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Maximising outcomes in adjuvant breast cancer

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Node-positive breast cancer represents a major problem, with approximately 500,000 new cases diagnosed each year. Furthermore, this condition carries a grave prognosis. The results of a study by Brenner and Hakulinen, published in the *Journal of Oncology* in 2004 suggested that the great majority of young patients with node-positive disease who were diagnosed in the pre-adjuvant therapy era, would ultimately die from their cancer [1]. More encouraging news came from the 15-year follow-up of the Oxford overview, which was published in *The Lancet* on 14 May, 2005 [2] and suggests that we have underestimated the progress made thus far. Comparison of the outcomes in patients who received polychemotherapy compared with those who did not, revealed a 36% reduction in the risk of recurrence and a 29% reduction in the risk of death in patients who received polychemotherapy and who were under 50 years of age. In patients aged between 50 and 59 years, the use of polychemotherapy was associated with a 19% reduction in the risk of relapse and a 12% reduction in the risk of death. When the use of anthracyclines was factored into the analysis, it became apparent that compared with the standard CMF regimen (cyclophosphamide/methotrexate/5-FU), the inclusion of anthracyclines was associated with a further 15% relative reduction in the risk of mortality in pre-menopausal patients with node-positive disease [2]. This benefit was further improved upon by the addition of sequential paclitaxel to the doxorubicin/cyclophosphamide doublet, as demonstrated by the Cancer and Leukemia Group B (CALGB) 9344 study [3] in which, in an amendment to the original doxorubicin dose escalation design, patients were randomised to receive either four cycles of AC (doxorubicin; 60, 75, or 90 mg/m^2/cyclophosphamide; 600 mg/m^2) every 3 weeks, followed by either no further therapy or four cycles of 3-weekly paclitaxel at 175 mg/m^2. The addition of paclitaxel resulted in significant increases in both disease-free survival (DFS) and overall survival (OS) compared with AC, producing a 17% relative reduction in the risk of recurrence ($P = 0.0023$) and an 18% reduction in the risk of death ($P = 0.0064$). However, the adequacy of the control arm in this study was criticised, as patients in the AC arm received only four cycles of therapy, compared with eight cycles in the AC–paclitaxel arm [3]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B28 study also investigated the potential benefit of the addition of sequential paclitaxel to AC, and 3060 patients were randomised to receive either four cycles of AC (cyclophosphamide; 600 mg/m^2/doxorubicin; 60 mg/m^2) or four cycles of AC followed by four cycles of paclitaxel at the increased dose of 225 mg/m^2 [4]. While the addition of paclitaxel to AC produced a significant reduction in the risk of recurrence (17%; $P = 0.006$) that was similar to that demonstrated in the CALGB 9344 study, it did not produce a significant improvement in OS ($P = 0.46$). Although there was no evidence of significant interaction between treatment effect and hormonal status, the reduction in recurrence rate was greater in patients with hormone receptor-negative disease [4]. The European Cooperative Trial in Operable Breast Cancer (ECTO), the results of which were presented at the 2005 American Society of Clinical Oncology (ASCO) meeting by Gianni and colleagues, compared adjuvant therapy comprising A–CMF (doxorubicin followed by CMF) with AT–CMF (doxorubicin/paclitaxel followed by CMF). Compared with A–CMF, the inclusion of paclitaxel produced a significant

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improvement in DFS (hazard ratio [HR] = 0.66; $P = 0.01$), but not in OS [5].

Results from two further paclitaxel trials were presented at the 2005 San Antonio Breast Cancer Symposium (SABCS); the GEICAM 9906 [6] and Intergroup/CALGB C9741 [7] studies. The GEICAM 9906 study randomised 1248 patients with node-positive, operable breast cancer to receive either six cycles of $FE_{90}C$ (5-fluorouracil [5-FU]; 600 mg/m^2/epirubicin; 90 mg/m^2/cyclophosphamide; 600 mg/m^2, every 3 weeks) or four cycles of the same schedule followed by eight doses of weekly paclitaxel (100 mg/m^2). An interim analysis performed at a median of 47 months revealed a significant increase in 4-year DFS for the paclitaxel arm compared with $FE_{90}C$ alone (85.0% versus 79.0%; $P = 0.0008$), although given the small size of the study, this did not translate into a significant increase in OS, (94.0% and 92.4%, respectively: $P = 0.14$) [6]. The Intergroup/CALGB C9741 trial was designed as a two-by-two study to investigate the safety and efficacy of sequential versus concurrent AC therapy, followed by paclitaxel and the standard 3-weekly regimen versus a dose-dense regimen (every 2 weeks with granulocyte colony-stimulating factor [G-CSF]) [7]. The final analysis was performed after 6.5 years' follow-up, the results of which demonstrated that the best efficacy results with paclitaxel are achieved if it is delivered as a dose-dense regimen. However, the dose-dense AC–paclitaxel regimen was only superior to the standard 3-weekly paclitaxel regimen in patients with oestrogen receptor (ER)-negative disease [7].

