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Docetaxel and trastuzumab in the adjuvant setting: translating SABCS into clinical practice

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The recent 2005 San Antonio Breast Cancer Symposium (SABCS) was the forum for the presentation of data from two studies that investigated the efficacy and safety of combination therapy comprising trastuzumab and docetaxel in patients with early-stage breast cancer that overexpresses the human epidermal growth factor 2 (HER2) receptor. These studies are the Breast Cancer International Research Group (BCIRG) 006 trial and the FinHER trial, both of which hold particular interest from a scientific point of view.

Overexpression of the HER2 receptor occurs in 20–30% of breast cancers and represents an aggressive form of the disease that does not respond well to chemotherapy. As such, HER2 overexpression is associated with a poor prognosis, with the median survival from first diagnosis being only 3 years, compared with a figure of 6–7 years for patients with normal levels of HER2 oncoprotein expression [1]. Trastuzumab has been identified as the treatment of choice for patients with HER2-positive disease and, in an attempt to maximise the potential of this agent in breast cancer, preclinical investigations were conducted to assess its performance with cytotoxic agents. The results of these studies revealed that whereas the combination of trastuzumab and paclitaxel was additive, the combination of trastuzumab with docetaxel or carboplatin was found to be synergistic [2]. Thus, the combination of trastuzumab and docetaxel was deemed to be a viable combination for consideration in the clinical setting. Indeed, in the metastatic setting, combination therapy comprising trastuzumab and docetaxel has produced an impressive increase in overall survival (OS) of 8.5 months compared with single-agent docetaxel, resulting in a median OS of 31.2 months for patients with metastatic disease [3]. The promising results of this, and other studies [4], coupled with the aggressive nature of HER2-positive disease, led to the initiation of a number of studies investigating the use of trastuzumab in the adjuvant setting. One of these studies – the BCIRG 006 trial – was designed to investigate the efficacy and safety of combination therapy comprising trastuzumab and docetaxel. The rationale for this study was based on a number of considerations, including the approval of trastuzumab (either as monotherapy or in combination with a taxoid) for the treatment of HER2-positive, metastatic breast cancer and evidence that docetaxel is one of the most active chemotherapeutic agents for the treatment of metastatic breast cancer [5–11] In addition to the reported synergism between trastuzumab and docetaxel [2], the observation of a similar interaction between trastuzumab and carboplatin formed the basis for the inclusion of a non-anthracycline, docetaxel/trastuzumab triplet in the BCIRG 006 study. Thus, in this three-arm study, patients ($n = 3222$) with node-positive or high-risk, node-negative, HER2-positive disease, were randomised to receive therapy with either AC–T; a control regimen comprised of four, 3-weekly cycles of AC (doxorubicin; 60 mg/m^2/cyclophosphamide 600 mg/m^2) followed by four, 3-weekly cycles of docetaxel (100 mg/m^2), or one of two experimental regimens; either AC–TH (four cycles of 3-weekly AC followed by four cycles of 3-weekly docetaxel [100 mg/m^2] plus 1 year of trastuzumab therapy [4 mg/kg loading dose followed by

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2 mg/kg]), or TCH (a non-anthracycline-containing regimen comprising docetaxel [75 mg/m^2], carboplatin [AUC 6] and trastuzumab [4 mg/kg loading dose followed by 2 mg/kg]) [12]. The primary endpoint of this study was disease-free survival (DFS), and secondary endpoints were comparison of OS, toxicity and the identification of pathological and molecular markers. The interim results were presented at the 2005 San Antonio Breast Cancer Symposium, after a median follow-up of 23 months and 322 events. Compared with the control arm, both trastuzumab-containing regimens produced statistically significant increases in 4-year DFS. Thus, compared with the control regimen, the AC–TH regimen produced an absolute increase in 4-year DFS of 11%, from 73% to 84%, which was highly statistically significant ($P = 0.0000005$; Fig. 1) and corresponded to a 51% reduction in the relative risk of relapse. The 4-year DFS rate in patients who received TCH was 80%, which, like the AC–TH regimen, was superior to that achieved with the AC–T regimen ($P = 0.000153$). The relative reduction in the risk of relapse for TCH compared with AC–T was 39%, with 98 events in the TCH arm compared with 147 in the control arm (Fig. 1) [12]. At this stage, there was no significant difference between the two trastuzumab-containing regimens ($P = 0.16$) and the secondary endpoint of OS had not been reached.

