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Conclusions

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It is now widely accepted that breast cancer is not a single disease and that tumours can arise from different types of breast tissue. As discussed in this supplement, factors such as hormone-receptor status, human epidermal growth factor 2 (HER2)-receptor status and nodal status also contribute to the wide spectrum of pathologies that are commonly referred to as breast cancer. In addition, many cellular factors can contribute to tumour development, including growth factors, cytokines, nuclear receptors and survival factors. As such, the task of determining the best treatment approach for each subtype of breast cancer is not easy. A number of studies have identified prognostic and predictive gene signatures that have proven to be superior to conventional prognostic indicators as tools for the prediction of disease outcome and response to treatment [1]. However, despite these major technological advances, a number of confounding issues remain regarding the potential clinical utility of gene expression profiling. The joint Breast International Group (BIG) and European Organisation for Research and Treatment of Cancer (EORTC) Microarray In Node-negative Disease may Avoid ChemoTherapy (MINDACT) trial has been designed to address these issues and aims to correlate genomic and clinical information in 6000 women with node-negative breast cancer.

Treatment tailoring for the individual patient has, therefore, become the major challenge for oncologists. Today, most breast cancer patients are offered some type of systemic therapy, and it therefore follows that oncologists should provide the chemotherapy that will give patients the best outcome. The two major applications of translational research are the identification of predictive factors and the identification of new therapeutic targets. The results of clinical trials and meta-analyses have had a major impact on treatment recommendations for both early-stage and advanced disease. In the metastatic setting, the results of the first and only head-to-head study that directly compared the two taxoids demonstrated that, compared with paclitaxel, docetaxel exhibited a superior efficacy profile, increasing overall survival (OS) from 12.7 to 15.4 months – a significant improvement of 2.7 months [2]. Although treatment with docetaxel was associated with an increased toxicity compared with paclitaxel, this did not result in a statistically significant difference in global quality of life scores. Due to the more recent understanding of the schedule dependency of paclitaxel, it is widely thought that the 3-weekly regimen used in the TAX 311 trial discussed is inferior to newer, weekly schedules. Several phase II studies have evaluated the safety and efficacy of weekly paclitaxel as single-agent therapy in patients with metastatic breast cancer reporting response rates of 22–53% in pretreated patients, and median time to progression (TTP) of 5–6 months [3–7]. The four-arm ECOG E1199 study compared weekly and 3-weekly regimens of both taxoids, but this study was not designed to compare each of the four arms. As such, whereas 3-weekly paclitaxel is now known to be a suboptimal schedule for administration of this agent, it is also known that a weekly regimen is an inappropriate schedule for administration of docetaxel, due to tolerability and quality-of-life issues. As such, it could be argued that the results of the ECOG E1199 study, which to date suggest that there is no difference in disease-free survival between the two taxoids, were influenced by the inclusion of a suboptimal docetaxel regimen.

The main toxicity associated with docetaxel is febrile neutropenia, but its prevention can be effectively achieved through the use of prophylactic granulocyte colony-stimulating factor (G-CSF). This was clearly demonstrated in a study by Vogel and colleagues [8], in which prophylactic G-CSF therapy was shown to significantly decrease the incidence of febrile neutropenia, incidence of febrile neutropenia-related hospitalisation and use of anti-infectives. Dose reduction is another very efficient approach, as demonstrated by Mouridsen and colleagues [9], who reported a significant reduction in the incidence of febrile neutropenia and in docetaxel-related infection, with a dose reduction from 100 mg/m^2 to 60 mg/m^2.

Early preclinical studies, which were based on the synergistic rather than additive outcomes observed with the addition of docetaxel to trastuzumab in *in vitro*

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studies on HER2-positive cell lines [10], suggested that this combination would produce promising results in the clinical setting. The advantages of the docetaxel/trastuzumab combination have indeed now been demonstrated in the clinical setting, with the recently published M77001 trial reporting an impressive OS of 31.2 months – an increase of 8.5 months compared with docetaxel monotherapy [11]. Interim analyses of adjuvant studies investigating docetaxel/trastuzumab combinations are now becoming available, and recently released results of the BCIRG 006 trial have demonstrated impressive disease-free survival (DFS) rates [12] for two docetaxel/trastuzumab combinations: the AC–TH regimen (adriamycin/cyclophosphamide followed by docetaxel/trastuzumab) and the TCH regimen (docetaxel/trastuzumab/carboplatin); the latter, in spite of the exclusion of an anthracycline. The lack of cardiotoxicity of the TCH regimen [13], combined with its demonstrated efficacy, offers a real hope for patients with early-stage breast cancer.

Combination therapy comprising docetaxel and trastuzumab therefore offers a clear advantage for the proportion of patients with HER2-positive disease. Similarly, the results of the Breast Cancer International Research Group (BCIRG) 001 trial [14] and the French Federation of Cancer Centres' PACS 01 trial [15] have demonstrated that docetaxel-containing regimens, when used as adjuvant therapy, can offer an extremely good chance of survival for patients with HER2-negative disease. For example, the substitution of three cycles of the $6FE_{100}C$ regimen with three cycles of docetaxel ($3FE_{100}C$–3T) produced a probability of OS of 90.7%, which was a statistically significant improvement on the already very respectable figure of 86.7% achieved with the $6FE_{100}C$ regimen [15]. In addition, thus far, the beneficial effects of these regimens appear to be applicable to most patient subsets, and to be independent of hormone receptor status and the number of positive nodes. The PACS 01 trial investigated the benefits of sequential docetaxel, and has demonstrated that the addition of docetaxel produced significant increases in both DFS and in OS. The results of ongoing trials, including the Taxotere® as Adjuvant Chemotherapy trial (TACT), in which a regimen comprising four cycles of FEC followed by four cycles of docetaxel will be compared with eight cycles of FEC or epirubicin followed by the CMF regimen (cyclophosphamide/methotrexate/5-fluorouracil), are eagerly awaited.

The effectiveness of the TC regimen (docetaxel/cyclophosphamide) with a concomitant absence of cardiac toxicity – which has already been demonstrated in the metastatic setting – has now been investigated in the adjuvant setting [16]. Compared with the standard AC regimen, the TC regimen produced a longer DFS and was the better-tolerated adjuvant regimen and, as such, should be discussed as the standard therapy to replace the AC regimen in patients with low-risk early-stage breast cancer [16].

So, in answer to the question "Breast cancer: the beginning of the end or the end of the beginning?", I firmly believe that we are at the end of the beginning. The two taxoids docetaxel and paclitaxel have recently been shown to be clinically different in metastatic breast cancer. Prophylactic growth factor support permits the safe and effective use of full-dose docetaxel. The addition of trastuzumab is a key component of therapy for patients with HER2-positive tumours and triple therapy comprising docetaxel, carboplatin and trastuzumab – the TCH regimen – is now a real alternative as a non-anthracycline standard for these patients. In the future, ongoing questions regarding cytotoxic therapy will need to be answered, and the potential benefit of combination therapies with novel therapeutics, such as bevacizumab and lapatinib, will need to be investigated. Further development of the understanding and use of genomic/proteomic approaches will help the oncology community to reach the nearing goal of therapeutic individualisation. These developments promise to offer an improved potential for cure and will ensure that all patients receive a treatment regimen that is optimised to their specific clinical needs.

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