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EJC Supplements Vol. 4 No. 5 (2006) 13–17

EJC Supplements

www.ejconline.com

Docetaxel versus paclitaxel in the adjuvant setting: translating SABCS into clinical practice

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Keywords: Third-generation regimens; Taxoid; Adjuvant; Standard

There are now a large number of chemotherapy options for the treatment of early-stage breast cancer. As such, to aid in our decision making, an ordering of the different regimens is required. One way to achieve this is by considering first-, second-, and third-generation trials. The early first-generation studies were conducted over a quarter of a century ago and compared no therapy with a triple regimen (CMF) comprising cyclophosphamide, methotrexate and 5-fluorouracil (5-FU). In addition, low-dose anthracycline regimens, including the low-dose $FE_{50}C$ regimen (5-FU, epirubicin and cyclophosphamide) and the AC regimen (four cycles of doxorubicin/cyclophosphamide), played an integral role in these first-generation studies. The next step in the development of more effective regimens was the investigation of the efficacy of second-generation regimens and consequently, a number of trials were conducted to compare first and second-generation regimens directly. Such trials included a comparison of six cycles of 3-weekly CMF with six cycles of 3-weekly FAC (5-FU/doxorubicin/cyclophosphamide), which demonstrated superiority of the anthracycline-containing regimen [1], and also, the French adjuvant trial that compared six cycles of $FE_{50}C$ with six cycles of $FE_{100}C$, which demonstrated that the latter produced a superior disease-free survival (DFS) and overall survival (OS) [2]. In addition, two North American trials – the Cancer and Leukemia Group B (CALGB) 9344 and National Surgical Adjuvant Breast and Bowel Project (NSABP) B28 studies – compared four cycles of AC with the same therapy followed by four cycles of paclitaxel [3,4]. Further advance was sought in third-generation studies, the results of which yielded further improvements through the inclusion of docetaxel in standard regimens, and also through the use of innovative scheduling methods.

The results of a study that reported on the effectiveness of a new, non-anthracycline, second-generation regimen – the TC regimen (docetaxel; 75 mg/m^2/cyclophosphamide; 600 mg/m^2) – compared with the older AC regimen, were presented at the 2005 San Antonio Breast Cancer Symposium (SABCS). In this, the US Oncology 9735 study [5], patients were randomised to receive four, 3-weekly cycles of either standard-dose AC (doxorubicin; 60 mg/m^2/cyclophosphamide; 600 mg/m^2; $n = 510$) or TC ($n = 506$). 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 was not statistically significant, but there was a trend in favour of TC (hazard ratio [HR] = 0.76; 24% relative reduction in the risk of mortality). Subset analysis revealed that the TC regimen was equally efficacious in both oestrogen receptor (ER)-negative and in ER-positive tumours [5]. On the basis of these data, the TC regimen – which produced a longer DFS compared with standard AC – could be considered a good choice as a non-anthracycline-containing therapy for the treatment of patients with low-risk disease. Like the AC regimen, it can be given over 12 weeks and its toxicity was modest, with a 6% risk of neutropenic fever compared with 3% for AC.

We now have the results of five trials that have investigated either the inclusion of a taxoid or different schedules for the administration of paclitaxel. The Breast Cancer International Research Group (BCIRG) 001 (TAX 316) trial was published in the *New England Journal of Medicine* in

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June 2005 [6]; the final analysis of the PACS 01 trial was reported at the 2004 SABCS meeting [7], and results of two paclitaxel studies – the Spanish GEICAM 9906 study [8], the Intergroup/CALGB 9741 study [9] and also, the Eastern Co-operative Oncology Group (ECOG) E1199 study [10], which compared the two taxoids directly – were reported at the 2005 SABCS meeting.

