 which equates to about 36,500 new cases annually in England. The five year survival rate is approximately 80%.**
- **The taxane compounds, docetaxel and paclitaxel, are licensed for use as adjuvant therapy in early stage breast cancer. Docetaxel is licensed for concurrent use with doxorubicin and cyclophosphamide. Paclitaxel is licensed as monotherapy after a course of an anthracycline and cyclophosphamide. When used as adjuvant therapy the licences for both drugs stipulate use in node-positive early stage breast cancer.**
- **The efficacy of both regimens has been proven in large phase III randomized trials. The principle outcome measure is disease free survival. Significant increases in disease free survival do not always correlate with significant increases in overall survival in the studies evaluated; this may be due to the relatively short period of follow-up.**
- **Both taxane regimens demonstrated significant increases in the prevalence of adverse effects against comparator regimens in the evaluated studies. For example, docetaxel in combination with doxorubicin and cyclophosphamide demonstrated a prevalence of grade 3, 4, or severe non-haematological adverse events of 36.3% against 26.6% in the comparator arm using 5-fluorouracil in combination with doxorubicin and cyclophosphamide. Paclitaxel, when used sequentially to doxorubicin and cyclophosphamide, demonstrated adverse effects related to neurosensory toxicity of approximately 15%.**
- **Of particular note is the increase in neutropenia and febrile neutropenia, often resulting in the requirement for supportive therapy. Docetaxel, when substituted for 5-fluorouracil, was associated with a prevalence rate for grade 3< neutropenia of 65.5% compared to 49.3%, and a prevalence rate for febrile neutropenia of 28.8% compared to 4.4%. Paclitaxel, sequential to doxorubicin and cyclophosphamide, demonstrated an prevalence of febrile neutropenia of grade 3< of 3%.**
- **The taxanes should only be prescribed and administered by clinicians with experience in oncology.**
- **The cost of a complete course of docetaxel, as per the product license, is £6,138. The cost of a complete course of paclitaxel, as per the product license, is £1,954.**
- **Trials are on-going investigating the use of the taxane compounds in an adjuvant setting in different combinations, at different dose intensities and in comparisons with other drugs. There are also on-going trials investigating the use of taxanes in the neo-adjuvant setting.**

## BACKGROUND

Breast cancer is the most common malignancy in females in the UK and is the most common cause of cancer mortality in women.<sup>1</sup> In England in 2003 there were 36,500 new cases of breast cancer in women, representing an incidence rate of 144 per 100,000 of the female population. In the same year 10,500 women died of breast cancer.<sup>1,2</sup> Approximately 80% of breast cancers are diagnosed at an early stage<sup>3</sup> (stages I to IIIa, see appendix 1). The five year survival rate for women diagnosed in the period 1998 – 2001 is 80%.<sup>1</sup> 80% of new cases are diagnosed in women aged 50 and over,<sup>1</sup> with the peak age range for diagnosis being 55 to 59 years.<sup>2</sup> The incidence in women younger than 30 is low, representing about 0.3% of all new cases<sup>2</sup> while the cumulative incidence in males is less than 1% of all new cases.<sup>4</sup>

An invasive breast cancer is one in which there is dissemination of cancer cells outside the basement membrane of the ducts and lobules into the surrounding adjacent normal tissue.<sup>5</sup> The presence or absence of axillary lymph node involvement is a strong predictor of survival from breast cancer, and should be considered when treatment decisions are made.<sup>6</sup> When invasive breast cancer is diagnosed the extent of the disease should be assessed and the tumour staged. The two staging classifications in current use are the tumour node metastases (TNM) system and the International Union Against Cancer (UICC) system which incorporates the TNM classification (see appendix 2).<sup>5</sup>

Data published in 2003, but relating to the period 1990 to 1992, indicated a prevalence of early stage node-positive breast cancer (T1-3,N+,M0) in two regional UK populations (n=559) of approximately 21% of all presenting breast cancers; the same study reported a pan-European (n=4,478) prevalence rate of 31%.<sup>7</sup> A separate UK study (n=1,440) reported that 49.8% of all presenting breast cancers were node-positive at the time of diagnosis.<sup>8</sup>

