ELSEVIER

EJC Supplements Vol. 4 No. 4 (2006) 1–3

EJC Supplements

www.ejconline.com

Breast cancer: not a single disease

Matti Aapro

Multidisciplinary Oncology Institute, Route du Muids 1, 1272 Genolier, Switzerland

Keywords: Breast; Docetaxel; EORTC; Paclitaxel; Trastuzumab

In 2004 in Europe, there were an estimated 2,886,800 diagnoses of cancer, of which breast cancer accounted for 13% of cases. In the same year, breast cancer was the cause of 129,000 deaths in Europe [1]. The expected number of cancer deaths in the European Union fell by over 9% between 1985 and 2000 [2]. When embarking on any discussion concerning breast cancer, it is important to begin by noting that we are winning the battle against this disease. For example, figures reveal that since 1990, there has been a reduction in breast cancer mortality of up to 33% in the United Kingdom, indicating that we are making progress in the treatment of breast cancer. Over the past several decades, the risk of breast cancer in developed countries has increased by 1–2% annually [3], and cancer registries suggest that age-standardised incidence rates are rising even more rapidly in regions such as Africa and Asia [4]. These considerations make the advances to date even more remarkable.

However, we are still learning about this complex disease, and one of the most striking advances is the recent recognition that breast cancer is not a single disease. We have long known that different histological subtypes of breast cancer exist, but nonetheless, when the obvious diagnosis has been made, similar treatment strategies are adopted in many subtypes of breast cancer. Now, we know that this approach is too simplistic to be able to offer all patients the best treatment for their disease.

Recently, we have seen dramatic advances in the laboratory techniques used in the diagnosis of breast cancer. Although before 1980 diagnosis relied solely on histological techniques, the development and routine use of single-gene predictor techniques, such as immunohistochemistry and fluorescence *in situ* hybridisation (FISH), have permitted more specific diagnoses of breast cancer. Even newer techniques, such as DNA microarrays, single-nucleotide polymorphism (SNP) analysis, multiplex polymerase chain reaction (PCR) and proteomics, offer the possibility of examining a very large number of genes and proteins from a single biopsy. These techniques are being used to develop breast cancer predictors that comprise many genes rather than merely a single marker. A seminal paper by Perou and colleagues [5] reported an interesting finding regarding the differentiation of the pathways that contribute to the development of different subtypes of breast cancer. The results of this study demonstrated that, whereas basal-like tumours and human epidermal growth factor receptor 2 (HER2)-positive tumours tended to be oestrogen-receptor (ER)-negative, those tumours that develop in the luminal area tended to be ER-positive [5].

In the advent of the new translational approach to research, two main applications will arise: the identification of predictive factors and the identification of new therapeutic targets. Indeed, many research groups are asking questions regarding the current knowledge of the genetics of breast cancer and the impact that this will have on the use of chemotherapy in patients with breast cancer. One such example is a study from the European Organisation for Research and Treatment of Cancer (EORTC) and the Breast Cancer International (BIG) groups, which will build on the results of preclinical experiments that indicated that tumours with a mutation of the p53 gene exhibited differential responses to chemotherapy, manifested as decreased sensitivity to anthracyclines and increased sensitivity to taxoids. In the BIG-p53 trial, patients with large, operable, locally advanced tumours were randomised to receive neoadjuvant chemotherapy comprising either docetaxel or non-docetaxel chemotherapy. About 1470 patients have been enrolled to date, and the investigators aim to enroll a total of approximately 1800 patients. In addition, a series of translational research substudies – the "Thank God It's Frozen" (TGIF) studies – will investigate a variety of different subtypes of breast tumour. The TGIF 1 study has reported the identification of a third tumour type, the molecular apocrine group, in addition to the basal and luminal tumours [6]. The TGIF 2 trial investigated the presence of a gene profile predictor for a pathological complete response (pCR) after neoadjuvant chemotherapy with anthracyclines or docetaxel in hormone receptor (HR)-negative tumours. Preliminary results of the study, presented at the 2005 San Antonio Breast Cancer

* Tel: +41 (0)22 366 91 34; Fax: +41 (0)22 366 91 31.
E-mail address: maapro@genolier.net (M. Aapro).