The BCIRG 001 (TAX 316) trial studied the effects of substituting 5-FU in the FAC regimen with docetaxel, producing the TAC regimen [6]. In this study, 1491 women with axillary node-positive breast cancer were randomised to receive six cycles of 3-weekly treatment with either FAC or TAC as adjuvant chemotherapy after surgery. The primary endpoint was DFS and secondary endpoints were OS, toxicity and quality of life. Patients in both arms of this study received the same concentrations of doxorubicin (50 mg/m^2) and cyclophosphamide (500 mg/m^2), with patients in the TAC arm receiving 75 mg/m^2 docetaxel in place of 5-FU. Intent-to-treat (ITT) analyses revealed that patients in the docetaxel (TAC) arm had a cumulative probability of DFS of 75%, compared with 68% for patients who received FAC. This 7% absolute increase was statistically significant at the 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 survival, which was 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 (Fig. 1) [6]. The DFS benefit associated with the TAC regimen was statistically superior to that achieved with FAC, in patients with both ER-positive and in ER-negative tumours.

Having established the $FE_{100}C$ regimen as an effective second-generation regimen for the treatment of early-stage, node-positive breast cancer, the French Group conducted the PACS 01 trial, in which 1999 women with hormone receptor-positive tumours were randomised to receive either six cycles of 3-weekly $FE_{100}C$ or a regimen in which the last three cycles of $FE_{100}C$ were substituted with three cycles of 3-weekly, sequential docetaxel at 100 mg/m^2 ($3FE_{100}C$–3T) [7]. In this study, patients with hormone receptor-positive disease were prescribed daily tamoxifen treatment for 5 years following completion of chemotherapy. Patients in the docetaxel arm experienced a statistically significant increase in both DFS and OS compared with those who received six cycles of $FE_{100}C$. The probability of DFS was increased from 73.2% in the $6FE_{100}C$ group to 78.3% 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%; Fig. 2), which corresponded to a 23% relative reduction in the risk of death ($P = 0.017$). Again, there was no interaction according to HR status.

The third generation paclitaxel studies were presented at the recent 2005 SABCS meeting. In the first of these – the GEICAM 9906 study – 1248 patients with node-positive, operable breast cancer were randomised to receive either six cycles of $FE_{90}C$ (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 cycles of weekly paclitaxel (100 mg/m^2) [8]. This interim analysis was performed at a median of 47 months, and revealed a significant increase in 4-year DFS for the paclitaxel arm compared with $FE_{60}C$ alone (85.0% versus 79.0%; $P = 0.0008$), which corresponded to a 37% relative reduction in the risk of relapse. However, this did not translate into a significant improvement in OS (94.0% and 92.4%, respectively; $P = 0.14$). There was no interaction with the number of positive nodes, menopausal status, or ER status. Subset analysis revealed that the $4FE_{90}C$–8P regimen demonstrated improved efficacy compared with $6FE_{90}C$ in both ER-positive and ER-negative populations. Although the difference in this benefit did not differ significantly between these two groups, the magnitude of benefit was markedly greater in patients with ER-negative disease [8]. Compared with the $6FE_{90}C$ regimen, the $4FE_{90}C$–8P regimen was better tolerated and demonstrated a trend for a reduced incidence of febrile neutropenia (9% versus 5%, respectively).

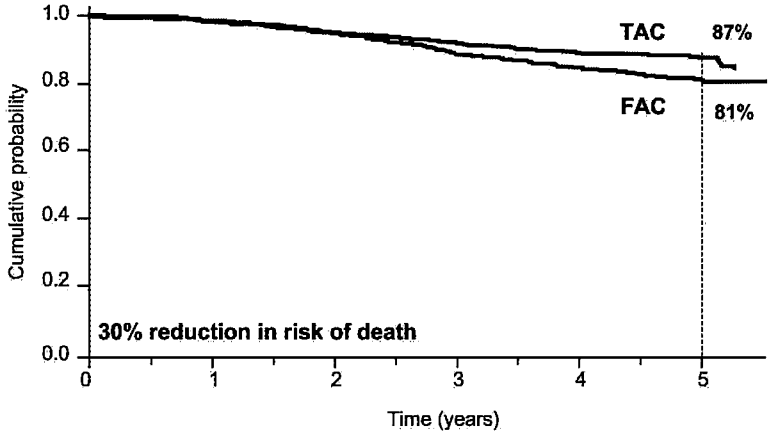

Fig. 1. BCIRG 001: overall survival (ITT).