All three regimens were well tolerated and more than 90% of the planned therapy was administered. Furthermore, there were no major differences in the incidence of major haematological toxicities between the three regimens, although there was a very slight increase (~1%) in the incidence of febrile neutropenia in the AC–TH arm and a slight increase in incidence of thrombocytopenia in the TCH arm, compared with the other two respective arms. All three regimens appear to be safe and manageable with regard to non-haematological toxicities, and the lower incidence of such toxicities in the TCH arm are probably explained by the lower dose of docetaxel [12].

The incidence of cardiac events in the AC–TH arm was significantly increased compared with the AC–T control

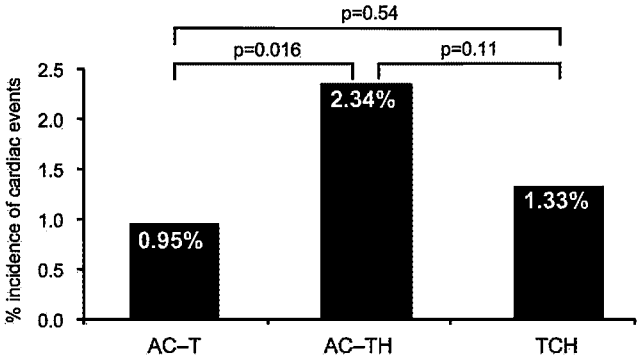

Fig. 2. BCIRG 006: cardiac safety.

arm (2.34% versus 0.95%; $P = 0.016$, Fig. 2), and although this is a doubling in incidence for the trastuzumab-containing arm, it compares well with the corresponding figures from the combined analysis of the North Central Cancer Treatment Group (NCCTG) 9831 and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 trials, which reported a four-fold increase in the incidence of cardiac toxicity in the AC–paclitaxel/trastuzumab arm compared with the AC–paclitaxel arm [13]. Returning to the BCIRG 006 trial, the incidence of cardiac toxicity in the TCH arm did not differ significantly compared with the AC–T arm (1.33% versus 0.95%; $P = 0.54$; Fig. 2). In a similar pattern to that of the overall incidence of cardiac events, the rate of >10% relative decline in left ventricular ejection fraction (LVEF) was approximately doubled in the AC–TH arm (17.3%) compared with the AC–T arm (9.0%; $P = 0.002$) and the TCH arm (8%; $P < 0.0001$). The incidence of >10% decline in LVEF in the TCH group did not differ significantly from the AC–T group ($P = 0.493$) [12].

Although, as anticipated, the TCH regimen was associated with a statistically significant reduced risk of incidence of cardiac events compared with the AC–TH arm, this regimen was not as efficacious as anticipated. These findings may be explained by the hypothesis that co-amplification of the genes encoding topoisomerase (topo) II alpha and

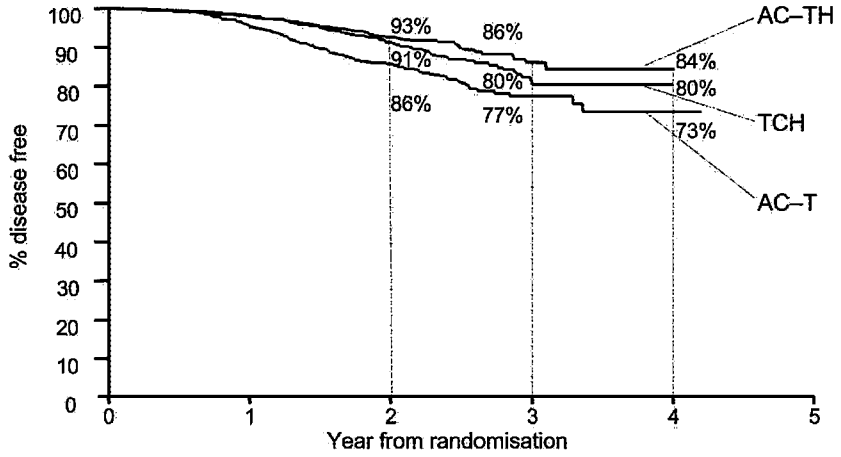

Fig. 1. BCIRG 006: 4-year disease-free survival.