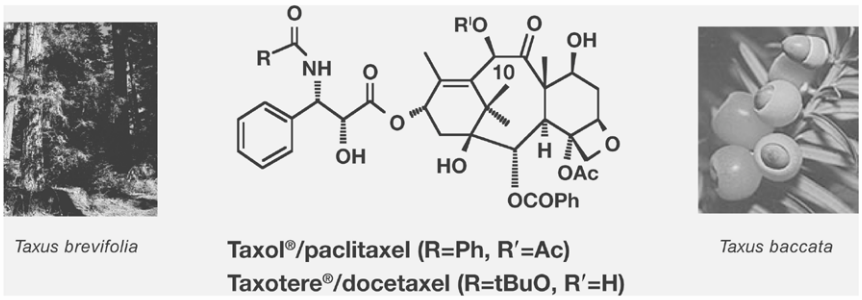

Fig. 1. The chemical structures of the taxoids

Symposium (SABCS), did not find a genetic signature for a pathological complete response to anthracycline-based treatment [7]. Perhaps the one trial that provides the greatest potential for influencing the future of treatment is the joint EORTC and BIG MINDACT (Microarray In Node-negative Disease may Avoid ChemoTherapy) study. This study will prospectively analyse the clinical–pathological risk of 6000 women with node-negative breast cancer, with the aim of correlating clinical and genetic profiles to identify the patients who will most benefit from chemotherapy. As the comparison of anthracycline-based chemotherapy with a docetaxel–capecitabine regimen (the latter of which is likely to exhibit increased efficacy and reduced long-term toxicities) is also a main objective of this study, it is anticipated that the results may provide insight into which patients will benefit most from taxoid therapy. However, until we fully understand the place of such findings with respect to treatment tailoring, we must continue in our efforts to further our knowledge of chemotherapy so that we can provide the best outcomes for our patients.

As such, at present, the necessary skills for treating breast cancer include knowledge of the current literature, dialogue with the patient, and specific tailoring of currently available treatments. Consideration must be given, not only to the fact that breast cancer is not a single disease, but also to the knowledge that all chemotherapeutic agents are different, even those within the same class. One such example is the taxoid class. Differences between docetaxel (Taxotere®) and paclitaxel (Taxol®) have been evident since their initial discovery. Paclitaxel was isolated from the bark of the Pacific yew tree *(Taxus brevifolia)*, whereas docetaxel was, some years later, prepared from 10-deacetylbaccatin III, isolated from the needles of the European yew tree (*Taxus baccata*) (Fig. 1).

Even though differences were obvious at such an early stage in the development of these agents, it is only recently that we have been able to make a direct comparison of the clinical usefulness of the two taxoids. In this supplement, Dr Stephen Jones discusses the results of the recently published TAX 311 study [8], in which the use of docetaxel or paclitaxel after previous failure of anthracycline therapy was directly compared. The TAX 311 trial is the first and only head-to-head comparison of taxoid monotherapy in the metastatic setting. At the time during which the TAX 311 study was conducted, the schedule dependency of paclitaxel had not been identified. However, an ongoing Eastern Co-operative Oncology Group study (E1199) has factored this into a comparison of the two taxoids in the adjuvant setting, and the results of this study will also be discussed by Stephen Jones.

Professor Michel Marty discusses the recent advances in the treatment of patients with HER2-positive breast cancer with the use of trastuzumab; in particular, in combination with docetaxel.

