Meeting report

26th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, USA, 3–6 December 2003: update on clinical research

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Abstract

The San Antonio Breast Cancer Symposium is an international meeting dedicated to the translation of advances in cellular and molecular biology of breast disease into clinical improvements in prevention, diagnosis and treatment. This report summarizes the clinical highlights of the 26th annual meeting held in San Antonio, Texas on 3–6 December 2003. Breast care for women will be improved by reports concerning optimal adjuvant hormonal therapy, advances in chemotherapy and a shift in the clinical philosophy of breast cancer care from maximum tolerable treatment to minimum effective therapy.

Keywords: breast cancer, chemotherapy, clinical research, hormone therapy, meeting report

Introduction

Clinicians and scientists from more than 80 countries convened in San Antonio, Texas on 3–6 December 2003 for the 26th annual San Antonio Breast Cancer Symposium. The symposium was directed by C Kent Osborne and Charles A Coltman, Jr. More than 6000 attendees participated in the discussion and presentation of scientific advances, which covered the entire spectrum of breast cancer research including cellular and molecular biology, etiology, prevention, diagnosis and treatment. The present report will focus on the clinical highlights of the meeting. Audiovisual highlights of the symposium are available electronically (http://www.sabcs.org) and abstracts are available online (http://www.abstracts-on-line.com/abstracts/BCS/).

Optimal adjuvant hormonal therapy

Paul Goss, on behalf of the National Cancer Institute of Canada Clinical Trials Group, presented the first evidence that patients with hormone-sensitive, early-stage breast cancer may benefit from sequential hormonal therapy. The investigators randomized 5187 postmenopausal women who had completed 5 years of adjuvant tamoxifen to either letrozole or placebo [1]. At a median follow-up of 2.4 years, the estimated 4-year disease-free survival (DFS) was 93% in the letrozole group and 87% in the placebo group ($P = 0.00008$). This represents a 43% overall reduction in the risk of recurrence. The toxicity assessment showed increased hot flashes, arthralgias and myalgias in the letrozole-treated group and showed increased vaginal bleeding in the placebo group. Patients treated with letrozole had a trend toward a higher incidence of new diagnoses of osteoporosis. Unfortunately, we do not have information regarding the long-term toxicities of this approach, and the study will not yield this information since the majority of patients in the placebo arm have elected to switch to letrozole therapy.

Francesco Boccardo (University of Genoa, Italy) presented the results of a randomized study comparing adjuvant anastrozole after 2–3 years of adjuvant tamoxifen with continued tamoxifen. Both groups of patients were to receive a total of 5 years of therapy. A total of 448 patients with node-positive, estrogen receptor (ER)-positive disease enrolled. At a median follow-up of 3 years, patients switched to anastro-

CI = confidence interval; CVAP = cyclophosphamide, doxorubicin, vincristine and prednisolone; DFS = disease-free survival; ER = estrogen receptor; HR = hazard ratio; PgR = progesterone receptor; TAC = docetaxel, doxorubicin and cyclophosphamide.

zole had fewer clinical events (17 events) than patients remaining on tamoxifen (45 events). Clinical events included local–regional recurrence, distant metastases, second primary cancers (including endometrial cancer) and death from any cause. Each type of clinical event was reduced in the patients switched to anastrozole.

These two studies indicate that there may be benefit in treating early-stage, hormonally responsive breast cancer with sequential hormonal therapy. However, the sequences studied to date are limited to tamoxifen followed by an aromatase inhibitor. Results from the Arimidex, Tamoxifen Alone or in Combination trial have led many women to receive adjuvant aromatase therapy as the initial treatment [2,3]. Mitch Dowsett, on behalf of the Arimidex, Tamoxifen Alone or in Combination investigators, presented an analysis of time to recurrence in the Arimidex, Tamoxifen Alone or in Combination trial according to ER and progesterone receptor (PgR) status. At 47 months of median follow-up, the hazard ratio (HR) for DFS was 0.86 (95% confidence interval [CI] = 0.76–0.99, $P = 0.03$) for the overall study population and was 0.82 (95% CI = 0.70–0.96, $P = 0.014$) in the ER-positive and/or PgR-positive group favoring anastrozole. However, the magnitude of benefit was influenced by the ER and PgR status. The greatest reduction in risk was seen in the ER-positive, PgR-negative group (HR = 0.48, 95% CI = 0.33–0.71). This is statistically different from the HR of 0.82 (95% CI = 0.65–1.03) in the ER-positive and PgR-positive group ($P = 0.05$), and may be a clue to the etiology of tamoxifen resistance.