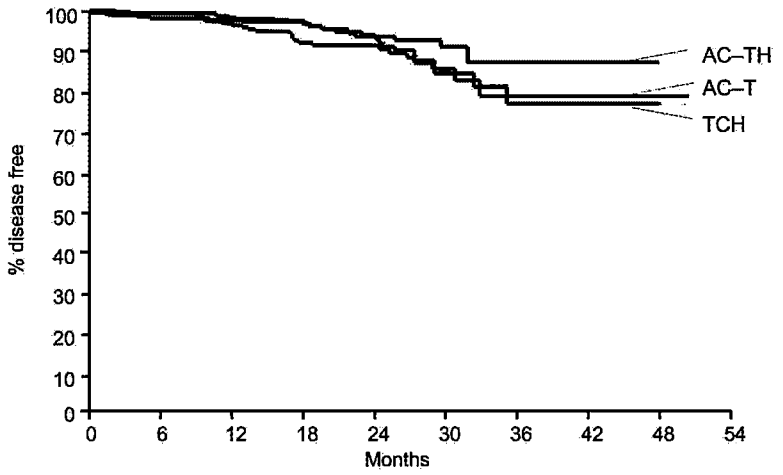

Fig. 3. BCIRG 006: effectiveness of the AC–TH and TCH regimens in patients with co-amplification of topo II and HER2/neu.

HER2/neu confers sensitivity to anthracycline therapy. As such, it would be expected that non-anthracycline-containing regimens such as the TCH regimen would not perform as well in patients of this genotype. Indeed, a prospectively planned analysis of the BCIRG 006 study population revealed that approximately 35% of this cohort demonstrated co-amplification of topo II alpha and HER2/neu, and also, that in this patient population, the DFS rate achieved with the AC–TH regimen was improved compared with the AC–T or TCH regimens (Fig. 3).

Conversely, in patients without co-amplification of the topo II and HER2/neu oncoproteins, the TCH regimen was almost as effective as the AC–TH regimen (Fig. 4) [12]. Therefore, the presence of co-amplified topo II and HER2/neu is a predictive factor for the effectiveness of anthracycline/trastuzumab-based regimens.

In summary, the results of this trial demonstrate a highly statistically significant DFS benefit for two docetaxel/trastuzumab-containing regimens after a short follow-up of 23 months. Compared with AC–T control arm, the AC–TH regimen was associated with a 51% reduction in the risk of relapse (hazard ratio [HR] = 0.49; $P = 0.0000005$) and the TCH regimen was associated with a 39% reduction in risk of relapse (HR = 0.61; $P = 0.000153$). At present, there is no statistically significant difference in DFS between the two experimental arms. There was a significantly higher incidence of cardiac toxicity in the AC–TH arm, but not in the TCH arm, compared with the AC–T arm. Similarly, there was a significantly higher incidence of asymptomatic and persistent LVEF declines in the AC–TH arm compared with the AC–T and the TCH arms. There was no significant difference in the incidence of haematological toxicity between the three treatment arms, and all treatments appeared to be safe with manageable toxicities. Moreover, they were well tolerated with more than 90% of cycles administered. Co-amplification of the topo II alpha gene occurred in approximately 35% of HER2-positive patients and may confer a therapeutic advantage to anthracycline/trastuzumab combination regimens. The 65% of HER2-positive patients who did not have co-amplification of topo

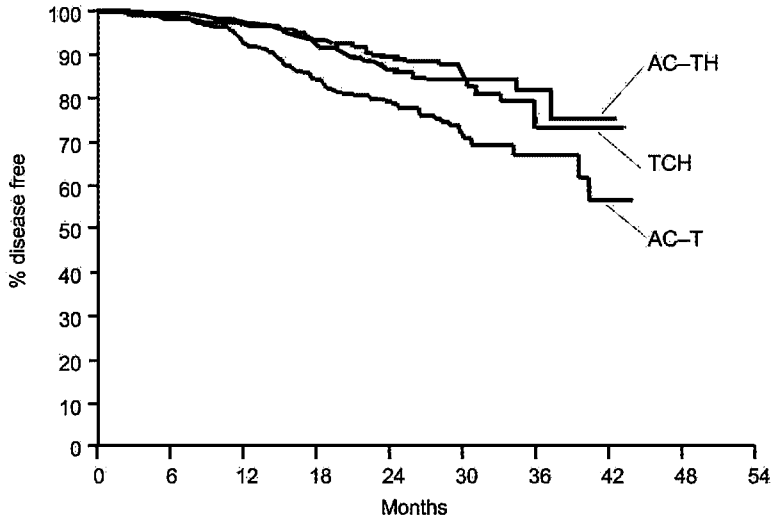

Fig. 4. BCIRG 006: effectiveness of the AC–TH and TCH regimens in patients without co-amplification of topo II and HER2/neu.

II alpha did not appear to experience the same benefit from anthracycline-containing regimens and therefore, in the future, such patients may be ideal candidates for efficacious non-anthracycline-based regimens such as TCH.

