Meeting report

25th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, USA, 10–14 December 2002 Update on clinical research

Alistair Ring and Julia Head

Breast Unit, Department of Medicine, Royal Marsden Hospital, London, UK

Corresponding author: Alistair Ring (e-mail: aring@icr.ac.uk)

Received: 8 January 2003 Accepted: 15 January 2003 Published: 5 February 2003

Breast Cancer Res 2003, **5**:113-116 (DOI 10.1186/bcr576)

See preclinical and translational report, page 109

Abstract

The Annual San Antonio Breast Cancer Symposium has become a key forum for the presentation and discussion of both translational scientific aspects as well as clinical aspects of breast cancer care. In this report of the 25th Annual Meeting, an update of the salient clinical data is presented. The findings of the CALGB 9741 trial, an updated analysis of the Arimidex, Tamoxifen, Alone or in Combination study, and other significant paper and poster presentations are discussed. Summaries are also given of the clinical plenary lectures and minisymposia on adjuvant therapy and aromatase inhibitors.

Keywords: adjuvant chemotherapy, anastrozole, aromatase inhibitor, tamoxifen, trastuzumab

Introduction

The 25th Annual San Antonio Breast Cancer Symposium attracted nearly 5000 physicians and researchers in breast oncology, as well as other health care professionals and patient advocates with an interest in breast cancer. This meeting has become a key forum for the presentation and discussion of both translational scientific aspects as well as clinical aspects of breast cancer care. The present report will focus on the clinical highlights of the meeting. The preclinical and translational research presented at the meeting is discussed in another report, also published in the present issue of *Breast Cancer Research* [1].

This year, the traditional WL McGuire memorial lecture was given by Michael Baum (University College London, UK). Baum described his 30 years' experience in breast cancer research in an entertaining and wide-ranging talk. In particular, he outlined what he sees as a paradigm shift in the design of clinical trials from an empirical approach to a hypothesis-driven approach. There were two further clinical plenary lectures, given by Stephen Feig (Mount Sinai School of Medicine, New York, USA) and Craig Jordan (University of California, San Francisco, CA, USA). These critical, informative reviews concerned the validity and interpretation of existing mammography trials. There were also minisymposia addressing the changing face of adjuvant therapy and the use of aromatase inhibitors. General sessions comprised short communications of original research, panel discussions of clinical scenarios and more than 500 poster presentations.

Adjuvant therapy

The current status of adjuvant chemotherapy was summarised in a minisymposium by Hyman Muss (University of Vermont, Burlington, VT, USA) and Charles Vogel (University of Miami, FL, USA). On the basis of data from the Oxford Overviews, chemotherapy regimes that incorporate anthracyclines are still preferred to those that do not. This was reinforced by an update of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.5 trial given by Kathleen Pritchard (Toronto-Sunnybrook Cancer Center, Toronto, Canada), which demonstrated superiority of an anthracycline regime (cyclophosphamide, epirubicin and 5-fluorouracil) over cyclophosphamide, methotrexate and 5-fluorouracil (10-year disease free survival, 52% versus 45%; $P=0.005$) [2].

ATAC = Arimidex, Tamoxifen, Alone or in Combination; BCIRG = Breast Cancer International Research Group; CALGB = Cancer and Leukaemia Group B; HER-2 = human epidermal receptor-2; TPC = trastuzumab + paclitaxel + carboplatin.

In some groups such as the elderly or high-risk node-negative patients, however, it may be possible and desirable to omit the anthracycline component, and this is being investigated by the Cancer and Leukaemia Group B (CALGB 40101 and CALGB 49907). On the basis of results from the Breast Cancer International Research Group (BCIRG) 001 and CALGB 9344 trials, many oncologists in the United States also incorporate a taxane into adjuvant chemotherapy regimes. Trials are underway to assess whether paclitaxel or docetaxel (weekly or three-weekly) is the best agent in the adjuvant setting.

