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Overview of docetaxel at the 2005 San Antonio Breast Cancer Symposium

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Among the novel chemotherapeutic drugs introduced in the 1990s, the taxoids have emerged as the most powerful compounds in the treatment of breast cancer and are now considered the state-of-the-art treatment for this disease. The two taxoids – docetaxel (Taxotere®) and paclitaxel (Taxol®) – were introduced as components of chemotherapy for breast cancer over a decade ago, and the development of both these agents has occurred largely in parallel; thus, I will discuss the 'tale of two taxoids'. The conclusions of this tale are yet to be written, and there is no short cut – any final determination about these therapies will be data driven.

Any sense of complacency with regard to either of these agents was tested in 2002 with the disclosure of results from two pivotal studies. The first of these was the Cancer and Leukemia Group B (CALGB) 9741 trial that was designed to investigate the potential improvement in the efficacy through a 2-weekly scheduling of paclitaxel. This 2-weekly schedule was thought to have unique pharmacokinetic properties and was referred to as 'dose-dense' therapy. Thus, 2005 patients with node-positive disease were randomised to receive either sequential or concurrent doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), followed by paclitaxel (175 mg/m^2 over 3 hours), either as the conventional 3-weekly regimen or as a 2-weekly regimen administered with granulocyte colony-stimulating factor (G-CSF) [1]. The median time on study was 36 months. Interim results of this study were presented by Marc Citron at the San Antonio Breast Cancer Symposium (SABCS) in 2002 and later published in the *Journal of Clinical Oncology* [2] and the trial was heralded as a potential breakthrough in the treatment of breast cancer. When the data from 36 months' follow-up were presented, showing significant absolute increases in disease-free survival (DFS) and overall survival (OS) of 4% and 2%, respectively, the hope was that, over time, these survival curves would continue to separate in favour of dose-dense therapy. In December 2005, at the annual SABCS meeting, Cliff Hudis presented the final analysis at 6.5 years' follow-up. Disease-free survival was increased by 5% ($P = 0.012$) in patients who received dose-dense therapy compared with those who received the conventional 3-weekly regimen, and OS was increased by approximately 3%, with a P-value of 0.049 (Fig. 1) [1].

While there is no advantage in debating the magnitude of significance of the OS benefit, one cannot help but wonder if these data do actually support the kinetic hypothesis for dose-dense therapy and indeed, the most recent results of the CALGB 9741 study were somewhat disappointing, regardless of the observed benefit of 2-weekly compared with 3-weekly sequential paclitaxel therapy.

Six months earlier, at the 2005 American Society of Clinical Oncology (ASCO) meeting, the results of the Breast Cancer International Research Group (BCIRG) 001 (TAX 316) trial were presented. This trial investigated the efficacy and safety of the TAC regimen (docetaxel; 75 mg/m^2/doxorubicin; 50 mg/m^2/cyclophosphamide; 500 mg/m^2) in comparison with the FAC regimen (5-FU; 500 mg/m^2/doxorubicin; 50 mg/m^2/cyclophosphamide; 500 mg/m^2) [3]. Between June 1997 and June 1999, 1491 patients were randomised and the first results were presented by Jean-Marc Nabholtz at the 2002 ASCO

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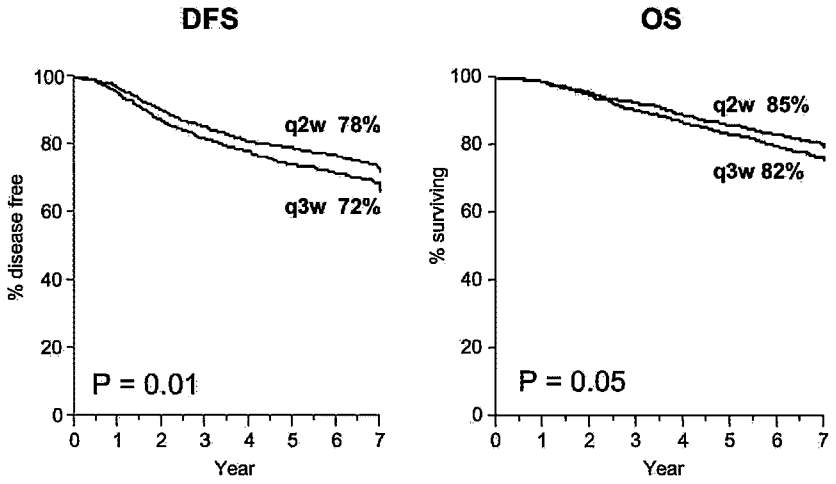

Fig. 1. CALGB C9741: efficacy results.