Where surgery is considered appropriate treatment for breast cancer several surgical options with various levels of breast tissue conservation are available. A radical mastectomy is one of the oldest breast surgical procedures but is now rarely performed. This procedure involves removal of the whole breast and associated chest muscles, and the lymph nodes draining the breast. Subsequently the technique has been improved and less radical forms of mastectomy have been developed, for example the simple mastectomy which involves removal of the breast tissue only. An even more conservative procedure is the lumpectomy in which only the tumour and some tissue around it are removed. A lumpectomy is often followed by a course of radiation to further reduce the risk of cancer recurrence. When chemotherapy is administered after surgery of any type, it is known as adjuvant chemotherapy.<sup>9</sup>

Ensuring that adjuvant therapy is always offered to women with primary breast cancer, when appropriate, may be expected to reduce recurrence and improve survival rates.<sup>10</sup> In 2002 the National Institute of Clinical Excellence recommended that almost all patients with invasive breast cancer should be offered adjuvant systemic therapy (hormone therapy and/or chemotherapy).<sup>10</sup> Women at intermediate or high risk of recurrence, who have not had neo-adjuvant chemotherapy, should normally be offered four to eight cycles of multiple-agent chemotherapy which includes an anthracycline.<sup>10</sup>

Despite many trials of adjuvant chemotherapy for breast cancer, the optimum regimen remains unclear and there are wide variations between UK oncologists in prescribing habits.<sup>10</sup>

Anthracycline-based regimens are increasingly being used for adjuvant therapy in the UK. Common regimens include 5-fluorouracil, epirubicin & cyclophosphamide (FEC) and doxorubicin & cyclophosphamide (AC).<sup>10</sup> Adjuvant chemotherapy that includes an anthracycline such as doxorubicin or epirubicin is more effective than the cyclophosphamide, methotrexate and 5-fluorouracil regimen (CMF).<sup>11</sup> Compared with CMF, anthracycline-containing regimens reduced the recurrence rate by 11% ( $p=0.001$ )<sup>12</sup> and increased five-year survival rates from 69% to 72% ( $p=0.02$ ).<sup>11</sup> A recent analysis also demonstrates that the absolute survival benefit is 3% at five years, and 4% at ten years.<sup>12</sup>

The number of patients receiving treatment has risen sharply over the last few years and many institutions have already moved away from the use of CMF for adjuvant therapy.<sup>5</sup> One particular anthracycline regimen is 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). This is better tolerated than CMF and fewer cycles are necessary to produce an equivalent level of benefit.<sup>5</sup>

## EFFICACY

### DOCETAXEL

Docetaxel (Taxotere<sup>®</sup>, sanofi-aventis) is licensed for the adjuvant treatment of node-positive breast cancer in combination with doxorubicin and cyclophosphamide.<sup>13</sup> The license was issued based on the results of the Breast Cancer International Research Group (BCIRG) 001 trial.<sup>14</sup>

BCIRG 001 was a phase III, randomised, open label, multi-centre trial that recruited 1491 patients between June 1997 and June 1999.<sup>14</sup> The trial compared a regimen of docetaxel, doxorubicin and cyclophosphamide (TAC) with a standard FAC regimen; 745 and 746 patients were recruited to each group respectively. Each regimen contained equal doses of doxorubicin and cyclophosphamide, equivalent dose intensity and an equal number of cycles of treatment. Specifically, the FAC regimen consisted of doses/m<sup>2</sup> body surface area (BSA) of doxorubicin 50mg, 5-fluorouracil 500mg, and cyclophosphamide 500mg. Docetaxel was administered at a dose of 75mg/m<sup>2</sup> BSA. There was a discrepancy in the additional therapies as the TAC group were administered pre-chemotherapy dexamethasone and post-chemotherapy antibiotics; otherwise the two groups were treated identically. Tamoxifen 20mg daily was prescribed to any patient with oestrogen and/or progesterone positive receptors and radiotherapy was administered as per local guidelines. The primary outcome was disease free survival, secondary endpoints were; overall survival, safety, and quality of life measured using the European organisation for research and treatment of cancer quality of life questionnaire, C30 version 2 and the breast cancer specific BR23 version 1. The results stated are from an interim analysis with a median follow-up of 55 months.

The TAC regimen produced disease free survival rates of 76.9% compared to 69.6% in the FAC group; this equates to estimated five year disease free survival of 75% and 68% respectively ( $p=0.001$ ). The majority of extra 'events' in the FAC group were distant (i.e. non-breast, non-node) metastasis.

The beneficial effects of TAC over FAC were only significant in the sub-group of patients with 1-3 affected nodes (hazard ratio (HR), 0.61; 95%CI, 0.46-0.82;  $p<0.001$ ); those with four or more affected nodes did not show a statistically significant benefit with the TAC regimen (HR, 0.83; 95%CI, 0.63-1.08;  $p=0.17$ ).