The second trial reported at the 2005 SABCS meeting that investigated therapy with docetaxel and trastuzumab was the FinHER study [14]. The results of this study were subsequently published in the *New England Journal of Medcine* in February 2006 [15]. In this trial, patients ($n = 1010$) with either node-positive or negative, >20 mm, progesterone receptor-negative tumours were randomised to receive treatment with either three cycles of 3-weekly docetaxel or eight cycles of weekly vinorelbine followed by three cycles of 3-weekly $FE_{60}C$ (5-fluorouracil [5-FU]; 600 mg/m^2/epirubicin; 60 mg/m^2/cyclophosphamide; 600 mg/m^2). In a second randomisation, the 232 (23%) patients who were HER2-positive received either nine cycles of weekly trastuzumab or no trastuzumab in addition to their chemotherapy. The primary endpoint of this trial was recurrence-free survival (RFS), defined as locoregional or distant recurrence of breast cancer, contralateral invasive breast cancer or death from a competing cause. The secondary endpoints were OS, toxicity/safety, and cardiac function. The patient and tumour characteristics were well balanced across the treatment arms, with the exception that there were more patients in the docetaxel arm than in the vinorelbine arm with tumour size >2 cm ($P = 0.02$). The results of the interim analysis, with a median follow-up of 38 months, revealed that the RFS rate was significantly higher in patients who received docetaxel compared with those who received vinorelbine (91.3% versus 86.4%; $P = 0.005$), corresponding to a 42% reduction in the risk of relapse. At this time, OS did not differ significantly between docetaxel and vinorelbine (96.4% and 95.5%, respectively). The administration of trastuzumab concurrently with docetaxel or vinorelbine, and prior to $FE_{60}C$, was effective in preventing recurrence, with the rate of RFS being significantly higher in patients who received trastuzumab compared with those who did not (89.3% versus 77.6%; $P = 0.01$). Again, the OS outcome between trastuzumab and no trastuzumab did not differ at this time – probably owing to the small number of events, however, there was a clear trend in favour of trastuzumab ($P = 0.07$) [15]. These results suggest that a shorter duration schedule of concurrent chemotherapy and trastuzumab may be as efficacious as the longer schedule consisting of chemotherapy followed by sequential trastuzumab. However, the absolute benefits of this new schedule need to be confirmed in a large, comparative study.

The challenge that we now face is the translation of this new information in to clinical practice and the daily decisions that need to be made regarding the management of patients with early-stage, HER2-positive breast cancer. Comparison of the data from the four trastuzumab studies conducted thus far reveal a similar efficacy across all regimens, suggesting that the benefit of trastuzumab therapy in patients with HER2-positive disease does not depend on the taxoid used. However, cross-trial comparison suggests that the cardiac toxicity profile for docetaxel-containing regimens appears to be better than that for paclitaxel-containing regimens. For example, when comparing taxoid/trastuzumab combinations with their respective control arms, the paclitaxel/trastuzumab regimen produced a four-fold increase in cardiac toxicity [13], whereas the docetaxel/trastuzumab regimen caused only a two-fold increase [12]. The cardiac toxicity profile of docetaxel/trastuzumab combinations was further improved upon by the non-anthracycline-containing TCH regimen, which demonstrated outcomes that were almost identical to the control arm. Therefore, the TCH regimen could be considered as an alternative trastuzumab-containing regimen for the treatment of patients with increased cardiac risk, especially in those patients with tumours that do not show co-amplification of the topo II gene.

In summary, in combination with our existing knowledge that docetaxel/trastuzumab combination therapy provides consistent benefits for patients with HER2-positive, metastatic breast cancer, as described in the M77001 trial by Marty and colleagues [3], the data presented at the 2005 SABCS demonstrate consistent benefits in the adjuvant setting. We have just learned from the interim results of the BCIRG 006 trial, that two docetaxel/trastuzumab-containing regimens (AC–TH and TCH) provide DFS benefits over the AC–T control [12]. In addition, the first results of the FinHER trial demonstrate a superior RFS for upfront treatment with docetaxel–FEC compared with vinorelbine–FEC [15]. In the BCIRG 006 trial, prospective analysis of topo II and HER2/neu amplification revealed that the TCH regimen may be a suitable option for patients who do not have co-amplification of HER2/neu and topo II, or those who are at increased risk of developing cardiac toxicities. As such, the present challenge is to develop a diagnostic test for the routine screening of topo II/HER2/neu co-amplification.

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