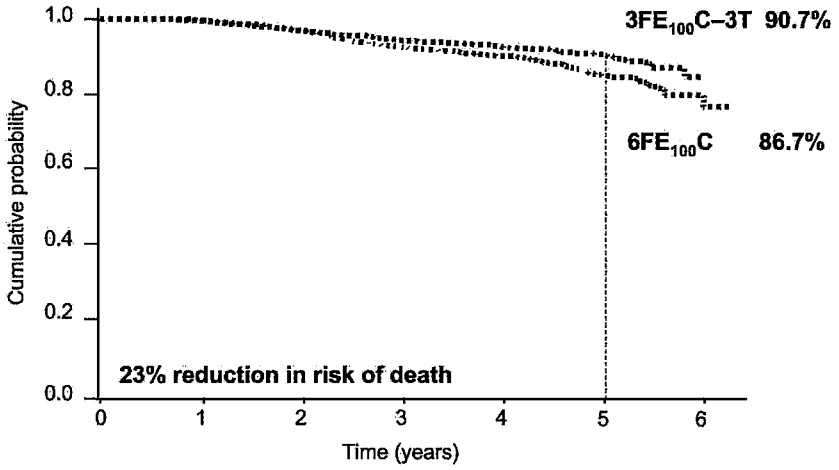

Fig. 2. PACS 01: overall survival (ITT).

The second paclitaxel study – the Intergroup/CALGB C9741 study – was a two-by-two factorial study designed to compare the safety and efficacy of sequential versus concurrent AC therapy both administered with sequential paclitaxel, and also to compare 3-weekly versus dose-dense (administered every 2 weeks with granulocyte colony-stimulating factor [G-CSF]) schedules [9]. The final analysis was performed after 6.5 years' follow-up and revealed that there was no significant difference in concurrent or sequential administration of AC, either in DFS or OS outcomes. Compared with 3-weekly paclitaxel, dose-dense paclitaxel was associated with a significant improvement in DFS; a 20% relative reduction in the risk of relapse (HR = 0.80; 95% CI 0.67–0.95; $P = 0.012$). This study continues to suggest an improvement in OS for dose-dense therapy compared with the standard 3-weekly therapy, but this advantage is less than that observed at the time of the original report [11]; now standing at a 15% relative reduction in the risk of mortality that just reached significance (HR = 0.85; $P = 0.049$) [9]. Whereas the difference in DFS (HR = 0.76; $P = 0.014$) and OS (HR = 0.79; $P = 0.039$) between the dose-dense schedule and the 3-weekly regimen was statistically significant in ER-negative patients, there was no statistically significant difference in either outcome in patients with ER-positive disease. There were no additional safety concerns with dose-dense therapy, although it is pertinent to note that in this study, the incidence of febrile neutropenia was defined as febrile neutropenia with hospitalisation, rather than solely incidence of febrile neutropenia, and in addition toxicity information was collected in only 20% of patients [9].

The last of the third-generation studies – the ECOG E1199 study – was designed as a two-by-two study to compare docetaxel and paclitaxel directly, when delivered either in 3-weekly or weekly schedules [10]. In this large, four-arm study, conducted in 5052 patients with operable stage II or IIIA, axillary node-positive or high-risk node-negative breast cancer, all patients received four cycles of standard AC (doxorubicin; 60 mg/m^2/cyclophosphamide; 600 mg/m^2) every 3 weeks followed by sequential therapy of 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). There were no balances in patient or tumour characteristics between the arms and the primary endpoint of the study was DFS at 5 years. The analysis presented at the 2005 SABCS meeting was based on data available from 4988 patients at a median follow-up of 46.5 months and a total of 856 DFS events and 483 deaths. The results of the predefined two-by-two comparison revealed that there were no significant differences between the taxoids (HR = 0.985; $P = 0.83$), or between the schedules (HR = 1.04; $P = 0.54$), with all hazard ratios essentially equalling one [10]. An exploratory, one-by-four analysis assessed whether any of the regimens was superior to the standard 3-weekly paclitaxel regimen. There were no differences in DFS or OS between paclitaxel and docetaxel, or between weekly and 3-weekly schedules. However, there were approximately 15% fewer relapses in patients who received weekly paclitaxel or 3-weekly docetaxel, compared with the standard 3-weekly paclitaxel regimen. Comparison of weekly and 3-weekly paclitaxel regimens suggested that the benefit of weekly paclitaxel was greater in the ER-negative population compared with the ER-positive population, although this analysis is exploratory, and at present there is no significant difference between the effects in the two populations [10]. There was a lower incidence of febrile neutropenia with weekly paclitaxel compared with 3-weekly docetaxel (1% versus 16%, respectively). The event rates were lower than expected in this study, and although the study was powered for analysis at 1400 events the data were released at 856 events. Further analyses are planned after 1042 and after 1400 events, and will provide a more definitive evaluation.