Of 221 deaths, 130 were in the FAC group and 91 in the TAC group (HR, 0.70; 95%CI 0.53-0.91;  $p=0.008$ ). The mean baseline quality of life scores for the two groups were both 72; after treatment the mean scores were 62 for TAC and 69 for FAC and at first follow up this had risen to 76 and 75 respectively; the mean scores remained very similar to these levels at all subsequent follow up points.

A U.S. Oncology Group study<sup>15</sup> compared doxorubicin 60mg/m<sup>2</sup> BSA and cyclophosphamide 600mg/m<sup>2</sup> BSA with docetaxel 75mg/m<sup>2</sup> BSA and cyclophosphamide 600mg/m<sup>2</sup> BSA. The patient group differed to the BCIRG study due to half of patients being node-negative at randomisation. After three years of follow-up, relapse rates were 9.6% and 6.7% respectively, although total cancer related mortality was marginally greater in the docetaxel group (2.9% v 3.4%). These results are available in abstract form only and significance parameters are not available.

The PACS 01 trial<sup>16</sup> also evaluated the use of docetaxel as adjuvant treatment. The study, which was conducted in France and Belgium, has not been finally reported and the results so far represent an interim analysis available in abstract form only. The study recruited 1999 post-surgery node-positive non-metastatic breast cancer patients who were randomised to receive either six cycles of FEC or three cycles of FEC followed by three cycles of docetaxel (FEC→T). The FEC→T group had an estimated five year survival rate of 78.3% compared to the FEC only group with a rate of 73.2% (hazard ratio, 0.83; 95%CI 0.69-0.99;  $p=0.041$ );<sup>17</sup> overall survival rates were 90.7% and 86.7% respectively ( $p=0.017$ ).<sup>18</sup>

## **PACLITAXEL**

Paclitaxel (Taxol<sup>®</sup>, Bristol-Myers Squibb Ltd) is licensed for the adjuvant treatment of node-positive breast cancer following anthracycline and cyclophosphamide therapy.<sup>19</sup> A generic paclitaxel is also available from Mayne Pharma plc. Two large phase III trials have investigated the use of paclitaxel in this setting;

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28<sup>20</sup> investigated whether four cycles of adjuvant AC followed by four cycles of paclitaxel (AC→P) would prolong disease free and overall survival compared to four cycles of AC alone. The trial recruited 3060 patients; 1529 in the AC group and 1531 in the AC→P group. Patients aged  $\geq 50$  years, and those with hormone receptor positive status, were prescribed tamoxifen 20mg daily for five years. Adjuvant radiotherapy was administered after the last course of chemotherapy to all patients who had undergone a lumpectomy. In line with standard practice, patients receiving paclitaxel were also pre-medicated with dexamethasone, an intravenous antihistamine and an intravenous histamine H<sub>2</sub> receptor antagonist.<sup>19, 20</sup> In the presence of grade 3 or 4 infection and/or neutropenia/febrile neutropenia, granulocyte colony stimulating factor (GCSF) was also administered; prophylactic antibiotics were permitted under certain conditions. After a median follow up of 64.6 months, disease free survival for the AC group was 70% compared to 74% in the AC→P group ( $p=0.006$ ). However this benefit has, so far, not translated to a significant increase in overall survival, with rates of 83% in the AC group and 84% in the AC→P group ( $p=0.46$ ).

A planned sub-group analysis was performed on hormone receptor status and this demonstrated a significant disease free survival benefit for hormone receptor positive patients only (relative risk, 0.77; 95%CI 0.65-0.92;  $p=0.004$ ).

This group accounted for the majority of patients in the trial and could almost entirely account for the overall gain in disease free survival seen with AC→P.