However, a report of the CALGB 9741 trial given by Mark Citron on behalf of the CALGB highlighted the potential importance not only of the agents used, but of the dose density of adjuvant chemotherapy [3]. CALGB 9741 is a randomised phase III trial of sequential chemotherapy using doxorubicin, cyclophosphamide and paclitaxel, or concurrent doxorubicin and cyclophosphamide followed by paclitaxel at 14-day intervals versus 21-day intervals. Patients on the 2-week schedules were given prophylactic filgrastim support. Disease-free survival at 3 years follow-up was superior for dose-dense versus conventional scheduling (85% versus 81%, $P=0.0072$). Overall survival was also superior (92% versus 90%, $P=0.014$), but there was no difference in these outcomes based on the use of sequential versus concurrent therapy. There were no neutropaenia-related deaths, and fewer cases of grade 4 neutropaenia were encountered in the dose-dense arms of the study. The number of events so far experienced has been lower than expected from the null hypothesis, such that the results of this trial must be regarded as preliminary. Nonetheless, dose density may prove to be an important determinant of the efficacy of adjuvant chemotherapy.

At the 24th Annual San Antonio Breast Cancer Symposium, Baum presented a first analysis of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial. At this year's meeting, Aman Buzdar (MD Anderson, Houston, TX, USA) presented a further analysis (median followup, 47 months) on behalf of the international trialists group [4]. The trial randomised 9366 postmenopausal women with breast cancer (who had completed surgery, radiotherapy and/or chemotherapy) between the adjuvant endocrine therapy arms. When first published (median followup, 33 months), an improved disease-free survival was reported for anastrozole over tamoxifen (89.4% versus 87.4%, $P=0.013$), with the combination arm offering no advantage over tamoxifen alone [5]. Buzdar's report focused on the monotherapy arms of the study. The probability of a first event (local or distant recurrence, new primary breast cancer or death) was lower at 48 months in the anastrozole arm compared with the tamoxifen arm (14% risk reduction, $P=0.03$). The absolute difference in first-event rates between the arms has increased from 1.5% at 3 years to 2.4% at 4 years. Benefits were greater still in the group known to be hormone receptor-positive (2.9% absolute difference at 48 months).

An additional 7 months of safety data were presented in poster form by Richard Sainsbury (Royal Free and University College Medical School, London, UK) on behalf of the ATAC trialists group [6]. These data continue to show lower rates of endometrial cancer, thromboembolic events and cerebrovascular events with anastrozole than with tamoxifen. There were also significantly fewer withdrawals due to drug-related adverse events in the anastrozole-treated group (5.1% versus 7.2%, $P<0.0001$). However, there were more musculoskeletal events and fractures in the anastrozole arm (30.3% versus 23.7%, and 7.1% versus 4.4%, respectively). Buzdar concluded that the data support the use of adjuvant anastrozole in this patient population. Several other planned and ongoing trials are also looking at the role of adjuvant aromatase inhibitors, given alone or in combination with selective estrogen receptor modulators, sequentially or concurrently, and for differing durations.

The increased fracture rate seen in the ATAC trial patients receiving anastrozole is of concern, and it may be that some of these patients benefit from the concurrent use of bisphosphonates. Of relevance to this, data presented by Michael Gnant (Austrian Breast and Colorectal Study Group, Vienna, Austria) demonstrate that the bisphosphonate zoledronate may be able to counteract bone mineral density loss in premenopausal women treated with goserelin and anastrozole [7].

Aromatase inhibitors

Following on from the ATAC data, a minisymposium was devoted to the topic of aromatase inhibitors, with emphasis on response prediction, breast cancer prevention and clinical application.

Matthew Ellis (Duke University Breast Cancer Program, Durham, NC, USA) gave an overview of current clinical practice. While the superiority of aromatase inhibitors over tamoxifen is generally accepted in cases of advanced disease, their use in the adjuvant setting is still controversial and it is important to look at all aspects of their use, including the long-term side effects. The development of resistance is of particular concern. Research in recent years has focused on human epidermal receptor-2 (HER-2)-driven activation of the oestrogen receptor as a major mechanism of resistance to endocrine therapy. While this is certainly relevant, it is unlikely to represent the whole story. *In vitro* data show that letrozole-resitant cells have a low rate of HER-2 positivity and continue to proliferate in a manner that suggests independence from the oestrogen receptor. Similarly, in cases of advanced disease, primary resistance to letrozole can still develop

despite the presence of trastuzumab, suggesting that other growth stimulatory pathways are also important. Ellis stressed the need for further trials to assess the efficacy of aromatase inhibitors in the adjuvant and neoadjuvant setting, to examine potential synergy when combined with novel signalling agents, and to investigate novel mechanisms of resistance.