meeting, after a median of 33 months' follow-up [4]. These results were every bit as impressive as those that were to be presented for dose-dense paclitaxel 6 months later. Disease-free survival was significantly increased in patients who received the TAC regimen compared with the FAC regimen (82% versus 74%; hazard ratio [HR] = 0.68; $P = 0.001$), and OS was also increased with TAC compared with FAC (92% versus 87%; HR = 0.76), although this difference did not reach significance at the time. The final results of the BCIRG 001 study were published in the *New England Journal of Medicine* in June 2005 by Miguel Martín and colleagues [3]. After a median of 55 months' follow-up, compared with the FAC regimen, the TAC regimen produced an absolute increase in DFS of 7% (75% versus 68%), which was significant at the $P = 0.001$ level and corresponded to a 30% increase in the relative risk of relapse. Even more impressively, the TAC regimen was associated with an absolute increase in OS of 6% (87% versus 81% with FAC), which was also highly significant ($P = 0.008$) [3] and represented a 28% relative reduction in the risk of death (Fig. 2). This improvement in OS is among the most robust seen to date, and as such the TAC regimen deserves to be recognised as a standard therapy for the treatment of patients with node-positive, early-stage breast cancer.

The story surrounding the two taxoids – docetaxel and paclitaxel – further evolved with the disclosure of data from the Eastern Co-operative Oncology Group (ECOG) 1199 study, in which they were compared directly. Between October 1999 and January 2002, 5052 patients with node-positive or high-risk node-negative breast cancer were randomised to receive AC followed by a one of four taxoid regimens [5]. All patients received four, 3-weekly cycles of AC (doxorubicin; 60 mg/m^2/cyclophosphamide; 600 mg/m^2) followed by 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). The primary endpoint of the trial was DFS, and the study was powered to compare docetaxel versus paclitaxel and 3-weekly versus weekly schedules. However, it was not powered for a pairwise comparison between the four arms.

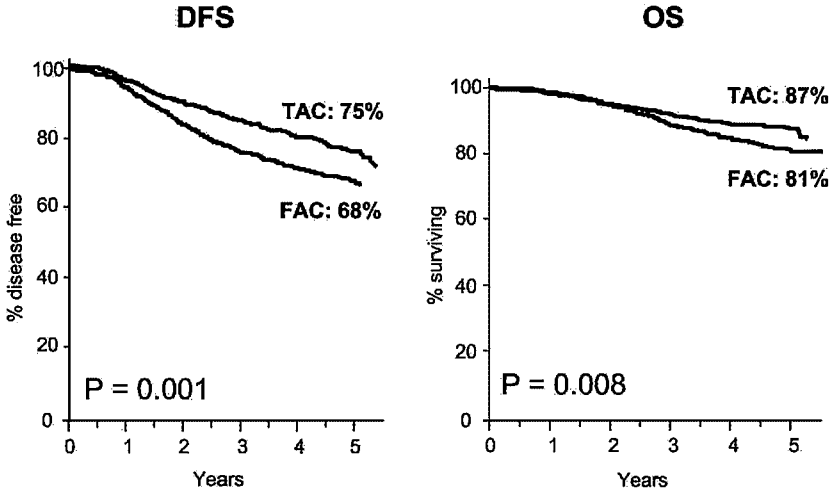

Fig. 2. BCIRG 001: efficacy results.

The first results were presented at the 2005 SABCS meeting after a median follow-up of 46 months and when considered with respect to the original statistical plan, merely suggest that paclitaxel is best delivered as a weekly regimen, and docetaxel as a 3-weekly regimen. Thus, it appears that dose-dense therapy is suitable as an alternative to a 3-weekly delivery schedule, for paclitaxel only.

The results of these trials raise the question of which taxoid and which regimen will produce the best outcome for patients. Three ongoing trials may answer this question; namely the BCIRG 005 trial, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B30 trial and the NSABP B38 trial. It is possibly the NSABP B38 trial that will provide the most definitive analysis. This trial will compare the TAC regimen (docetaxel; 75 mg/m^2/doxorucibin 50 mg/m^2/cyclophosphamide; 500 mg/m^2) as the standard arm, with a dose-dense regimen of AC (doxorubicin 60 mg/m^2/cyclophosphamide; 600 mg/m^2) followed by paclitaxel (175 mg/m^2) and with a dose-dense regimen of AC followed by paclitaxel plus gemcitabine (2000 mg/m^2). The addition of gemcitabine to paclitaxel in a dose-dense regimen does raise the question of exactly how much dose-dense therapy it will take to produce a significant efficacy difference compared with the TAC regimen. Accrual to the NSABP B38 trial has been outstanding, with more than 2200 patients entered since October 2004.