The large phase III Cancer and Leukaemia Group B (CALGB) trial,<sup>21</sup> involved paclitaxel in a similar patient group; the results stated are obtained from analysis with a median follow up of 69 months. This trial investigated a range of three doses of doxorubicin, with or without the sequential addition of paclitaxel, in node-positive early stage breast cancer patients. Patients were randomly allocated a dose of doxorubicin (60, 75 or 90 mg/m<sup>2</sup> BSA) plus cyclophosphamide (at a constant dose of 600 mg/m<sup>2</sup> BSA) for four cycles followed by either four cycles of paclitaxel (AC→P) or no further treatment (AC). 3170 patients were recruited; 1590 patients were allocated to AC→P and 1580 allocated to AC alone. All patients who had undergone a lumpectomy also had radiotherapy which was administered after chemotherapy was completed. GCSF and prophylactic antibiotic therapy was mandatory for patients on the highest dose of doxorubicin and was subsequently administered to any patient who developed febrile neutropenia. 94% of patients were hormone receptor positive; all of this group and 21% of hormone receptor negative patients (i.e. >95% trial population) received tamoxifen for five years. The primary end point was duration of disease free survival; secondary end points were overall survival and safety. The trial demonstrated no statistically significant difference between the doxorubicin doses. The results comparing paclitaxel therapy did suggest a beneficial effect. Overall survival rates were 74.7% in the AC group compared to 78.5% in the AC→P group (p=0.0098) and disease free survival rates were 64.4% and 69.1% respectively (p=0.0011).

Buzdar et al<sup>22</sup> compared eight cycles of FAC to four cycles of paclitaxel followed by four cycles of FAC (P→FAC). The trial recruited 524 early stage breast cancer patients; a third of patients in each group received their first four cycles of treatment in the neo-adjuvant setting. The results stated are based on a median follow up of 60 months, nonetheless the results favour the paclitaxel containing regimen with estimated four year disease free survival rates of 86% vs. 83%. This difference was not statistically significant (p=0.09) but there is a trend towards benefit with time.

## ADVERSE EFFECTS

### DOCETAXEL

In comparison to the FAC regimen, the TAC regimen is associated with a higher prevalence of anaemia (91.5% v 71.7%; p<0.001) and of grade 3 or 4 anaemia (4.3% v 1.6%; p=0.003). This is associated with an increased requirement for blood transfusion (4.6% v 1.5%; p<0.001). The TAC regimen was also associated (p<0.001) with a higher prevalence of thrombocytopenia (39.4% v 27.7%), febrile neutropenia (28.8% v 4.4%) and neutropenic infection (20.4% v 10.8%). The TAC regimen was associated with a lower overall prevalence of neutropenia (71.4% v 82%; p<0.001) but higher prevalence of severe neutropenia (grade 3 or 4, 65.5% v 49.3%; p<0.001).<sup>14</sup>

Similar prevalence of non-haematological adverse effects were observed with TAC and FAC respectively for alopecia (97.8% v 97.1%; p=0.39), infection (39.4% v 36.3%; p=0.22) and anorexia (21.6% v 17.7%; p=0.05).

The TAC group were associated with a higher prevalence of asthenia (80.8% v 71.2%;  $p < 0.001$ ), stomatitis (69.4% v 52.9%;  $p < 0.001$ ), amenorrhoea (61.7% v 52.4%;  $p = 0.007$ ), diarrhoea (35.2% v 27.9%;  $p = 0.002$ ), peripheral oedema (33.7% v 12.6%;  $p < 0.001$ ) and myalgia (26.7% v 9.9%;  $p < 0.001$ ). The FAC group reported more frequent prevalence of nausea (80.5% v 88.0%;  $p < 0.001$ ) and vomiting (44.5% v 59.2%;  $p < 0.001$ ).<sup>14</sup> The overall prevalence of severe (i.e. grade 3 or 4) non-haematological adverse effects was 36.3% with TAC and 26.6% in the FAC group ( $p < 0.001$ ).<sup>14</sup>

### **PACLITAXEL**

Adverse effects observed in the CALGB and NSABP trials were not comprehensively reported or compared to the alternative trial treatments. The authors of the CALGB trial did report that the paclitaxel phase of treatment had a significantly reduced prevalence for most, if not all, adverse effects compared to the AC only phase.<sup>21</sup> Febrile neutropenia occurred in 3% of paclitaxel patients at grade 3 or 4 in the NSABP trial.<sup>20</sup>

## **DOSAGE, ADMINISTRATION AND COST**

### **DOCETAXEL**

The docetaxel administration schedule indicated for adjuvant breast cancer is 75mg/m<sup>2</sup> BSA once every three weeks for six cycles.<sup>13</sup> In the BCIRG trial 91.3% of patients completed six cycles.<sup>14</sup> The cost of an 80mg vial of Taxotere<sup>®</sup> is £534.75, and the cost of a 20mg vial is £162.75.<sup>23</sup> Assuming a BSA of 1.75m<sup>2</sup> and thus a dose of 131mg, the cost per dose/cycle is £1023 and the cost for six cycles is **£6,138**. The requirement for pre-medication with dexamethasone will increase the cost of treatment by a relatively small amount, however of greater bearing on the overall cost of treatment is an expected increase in the use of granulocyte colony-stimulating factor, as stated in the SPC.<sup>13</sup>

Using the five-year overall survival rates from the BCIRG trial of 87% and 81% for TAC and FAC respectively; 17 patients would need to be treated with TAC as opposed to FAC to ensure one extra survivor at five years after commencing treatment. Therefore the crude cost per life year gained is £104,346.