Despite a reduction in mortality from breast cancer, the incidence continues to rise and the need for preventative measures is clear. Mitch Dowsett (Royal Marsden Hospital, London, UK) acknowledged the potential role of aromatase inhibitors in this setting and outlined a number of forthcoming trials. However, he stressed the need for a well-developed strategy both in terms of who to treat and how to counteract unwanted side effects. Existing trials suggest that the preventative effects of tamoxifen are predominantly seen in those who are likely to develop oestrogen receptor-positive tumours. Features predicting for the development of oestrogen receptor-positive tumours (such as age, atypical hyperplasia, breast and bone density, and levels of oestradiol, oestrone and testosterone) may therefore become important components of preventative trial targeting.

Targeted therapy was taken further by William Miller (Edinburgh Breast Unit, Edinburgh, UK), who discussed the role of aromatase inhibitors in suppressing oestrogen locally within the breast tumour tissue, in addition to reducing circulating serum levels. Peripheral serum aromatase has been shown to fall by > 90% in women after 3 months of treatment and this is associated with a concomitant fall in serum oestradiol, but such a response cannot be predicted. Serum oestradiol levels in premenopausal women are high. Oestradiol reaches the breast via diffusion, and levels in the local breast tissue are predictably lower. However, this situation may be reversed in postmenopausal women; serum levels of oestradiol fall as ovarian function ceases but hormone levels within the breast can remain paradoxically high, suggesting that in some cases oestradiol may be synthesised *de novo* within the breast tissue. Infusional studies in postmenopausal women using radiolabelled androgen and oestrogen have provided evidence for oestrogen production, both peripherally and locally within the breast tumours themselves. There is interpatient variability but, overall, patients with high levels of *in situ* oestrogen synthesis respond well to treatment with aromatase inhibitors. This provides interesting insight into a possible predictor of response to these compounds, and also raises the possibility of enhancing treatment response using a method of local drug delivery.

Treatment of advanced breast cancer

The number of drug treatment options in metastatic breast cancer has increased in recent years, but this remains a highly challenging area, particularly in patients with relatively chemotherapy-resistant or heavily pretreated disease. Trastuzumab + paclitaxel has previously been shown to be superior to paclitaxel alone in HER-2-positive breast cancer [8].

Nicolas Robert (US Oncology Inc, Houston, TX, USA) presented encouraging results at this meeting of a collaborative phase III trial comparing the combination of trastuzumab + paclitaxel with the combination of trastuzumab + paclitaxel + carboplatin (TPC) in HER-2/neu-positive patients with advanced disease [9]. The objective response rate was greater with TPC versus than with trastuzumab + paclitaxel (52% versus 36%, $P = 0.04$). There was also a significant improvement in the time to progression with TPC (11.2 months versus 6.9 months). Similar findings were seen whether HER-2 status had been confirmed using immunohistochemical analysis or fluorescence *in situ* hybridisation. Although there was more myelosuppression with TPC, this was not accompanied by more septic or haemorrhagic episodes, and there was also no significant difference in the neurotoxicity observed.

A number of posters and presentations addressed the potential clinical efficacy of novel agents, either alone or in combination with conventional cytotoxics. Bevacizumab is a humanised monoclonal antibody to vascular endothelial factor that has shown clinical activity as monotherapy in patients with metastatic disease. Kathy Miller (Indiana Cancer Pavilion, Indianapolis, IN, USA) presented data from a phase III trial of bevacizumab in combination with capecitabine in patients who had received prior chemotherapy [10]. The overall response rate was superior for the combination arm over capecitabine alone (20% versus 9%), but no improvement in progression-free survival was observed. Moreover, the toxicity profile was poor with a significant increase in hypertension and thromboembolic events.