The first adjuvant docetaxel trial, BCIRG 001, compared the standard FAC regimen (5-FU; 500 mg/m^2/doxorubicin; 50 mg/m^2/cyclophosphamide; 500 mg/m^2) with the TAC regimen (in which the 5-FU was replaced with docetaxel at a dose of 75 mg/m^2) in 1491 patients with axillary node-positive breast cancer. Intent-to-treat (ITT) analyses revealed that patients in the docetaxel (TAC; $n = 744$) arm had a cumulative probability of DFS of 75% compared with 68% for patients who received FAC ($n = 736$). This 7% absolute increase was statistically significant at the $P = 0.001$ level and corresponded to a 28% relative reduction in the risk of relapse. Similarly, patients who received TAC experienced a 6% absolute increase in probability of OS: 87% compared with 81% for patients in the FAC group. Again, this difference was statistically significant ($P = 0.008$) and corresponded to a 30% relative reduction in the risk of death [8]. This is the single largest absolute OS benefit recorded in a taxoid versus non-taxoid study. Furthermore, the TAC regimen was statistically superior to the FAC regimen irrespective of ER status, with the HRs and P-values for ER-negative and ER-positive disease being HR = 0.69; $P = 0.0297$ and HR = 0.72; $P = 0.0076$, respectively [8].

The PACS 01 study was designed to minimise anthracycline exposure, through substitution of the last three cycles of the standard $6FE_{100}C$ regimen (5-FU; 500 mg/m^2/epirubicin; 100 mg/m^2/cyclophosphamide; 500 mg/m^2) with three cycles of docetaxel [9]. Thus, 1999 patients were randomised to receive either six cycles of 3-weekly $FE_{100}C$ or three cycles of 3-weekly $FE_{100}C$ followed by three cycles of 3-weekly docetaxel at 100 mg/m^2 ($3FE_{100}C$–3T) [9]. The probability of DFS was significantly increased from 73.2% in the $6FE_{100}C$ group to 78.4% in the $3FE_{100}C$–3T group, which corresponded to a 17% relative reduction in the risk of relapse ($P = 0.012$). Compared with $6FE_{100}C$, the $3FE_{100}C$–3T regimen produced a significant increase in OS of 4% (from 86.7% to 90.7%; $P = 0.017$), which corresponded to a 23% relative reduction in the risk of death [9].

The Eastern Co-operative Oncology Group (ECOG) 2197 study investigated the potential of the AT regimen (doxorubicin; 60 mg/m^2/docetaxel; 60 mg/m^2) in 2952 patients with node-positive or high-risk node-negative breast cancer [10]. Patients were randomised to receive either four cycles of AC (doxorubicin; 60 mg/m^2/cyclophosphamide; 600 mg/m^2) or four cycles of AT. There was no difference in DFS between these two regimens, but this may have resulted from the suboptimal docetaxel dose of 60 mg/m^2. The US Oncology 9735 study has now investigated the efficacy and safety of the non-anthracycline-containing TC regimen (docetaxel/cyclophosphamide), in which the standard docetaxel dose of 75 mg/m^2 was employed. The final results were reported by Stephen Jones at the 2005 SABCS meeting [11]. Patients ($n = 1016$) with stage I, II or operable stage III invasive breast cancer were randomised to receive four cycles of either standard-dose AC (doxorubicin; 60 mg/m^2/cyclophosphamide; 600 mg/m^2; every 3 weeks; $n = 510$) or TC (docetaxel; 75 mg/m^2/cyclophosphamide; 600 mg/m^2; every 3 weeks; $n = 506$). The 5-year DFS rate was significantly increased with TC compared with AC (86% versus 80%; $P = 0.015$) with a 33% relative reduction in the risk of recurrence. The difference in OS between the treatment arms is not yet statistically significant, but there is a trend in favour of TC, and the current hazard ratio is 0.76 [11]. On the basis of these data, the TC regimen could be considered as a standard, non-anthracycline alternative to replace AC in patients with low-risk, early-stage breast cancer.