### **PACLITAXEL**

The paclitaxel administration schedule indicated for adjuvant breast cancer is 175mg/m<sup>2</sup> BSA once every three weeks for four cycles.<sup>19</sup> In the CALGB trial 92% of patients commenced on paclitaxel completed four cycles.<sup>14</sup> The NHS Purchasing and Supplies Agency have negotiated a national contract price for generic paclitaxel vials.<sup>24</sup> Assuming a BSA of 1.75m<sup>2</sup>, a dose of 306mg is required. This is best achieved using a 300mg vial at a cost of £444.00 and a 30mg vial at a cost of £44.40. Therefore the cost per dose/cycle is £488.40 and the cost for four cycles is **£1,954**. Additional costs associated with paclitaxel treatment can be expected due to the requirement for pre-medication with dexamethasone, an intravenous antihistamine and an intravenous histamine H<sub>2</sub> receptor antagonist.<sup>19</sup>

Using the five-year overall survival rates from the CALGB trial (this was the only trial to show a significant difference in overall survival rates between the treatment groups) of 80% and 77% for AC\_P and AC respectively; 33 patients would need to be treated with four cycles of sequential paclitaxel following four cycles of AC to ensure one extra survivor at five years after commencing treatment. Therefore the crude cost per life year gained is £64,482.

## **TAXANES**

If the prevalence of early stage node-positive breast cancer in England is assumed to be 21% of all new cases,<sup>7</sup> and taking the annual breast cancer incidence rate in England of 73 per 100,000 population,<sup>2</sup> the incidence rate of newly diagnosed early stage breast cancer in females is 15 per 100,000 population. If it is assumed that all of those cases receive one of the appropriate taxane regimens the potential annual purchase costs for England are; £92,070 for docetaxel, and £29,310 for paclitaxel, per 100,000 population.

All prices stated exclude value added tax and do not take into consideration any purchase discount that may have been negotiated.

## **PLACE IN TREATMENT**

There is some evidence for using docetaxel in place of 5-fluorouracil in combination with doxorubicin and cyclophosphamide: in the patient group identified it offers some benefits in terms of five-year disease free survival and overall survival (7% and 6% in absolute terms respectively).<sup>14</sup> Questions have been raised concerning the doses in, and suitability of, the FAC regimen used in the BCIRG trial,<sup>25</sup> but on balance the control arm of the study is reasonable. The trial also excluded patients over 70 years of age,<sup>14</sup> and this could have implications on the applicability of the results to practice. In deciding on whether to use the TAC regimen consideration must be given to the extent of nodal involvement and an expected increase in adverse effects. It is interesting to note that the poor adverse effect profile of TAC compared to FAC was not strongly expressed in reported QoL scores.

The benefits of using paclitaxel are not as explicit. Between the two phase III trials, NSABP and CALGB, the absolute benefit in five-year disease free survival was 4% and 5% respectively, and the benefit in overall survival, which was only significantly observed in the latter trial, was 3%. It is worth noting that in both these studies paclitaxel was administered as additional therapy, i.e. there was no active control. Neither study addressed the issue of patient QoL or provided comprehensive reports on adverse effects. The intensity and frequency of adverse effects would appear to be less for paclitaxel alone compared to TAC.

Making comparisons of disease free survival rates across different trials is not straightforward because most trials use a unique definition.<sup>14, 20, 21</sup> Comparisons of overall survival in similar or identical populations are feasible even in the presence of relatively short periods of follow-up. On the basis of the evaluated studies the docetaxel, doxorubicin, and cyclophosphamide regimen appears to provide node-positive early stage breast cancer patients with greater benefit than an anthracycline and cyclophosphamide regimen followed by paclitaxel, although potentially to the detriment of a greater adverse effect profile and at greater cost.

## ARRANGEMENTS FOR PRESCRIBING

Because the drugs are cytotoxic and must be administered parenterally<sup>13, 19</sup> it is likely that they will remain entirely within secondary care.