Kathy Albain (Loyola University Medical Center, Maywood, IL, USA) discussed the results of an open-label, phase II, multicentre trial of ZD 1839 (Iressa) as monotherapy in advanced disease [11]. Of the patients, 14.3% achieved a partial response or stable disease for ≥ 5 months and, subjectively, Iressa appeared to improve symptoms of bone pain, although this was not a preplanned endpoint. While limited clinical activity has been reported to date, studies such as these are important as they demonstrate a proof of principal and support the design of further clinical trials.

Conclusion

Basic and translational research now exerts a considerable influence over clinical breast cancer treatment and research. The Annual San Antonio Breast Cancer Symposium is critical to the success of this relationship as it enables the dissemination of information between all sections of the breast cancer research and treatment community.

Competing interests

None declared.

References

1. Head JE, Ring A: **25th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, USA, 10–14 December 2002: Update on preclinical and translational research.** *Breast Cancer Res* 2003, **5**:109-112.
2. Levine MN, Pritchard KI, Bramwell VHC, Shepherd LE, Tu D, Paul N: **A randomized trial comparing CEF with CMF in premenopausal women with node positive breast cancer: update of NCIC CTG MA.5.** *Breast Cancer Res Treat* 2002, **76(suppl 1)**: A17.
3. Citron M, Berry D, Cirrincione C, Carpenter J,Hudis C, Gradishar W, Davidson N, Ingle J, Martino S,Livingstone R,Winer E, Muss H, Norton L: **Superiority of dose-dense (DD) over conventional scheduling (CS) and equivalence of sequential (SC) vs combination adjuvant chemotherapy (CC) for node-positive breast cancer (CALGB 9741,INT C9741).** *Breast Cancer Res Treat* 2002, **76(suppl 1)**:A15.
4. Aman Buzdar on behalf of ATAC Trialists' Group: **The ATAC trial in postmenopausal women with early breast cancer-updated efficacy results based on a median follow up of 47 months.** *Presented at the 25th San Antonio Breast Cancer Symposium*, San Antonio, Texas, USA, 10–14 December 2002 (abstract 13; new version).
5. The ATAC Trialists Group: **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial.** *Lancet* 2002, **359**:2131-39
6. Sainsbury R: **Beneficial side-effect profile of anastrozole comapred with tamoxifen confirmed by additional 7 months of exposure data: a safety update from the "Arimidex", Tamoxifen, Alone or in Combination (ATAC) trial.** *Breast Cancer Res Treat* 2002, **76(suppl 1)**:A633.
7. Gnant M, Hausmaninger H, Samonigg H, Mlineritsch B, Taucher S, Luschin-Ebengreuth G, Jakesz R: **Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± Zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: results of a randomized multicenter trial.** *Breast Cancer Res Treat* 2002, **76(suppl 1)**:A12.
8. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L: **Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2.** *N Engl J Med* 2001, **344**:783-792.
9. Robert N, Leyland-Jones B, Asmar L, Belt R,Ilegbodu D, Loesch D, Raju R, Valentine E, Sayre R, Albain K, Cobleigh M, McCullouh C, Fuchs L, Slamon D: **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in aptients with HER-2/neu positive advanced breast cancer.** *Breast Cancer Res Treat* 2002, **76(suppl 1)**:A35.
10. Miller KD, Rugo HS, Cobleigh MA, Marcom PK, Chap LI, Holmes FA, Fehrenbacher L, Overmoyer BA, Reimann JD, Vassel AV, Langmuir VK: **Phase III trial of capecitabine (Xeloda) plus bevacizumab (Avastin) versus capecitabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane.** *Breast Cancer Res Treat* 2002, **76(suppl 1)**:A36.
11. Albain K, Elledge R, Gradishar WJ, Hayes DF, Rowinsky E, Hudis C, Pusztai L, Tripathy D, Modi S, Rubi S: **Open-label, phase II, multicenter trial of ZD1839 ('Iressa') in patients with advanced breast cancer.** *Breast Cancer Res Treat* 2002, **76(suppl 1)**:A20.

Correspondence

Alistair Ring, Breast Unit, Department of Medicine, Royal Marsden Hospital, London SW3 6JJ, UK. Tel: +44 207 808 2619; fax: +44 207 376 3918; e-mail: aring@icr.ac.uk