Cross-trial comparison reveals that whereas the paclitaxel studies – CALGB 9344, NSABP B28, ECTO and GEICAM 9906, all of which are completed – all demonstrated improved DFS for paclitaxel-containing regimens, only one paclitaxel study – the CALGB 9344 trial – demonstrated an OS advantage. In comparison, of the four trials that investigated docetaxel – BCIRG 001, PACS 01, US Oncology 9735 and FinHER – all of which demonstrated superior DFS rates for docetaxel, already two of these (BCIRG 001 and PACS 01) also demonstrate significant OS advantages for docetaxel-containing regimens. However, as this is an indirect comparison, no definitive conclusions can be made from this analysis. A direct comparison of docetaxel and paclitaxel was conducted in the ECOG E1199 trial. In this two-by-two study, 5052 patients with operable stage II

or IIIA, axillary node-positive or high-risk node-negative breast cancer, received four cycles of standard AC therapy (doxorubicin 60 mg/m^2/cyclophosphamide 600 mg/m^2; every 3 weeks) followed by sequential therapy comprising either four cycles of 3-weekly paclitaxel (175 mg/m^2; control arm), 12 cycles of weekly paclitaxel (80 mg/m^2), four cycles of 3-weekly docetaxel (100 mg/m^2), or 12 cycles of weekly docetaxel (35 mg/m^2). It should be noted that neither of the docetaxel arms represented a standard evidence-based approach to adjuvant docetaxel therapy. In particular, the weekly docetaxel regimen used in this trial (12 consecutive weeks without a break) was highly unusual and patients in this arm received only 77% of the planned therapy. The primary comparisons revealed that there were no significant differences between either of the taxoids (HR = 0.99; $P = 0.83$), or between the schedules (HR = 1.04; $P = 0.54$), with all hazard ratios essentially equalling 1 [12]. An exploratory analysis of the four arms revealed that there were approximately 15% fewer relapses in the 3-weekly docetaxel and the weekly paclitaxel arms, compared with the standard 3-weekly paclitaxel regimen. Comparison of the two paclitaxel regimens produced a HR of 1.2, the inverse of which is a HR of 0.83 in favour of the weekly paclitaxel regimen – a DFS advantage that was similar to those observed in the early CALGB 9344 [3] and NSABP B28 [4] paclitaxel trials. There was also a trend for improvement with 3-weekly docetaxel compared with 3-weekly paclitaxel, but 4-year DFS rates did not significantly differ between any regimen [12]. The major difference in toxicity was an increased incidence of febrile neutropenia in the docetaxel arms. However, most oncologists now administer prophylactic growth factor support when using docetaxel, particularly in the adjuvant setting, as described by Miguel Martín and colleagues in their GEICAM 9805 study [13].

In summary, the standard adjuvant docetaxel-containing regimens are 6TAC and 3FE$_{100}$C–3T. For paclitaxel, dose-dense AC–paclitaxel is the most commonly used regimen, but AC followed by weekly paclitaxel might be an acceptable substitute. However, the practicalities of delivering these regimens differ, and this becomes apparent when the required number of hospital visits associated with each agent is compared. For example, administration of dose-dense paclitaxel demands eight hospital visits and eight G-CSF injections. By comparison, 3-weekly docetaxel regimens, whether delivered in the form of TAC or 3FE$_{100}$C–3T, requires only six hospital visits. Concomitantly, only six G-CSF injections are required with the TAC regimen, compared with eight for dose-dense paclitaxel. We now need to establish the best taxoid and regimen and a number of ongoing trials are directly addressing these questions. For example, the relative efficacy and safety of combination and sequential therapy with docetaxel is currently being assessed in the BCIRG 005 trial. In this trial, 3150 patients with node-positive, HER2-negative disease were randomised to receive either sequential therapy comprising four cycles of 3-weekly AC (doxorubicin; 60mg/m^2/cyclophosphamide; 600mg/m^2) followed by four cycles of 3-weekly docetaxel (100 mg/m^2; AC–T arm), or six cycles of 3-weekly TAC. The first efficacy data from this study are expected in March 2006. A Breast Intergroup (BIG) adjuvant trial has randomised 2887 patients to receive either four cycles of doxorubicin followed by three cycles of CMF; three cycles of doxorubicin followed by three cycles of docetaxel and then by three cycles of CMF; four cycles of AT (doxorubicin/docetaxel) followed by three cycles of CMF; or four cycles of AC (doxorubicin/cyclophosphamide) followed by three cycles of CMF.

Perhaps the one trial that will answer the question of whether TAC is superior to dose-dense AC–paclitaxel is the NSABP B38 trial. In this study, patients with histologically proven node-positive breast cancer have been randomised to receive either six cycles of 3-weekly TAC, four cycles of 2-weekly AC followed by four cycles of 2-weekly paclitaxel, or four cycles of 2-weekly AC followed by four cycles of 2-weekly paclitaxel plus gemcitabine. In conclusion, the data available from the large number of completed and ongoing trials, coupled with progress in the identification of different molecular subtypes of breast cancer and the subsequent individualisation of therapy, prove that we are indeed winning the battle against breast cancer.

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