## FUTURE DEVELOPMENTS

Trials are on-going investigating the use of the taxane compounds in an adjuvant setting in different combinations, at different dose intensities and in comparisons with other drugs, including some novel treatments, for example trastuzumab, bevacizumab, capecitabine, gemcitabine, and vaccine therapies. There are also on-going trials investigating the use of taxanes in the neo-adjuvant setting.<sup>26</sup>

The National Institute for Health and Clinical Excellence is currently considering the evidence for docetaxel and paclitaxel for early breast cancer in the single technology appraisal process. Decisions for both agents are expected in July 2006.<sup>27</sup>

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## APPENDICES

### APPENDIX 1. BREAST CANCER STAGE GROUPING <sup>28</sup>

Stage 0: Ductal carcinoma in situ is cancer that has not spread past the ducts or lobules of the breast (the natural boundaries). It is also called non-invasive cancer.

Stage I: The tumour is small and has not spread to the lymph nodes.

Stage IIa: Any one of these conditions:

- The tumour is smaller than 2 cm, and has spread to the axillary lymph nodes under the arm.
- The tumour is between 2 cm and 5 cm, but has not spread to the axillary lymph nodes.
- There is no evidence of a tumour in the breast, but there is cancer in the axillary lymph nodes.

Stage IIb: Any one of these conditions:

- The tumour is between 2 cm and 5 cm, and has spread to the axillary lymph nodes.
- The tumour is larger than 5 cm, but has not spread to the axillary lymph nodes.

Stage IIIa: Any of these conditions:

- The tumour is smaller than 5 cm, and has spread to the axillary lymph nodes.
- The tumour is larger than 5 cm, and has spread to the axillary lymph nodes.

Stage IIIb: The tumour has spread to the chest wall or caused swelling or ulceration of the breast or is diagnosed as inflammatory breast cancer. It may or may not have spread to the lymph nodes under the arm, but has not spread to other parts of the body.

Stage IIIc: Tumour of any size that has not spread to distant parts of the body, but has spread to the lymph nodes above the collarbone, under the collarbone, or both the nodes inside the breast and under the arm.

Stage IV: The tumour can be any size and has spread to distant sites in the body, usually the bones, lungs, liver, or chest wall.

**APPENDIX 2. ABRIDGED VERSION OF THE AMERICAN JOINT COMMITTEE ON CANCER COLLABORATIVE STAGING MANUAL – BREAST CANCER. <sup>29</sup>**

T0	No palpable tumour
T1	Tumour <2cm with no fixation to underlying muscle
T2	Tumour >2cm but <5cm with no fixation
T3	Tumour maximum diameter >5cm
T4	Tumour of any size with fixation to the chest wall or ulceration of the skin
N0	No palpable axillary lymph nodes
N1a	Palpable nodes not thought to contain tumour
N1b	Palpable nodes thought to contain tumour
N2	Nodes >2cm or fixed to one another and deep structures
N3	Supraclavicular or infraclavicular nodes
M0	No clinically apparent distant metastases
M1	Distant metastases are present

“a” indicates no attachment to the underlying muscles; “b” indicates there is attachment; T=tumour; N=node; M=metastases.

**Correlation of UICC and TNM classifications of tumours**

<b>UICC Stage</b>	<b>TNM Classification</b>
I	T1, N0, M0
II	T1, N1, M0; T2, N0-1, M0
III	any T, N2-3, M0; T3, any N, M0; T4, any N, M0
IV	any T, any N, M1

### APPENDIX 3. SUMMARY OF TRIALS

Key: MC – multi-centre; OL – open label; RT – randomised trial; ActC – active control; PIII – Phase 3; NC – no control; 95%CI – 95% confidence interval; CHF – congestive heart failure; LVEF – left ventricular ejection fraction; GCSF – granulocyte colony stimulating factor; TAC – docetaxel, doxorubicin and cyclophosphamide; FAC – 5-fluorouracil, doxorubicin and cyclophosphamide; DFS – disease free survival; OS – overall survival; FEC – 5-fluorouracil, epirubicin and cyclophosphamide; FEC→T – 5-fluorouracil, epirubicin and cyclophosphamide followed by docetaxel; AC – doxorubicin and cyclophosphamide; TC – docetaxel and cyclophosphamide; AC→P – doxorubicin and cyclophosphamide followed by paclitaxel; P→FAC – paclitaxel followed by 5-fluorouracil, doxorubicin and cyclophosphamide.