This tale becomes more complex when we consider the benefit of trastuzumab therapy in the adjuvant setting and also, the best chemotherapy template from which to provide the standard of care for patients with human epidermal growth factor 2 (HER2)-positive, early-stage breast cancer. More than 14,000 patients with early-stage, HER2-positive breast cancer have been randomised into four trials – the NSAPB B31, North Central Cancer Treatment Group (NCCTG) 9831, BCIRG 006, and HERceptin® Adjuvant (HERA) trials – that were designed to investigate the effectiveness of trastuzumab regimens in the adjuvant setting. The NSAPB B31 trial randomised approximately 2100 node-positive patients to receive therapy with either AC followed by paclitaxel, or AC followed by paclitaxel and 1 year of trastuzumab. In the NCCTG 9831 study, patients were randomised to one of three arms; concurrent AC followed by weekly paclitaxel, the same regimen followed by 1 year of trastuzumab after paclitaxel, or the same regimen plus 1 year of trastuzumab initiated concomitantly with paclitaxel. A recent joint analysis of the NSABP B31 and NCCTG 9831 studies demonstrated that the addition of trastuzumab to chemotherapy resulted in a highly significant DFS benefit, with an absolute increase in DFS of 18% at 4 years, which corresponded to a relative reduction in the risk of recurrence of 52%, with a two-tailed P-value of 3×10^{-12} [6]. Subsequent to the results of the joint analysis of these two studies, the data monitoring committee requested an unplanned interim analysis of the NCCTG 9831 study to compare the sequential and concurrent arms. These results revealed a 13% relative reduction in the risk of relapse for the sequential arm versus the control arm and a 36% relative reduction for the concurrent arm versus the sequential arm [7]. The HERA study compared 1 or 2 years' treatment with adjuvant trastuzumab given every 3 weeks with no therapy, in patients with HER2-positive and node-negative or node-positive breast cancer. The first interim analysis reported that compared with no treatment, treatment with trastuzumab for 1 year resulted in a 46% relative reduction in the risk of relapse [8]. The results of the 2-year treatment are yet to be reported.

The BCIRG 006 study used a docetaxel template and compared a standard arm of AC followed by docetaxel (AC–T), with AC followed by docetaxel plus 1 year's treatment with trastuzumab (AC–TH). This trial had a third, novel treatment arm, in which the anthracycline was eliminated and replaced with carboplatin, producing a triple therapy consisting of docetaxel, carboplatin and trastuzumab – the TCH regimen. Pairwise comparison of the AC–T and the AC–TH arms demonstrated a 51% relative reduction in the risk of relapse for the AC–TH regimen [9], a magnitude of benefit that was similar to that observed in the NSABP B31 trial, suggesting that the benefit of trastuzumab does not depend on the type of taxoid used. However, there is a suggestion of a decreased risk of cardiac toxicity for the combination of trastuzumab and docetaxel compared with the combination of trastuzumab and paclitaxel; while the incidence of symptomatic cardiac events observed with the paclitaxel-containing regimen was 4% [6], the corresponding figure for the docetaxel regimen was approximately halved, at 2.34% [9]. This, although not a direct comparison, is an important consideration, as reduction of the occurrence of such toxicities is especially important in the adjuvant setting. Indeed, this was the particular aim of substituting the conventionally used anthracycline with carboplatin in the TCH regimen, and the associated incidence of symptomatic cardiac toxicity for this regimen was 1.33%, which furthermore, did not differ significantly from the control arm [9]. This regimen was not as efficacious as anticipated, and although it produced a DFS benefit that was significantly greater than that achieved with the AC–T regimen (39% relative reduction in the risk of relapse), this fell short of that obtained in the AC–TH arm. Considering this, perhaps carboplatin was not the optimal choice of chemotherapeutic agent to use in the place of anthracyclines? Here, the results of the US Oncology 9735 trial that were presented by Stephen Jones at the 2005 SABCS meeting are of interest, in particular in relation to the outcome of the CALGB 9344 study, which demonstrated that there was no advantage to be gained by dose escalation of doxorubicin from 75 to 90 mg/m^2. In the US Oncology 9735 trial, patients were randomised to receive either four cycles of 3-weekly AC (doxorubicin; 60 mg/m^2/cyclophosphamide; 600 mg/m^2) or four cycles of 3-weekly TC (docetaxel; 75 mg/m^2/

cyclophosphamide; 600 mg/m^2) [10]. At a median time on study of 66 months, the 5-year DFS rate was significantly increased with TC compared with AC (86% versus 80%; $P = 0.015$), which resulted in a 33% relative reduction in the risk of recurrence. The difference in OS between the treatment arms was not statistically significant, but there is a trend in favour of TC, and the current HR is 0.76. Had this information been known at the time of the BCIRG 006 study design, maybe this trial would have been configured in a different manner, with the 'C' in the TCH arm possibly being cyclophosphamide, and not carboplatin. Now that we are aware of the results of the US Oncology 9735 study, we need to consider how to factor in the docetaxel/cyclophosphamide regimen into future studies with trastuzumab.

The studies reviewed here will be addressed in more detail in the remainder of this supplement. Professor Wolfgang Eiermann discusses docetaxel/trastuzumab combinations in the adjuvant setting, Dr Cliff Hudis discusses our lessons from the CALGB studies, Dr Peter Ravdin compares docetaxel and paclitaxel in the adjuvant setting and Gill Donovan discusses the management of chemotherapy-related toxicities. Finally, Dr John Crown provides an overview, with an emphasis on maximising outcomes in adjuvant breast cancer.

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