It is now universally acknowledged that the use of docetaxel and paclitaxel in addition to conventional therapy has led to an improvement in efficacy of therapy for patients with node-positive, early-stage breast cancer. In line with our increased knowledge about the diversity of breast cancer, the number of available treatment options for patients with these different disease subtypes has also increased. The most recent of these advances were highlighted at the recent 2005 SABCS meeting. One of the main topics for discussion at this meeting was the improved cardiotoxicity profiles of non-anthracycline-containing regimens, compared with older anthracycline-containing regimens. As such, the TC (docetaxel/cyclophosphamide) doublet has emerged as a new option for the treatment of patients with operable breast cancer [9]. The advantages of using a non-anthracycline regimen in patients with HER2-positive disease have been suggested in the BCIRG 006 trial. The first safety analysis – the results of which were released at the 13th European Cancer Conference (ECCO) meeting – demonstrated an incidence of cardiac events of less than 1% for the TCH (docetaxel [T]/carboplatin [C]/trastuzumab [H]) regimen, in which the traditionally used anthracycline (A) component of therapy was replaced with carboplatin [10].

The first efficacy analysis of the BCIRG 006 trial, presented at the 2005 SABCS meeting, revealed impressive disease-free survival (DFS) advantages for two docetaxel/trastuzumab-containing regimens – the AC–TH and TCH regimens – in comparison with the AC–T regimen (adriamycin/cyclophosphamide followed by docetaxel) [11]. Another interesting finding regarding the duration of adjuvant treatment with trastuzumab was demonstrated in the FinHER study [12], suggesting that the relative benefit of long-term treatment with trastuzumab needs to be confirmed in a large, comparative study.

These new data, in addition to a comparison of existing data for docetaxel and paclitaxel in the adjuvant setting, are discussed by Dr Paul Ellis. Questions that are now being asked regarding the identification of a particular subgroup of patients that will particularly benefit from taxoid therapy in the adjuvant setting will also be addressed by Paul Ellis.

References

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 2005, **16**(3), 481–8.
2. Boyle P, d'Onofrio A, Maisonneuve P, *et al.* Measuring progress against cancer in Europe: has the 15% decline targeted for 2000 come about? *Ann Oncol* 2003, **14**(8), 1312–25.
3. Forbes JF. The incidence of breast cancer: the global burden, public health considerations. *Semin Oncol* 1997, **24**(1 Suppl 1), S1-20–S1-35.
4. Sasco A. Epidemiology of breast cancer: an environmental disease? *APMIS* 2001, **109**, 321–332.
5. Perou CM, Sorlie T, Eisen MB, *et al.* Molecular portraits of human breast tumours. *Nature* 2000, **406**(6797), 747–52.
6. Farmer P, Bonnefoi H, Becette V, *et al.* Identification of molecular apocrine breast tumours by microarray analysis. *Oncogene* 2005, **24**(29), 4660–71.
7. Bonnefoi H, Delorenzi M, Becette V, *et al.* Is there a regimen-specific gene signature predicting for pCR after neoadjuvant chemotherapy in hormone-negative breast cancer patients? A microarray substudy of 119 patients included in EORTC 10994/BIG 00-01 trial. Poster presentation at the 2005 San Antonio Breast Cancer Symposium 2005: Abstr. 1040.
8. Jones SE, Erban J, Overmoyer B, *et al.* Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol* 2005, **23**(24), 5542–51.
9. Jones SE, Holmes FA, O'Shaughnessy JA, *et al.* Final analysis: TC (docetaxel/cyclophosphamide, 4 cycles) has a superior disease-free survival compared to standard AC (doxorubicin/cyclophosphamide) in 1016 women with early stage breast cancer. In: *SABCS 2005*; 2005, Abstr. 40.
10. Slamon D, Robert N, Pienkowski T, *et al.* BCIRG 006: Superior cardiac safety of adjuvant docetaxel (T), carboplatin (C) and trastuzumab (H) compared to doxorubicin (A) and cyclophosphamide (Cyc) followed by TH in patients with early stage breast cancer and altered HER2 gene. *Eur J Cancer Suppl* 2005, **3**(2), 74.
11. Slamon D, Robert N, Pienkowski T, *et al.* Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. In: *SABCS 2005*; 2005, Abstr. 1.
12. Joensuu H, Bono P, Alanko T, *et al.* Trastuzumab in combination with docetaxel or vinorelbine as adjuvant treatment of breast cancer: the FinHer Trial. In: *SABCS 2005*; 2005, Abstr. 2.