#### Summary of main clinical trials

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
BCIRG 001 Martin M et al <sup>14</sup>	RT, PIII, MC, OL, ActC	Six x three week cycles of TAC, or, six x three week cycles of FAC. All TAC patients received prophylactic ciprofloxacin and pre-chemotherapy dexamethasone. FAC patients only received antibiotic after neutropenic episode or infection. GCSF permitted if febrile neutropenia or infection observed. Tamoxifen 20mg daily for hormone receptor positive tumours.	1491 patients constitute the intention to treat population  745 in the TAC group and 746 in the FAC group.	Female, age 18-70, Karnofsky ≥ 80%, primary surgery for unilateral breast cancer with axillary node dissection, at least one axillary node positive for cancer.	Advanced breast cancer (i.e. T4, N2, N3, M1 tumours), history of other cancers, motor or sensory neuropathy grade ≥ 2, pregnancy, lactation, serious illness or condition other than breast cancer, prior therapy with anthracyclines or taxanes.	DFS defined as the time from randomisation to the date of clinical relapse, second cancer or death.	At median follow-up of 55 months, 172 events in the TAC group compared to 227 in the FAC group (P<0.001). Estimated five year DFS 75% with TAC and 68% with FAC (P=0.001). In sub-group with 1 to 3 affected nodes benefit of TAC hazard ratio 0.61; 95%CI 0.46-0.82; P<0.001. In sub-group with 4 ≥ nodes benefit of TAC hazard ratio 0.83; 95%CI 0.63-1.08; P=0.17.	In comparison to the FAC regimen, the TAC regimen had a greater prevalence of anaemia (91.5% v 71.7%; P<0.001), grade 3 or 4 anaemia (4.3% v 1.6%; P=0.003), and requirement for blood transfusion (4.6% v 1.5%; P<0.001). The TAC regimen also had statistically significant (P<0.001) greater Prevalence of thrombocytopenia (39.4% v 27.7%), febrile neutropenia (28.8% v 4.4%) and neutropenic infection (20.4% v 10.8%). The TAC regimen was associated with a lower overall prevalence of neutropenia (71.4% v 82%; P<0.001) but higher prevalence at grade 3 or 4 (65.5% v 49.3%; P<0.001).

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
PACS 01, Roché H et al <sup>16</sup>	RT, OL, MC, ActC, PIII	Six x three week cycles of FEC, or, FEC→T (three x three weekly cycles of each). GCSF and antibiotics were permitted only after proven requirement. Tamoxifen for hormone receptor positive tumours.	1999 patients constitute the intention to treat population 1006 in the FEC→T group and 996 in the FEC group.	Female, age 18-65 years, operable unilateral breast cancer (T1-3, M0), at least one involved axillary node.	Cardiac, hepatic, haematological or renal dysfunction, previous treatment for breast cancer.	Five year DFS rates.	Five year DFS in the FEC group was 73.2% compared to 78.3% in the FEC→T group; hazard ratio 0.83; 95%CI 0.69-0.99; P=0.041. In the sub-group of patients aged less than 50 years the hazard ratio was 0.98; 95%CI 0.77-1.25; P=0.69. In the sub-group of patients aged greater than 50 years the hazard ratio was 0.67; 95%CI 0.51-0.88; P=0.001. In the sub-group of patients with 1-3 positive nodes the hazard ratio was 0.76; 95%CI 0.58-1.00; P=0.042. In the sub-group of patients with at least 4 positive nodes the hazard ratio was 0.87; 95%CI 0.68-1.11; P=0.12.	Grade 3 or 4 toxicities for FEC→T and FEC respectively were neutropenia 7% & 9.5%, febrile neutropenia 2.5% & 1.6%, mucositis 1.2% & 0.9%, erythrocyte transfusion 0.2% & 2.3%, nail disorders 3% & 0.3%. The prevalence of febrile neutropenia in the 4 <sup>th</sup> cycle was significantly higher in the FEC→T group compared with FEC (P=0.001). CHF in FEC group 4%, 0% in FEC→T group. Decreased LVEF in FEC group 4%, 1% in FEC→T group.
Jones SE et al <sup>15</sup>	RT, PIII, ActC	Four x three week cycles of AC or, four x three week cycles of TC. Tamoxifen prescribed where indicated.	1016 patients; 510 in the AC group and 506 in the TC group.	Operable invasive breast cancer (stages I to III).	Neo-adjuvant treatment.	Efficacy (not defined)	Median follow-up of 36 months; Relapses in the AC group = 49; in the TC group = 34; Deaths from cancer in the AC group = 15; in the TC group = 17.	AC associated with significantly more nausea, vomiting and anaemia than TC. TC associated with significantly more leucopenia, and greater prevalence of oedema, paraesthesia, arthralgia.