To summarise, we now have a number of third-generation regimens from which we can choose to treat patients with early-stage breast cancer. Both taxoids play a central role in these regimens, but because of the differences

Table 1
Relative risk reduction outcomes of third-generation studies

Trial	Control	Exp. arm	N; follow up	Relapse (%)	Mortality (%)
BCIRG 001	6FAC	6TAC	1491; 4.6 years	28*	30*
PACS 01	$6FE_{100}C$	$3FE_{100}C$–3T	1999; 5 years	17*	23*
GEICAM 9906	$6FE_{90}C$	$4FE_{90}C$–8P q1w	1248; 3.9 years	36*	26‡
CALGB C9741	4AC–4P all q3w	4AC–4P all q2w	2005; 6.5 years	20*	15*
ECOG E1199	4AC–4P all q3w	4AC q3w 12P q1w	4988; 3.9 years	17†	–

*$P < 0.05$; †$P > 0.05$ and ≤ 0.10; ‡$P > 0.10$.

in the comparators used in these studies, no definitive statement can be made about which taxoid is the better agent. When defining the role of the different available regimens, the magnitude of benefit is an important consideration (Table 1). The results of the BCIRG 001 and PACS 01 trials demonstrate statistically significant improvements in DFS and OS for docetaxel-containing regimens [6,7]. Efficacy advantages have also been observed for paclitaxel regimens, as demonstrated by a DFS advantage in the GEICAM 9906 study [8] and DFS and OS advantages in the CALGB C9741 study [9]. The early results of the ECOG E1199 study did not reveal any difference between either the taxoid or schedule [10].

An intriguing rationale that may possibly explain why some patients obtain little benefit from a particular taxoid is the different outcome that docetaxel and paclitaxel have in patients with different ER status. In the docetaxel trials – the BCIRG 001 and PACS 01 studies – there were consistent, approximately equal benefits in both ER-negative and ER-positive patient populations. For the paclitaxel studies, although subgroup analysis in the GEICAM 9906 study revealed a benefit for paclitaxel in both ER-negative and ER-positive patients, the magnitude of benefit was markedly greater in patients with ER-negative disease [8]. Conversely, the results of the CALGB C9741 study revealed that dose-dense paclitaxel has no significant benefit in patients with ER-positive disease [9]. Another important comparative factor is toxicity. Although the incidence of febrile neutropenia is higher in docetaxel studies compared with paclitaxel studies, certain facts have to be borne in mind. Although in the BCIRG 001 study the incidence of febrile neutropenia was 24.7%, no G-CSF primary prophylaxis was permitted in this study, a practice that has been demonstrated in other studies [12] to significantly ameliorate the incidence of this toxicity from 24.6% to 6.5%. In addition, whereas the incidence of febrile neutropenia with dose-dense paclitaxel in the CALGB C9741 study appears low, two important points should be noted. The first is that patients who received dose-dense therapy also received primary prophylactic G-CSF therapy, and the second is that the definition of febrile neutropenia used in this study was that of febrile neutropenia resulting in hospitalisation, and as such the percentage incidence is lower than would otherwise be reported. As such, the assumption that there is no better taxoid is oversimplistic and a number of factors need to be considered when making the choice as to which third-generation regimen to use in the treatment of patients with early-stage breast cancer.

To conclude, the comparative efficacy of the third-generation regimens is unclear at present, because as yet, trials that directly compare the optimal regimens for each taxoid have not been conducted or reported. One such trial that is soon to be reported is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B38 study, in which patients with node-positive breast cancer were 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.

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