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
NSABP B-28, Mamounas EP et al. <sup>20</sup>	RT, OL, MC, NC, Pill	All patients received four x 3 week cycles of AC followed by either no further chemotherapy or four x 3 week cycles of paclitaxel (AC→P).	3060 patients; 1529 in the AC group, 1531 in the AC→P group.	Resected operable adenocarcinoma of the breast and at least one axillary node (T1-3, N0-1, M0), prior surgery with axillary node dissection, normal haematological parameters, adequate hepatic and renal function, at least 10years life expectancy excluding cancer diagnosis.	Previous history of any invasive breast cancer or ductal carcinoma in-situ, prior radiation, chemotherapy, immunotherapy or hormonal therapy for present breast cancer.	Primary end-points were DFS OS. DFS was defined as presence of local, regional or distant metastasis, contralateral breast cancer, non-breast primary cancer or death.	Median follow-up of 64.6 months; 463 DFS events in the AC group and 400 in the AC→P group, adjusted hazard ratio 0.83; 95%CI 0.72-0.95; P=0.006. 255 deaths in the AC group and 243 in the AC→P group, adjusted hazard ratio for OS 0.93; 95%CI 0.78-1.12; P=0.46	Poorly reported. Most common grade 3 or 4 effects in the AC→P group were neurosensory toxicity 15%, neuromotor toxicity 7%, arthralgia and/or myalgia 12%, febrile neutropenia 3%, thromboembolic events 1%. Six out of eight cases of myelogenous leukaemia or myelodysplastic syndrome occurred in the AC→P group.
CALGB 9344, Henderson IC et al. <sup>21</sup>	RT, OL, MC, NC, Pill	Random allocation to four x 3 week cycles of one of three different doses of doxorubicin and a constant dose of cyclophosphamide followed by random allocation to either no treatment (AC) or 4 x 3 week cycles of paclitaxel (AC→P). Additional standard therapy prescribed with paclitaxel. GCSF and ciprofloxacin prescribed in certain circumstances, tamoxifen for most patients.	3170 patients randomized analysis based on 3121; 1551 in the AC group and 1570 in the AC→P group.	Operable breast cancer with axillary nodal metastasis.	None identified	Duration of DFS, defined as time from entry to study to first locoregional recurrence, distant metastasis or death.	Median follow-up of 69 months: No statistically significant differences in DFS or OS with different doses of doxorubicin. DFS in AC→P group was 68.7% and in the AC group 63.7% (adjusted P=0.0023). OS in AC group was 74.2% and in the AC→P group was 78.2% (adjusted P=0.0064).	Poorly reported. Adverse effects observed in the AC→P group were, nausea grade 2, 3 or 4; 3%, vomiting grade 2, 3 or 4; 1%, stomatitis grade 2, 3 or 4; 1%. Moderate paraesthesia 15%, sensory neurotoxicity interfering with normal function 3%.

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Buzdar et al 22	RT, MC, OL, PIII, ActC	P→FAC, or, FAC. Some patients received their first four cycles of therapy prior to surgery. Additional standard therapy prescribed with P. GCSF prescribed in certain circumstances. Tamoxifen permitted.	542; 259 in the FAC group and 265 in the P→FAC group.	Female, Invasive breast cancer (T1-3, N0-1, M0). Granulocyte $\geq$ 1500/mm <sup>3</sup> , platelets $\geq$ 100,000/mm <sup>3</sup> , bilirubin $\leq$ 1 mg/100ml, serum creatinine $\leq$ 2.5mg/100ml	History of uncompensated CHF, concomitant or prior history of other invasive cancer (with some exceptions).	None explicitly identified, assumed to be relapse free survival (comparable to DFS)	Median follow-up of 60 months; estimated four year DFS 86% in the P→FAC group and 83% in the FAC group (P=0.09).	Prevalence (%) in the P→FAC group compared to the FAC group respectively; Febrile neutropenia: 44 & 24, infection $\geq$ grade 3; 9 & 6, myalgia $\geq$ grade 3; 33 & 4, paraesthesias $\geq$ grade 3; 15 & 2, transient arrhythmias; 3 & 5, treatment related CHF; 0 & 1.