Clinicians are challenged to predict which hormonal therapy is the optimal adjuvant treatment for an individual patient. Biomarkers are needed to predict responsive disease. Ian Smith and Mitch Dowsett (Royal Marsden Hospital, London, UK) presented data from the multicenter Immediate Preoperative Arimidex Compared to Tamoxifen (IMPACT) trial. This neoadjuvant trial randomized 330 postmenopausal women with ER-positive, invasive, operable breast cancer to receive 3 months of preoperative therapy with anastrozole, tamoxifen, or both. The trial objectives included the assessment of clinical response, the conversion of planned mastectomy to lumpectomy and the assessment of biomarker modulation. While neoadjuvant anastrozole allowed significantly more women previously judged to require a mastectomy to undergo breast-conserving surgery than did tamoxifen (46% versus 22%, $P = 0.03$), the overall response rates were not statistically different (37% versus 36%). The subgroup of patients with Her2-positive tumors was small (34 patients). However, these patients did have a higher response rate with anastrozole therapy than with tamoxifen (58% versus 22%).

Dowsett presented information regarding the impact of neoadjuvant therapy on the modulation of the proliferation marker Ki67. Two hundred and fifty-nine patients had tumor specimens available for analysis corresponding to pretreatment, 2 and 12 weeks post initiation of treatment. Interestingly, all three treatments (anastrozole, tamoxifen and their combination) reduced Ki67 expression with maximal mean reductions after only 2 weeks of therapy. Anastrozole had a significantly greater antiproliferative effect at both time points than did tamoxifen ($P < 0.01$) but the change in Ki67 did not correlate with response to therapy.

These interesting presentations challenge us with many new questions regarding optimal adjuvant hormonal therapy. The woman previously counseled that tamoxifen was the 'gold standard' may now be offered 5 years of adjuvant anastrozole as an alternative and counseled that anastrozole as compared with tamoxifen will result in a further 18% reduction in the relative risk of relapse. Alternatively, planning sequential adjuvant hormonal therapy may be best. Adjuvant tamoxifen followed by adjuvant letrozole resulted in a 43% reduction in the relative risk of recurrence in the study presented by Goss and colleagues [1]. Or possibly, the best alternative is 2–3 years of adjuvant tamoxifen followed by adjuvant anastrozole (associated with 64% reduction in the risk of relapse in the Boccardo study).

Advances in chemotherapy and target therapy

Papers presented at the meeting continue to highlight the improvements in DFS and overall survival that can be achieved in high-risk women when taxanes are added to anthracycline-based therapy. AW Hutcheon presented an update on the Aberdeen trial. Previously published results from this study indicate that even patients who are responding to an anthracycline-based neoadjuvant chemotherapy regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone; CVAP) benefit from switching to docetaxel [4]. One hundred and four patients who responded to neoadjuvant CVAP were randomized to receive four additional cycles of CVAP or four cycles of single-agent docetaxel before surgery. The pathologic complete response rate in patients receiving docetaxel was 34% compared with 16% for those continuing on CVAP. With a median follow-up of 60 months, patients receiving docetaxel had improved DFS (90% versus 72%, $P = 0.04$) and overall survival (97% versus 78%, $P = 0.04$).

Patients with node-positive breast cancer experience greater benefit from adjuvant docetaxel, doxorubicin and cyclophosphamide (TAC) than from 5-fluorouracil, doxorubicin and cyclophosphamide, according to John Mackey who updated previously presented results on behalf of the Breast Cancer International Research Group [5]. At a median follow-up of 55 months, DFS and overall survival favor the TAC arm. TAC resulted in a 28% reduction in the risk of relapse (HR = 0.72, $P = 0.0010$) and a 30% reduction in the risk of death (HR = 0.83, $P = 0.17$). However,

subgroup analysis revealed that the benefit in DFS was statistically significant only in the group with one to three positive nodes. Patients had a reduced risk of death with TAC treatment regardless of the Her2 status of their primary tumors (Her2-positive HR=0.60, Her2-negative HR=0.76). Cardiac toxicity did not seem prohibitive. Congestive heart failure was seen in 1.6% of patients receiving TAC and in 0.5% of those receiving 5-fluorouracil, doxorubicin and cyclophosphamide. One cardiac death was seen in each arm of the study.

Information presented at the meeting may help medical oncologists select which taxane to offer their patients. Stephen Jones (US Oncology, Dallas, TX, USA) presented the results of a multicenter, randomized, phase III comparison of docetaxel versus paclitaxel in 449 women with metastatic breast cancer. Docetaxel and paclitaxel were dosed at 100 mg/m^2 and 175 mg/m^2 every 3 weeks, respectively. Docetaxel was associated with an overall response rate of 32% versus 25% with paclitaxel ($P=0.10$), and the duration of response was significantly increased for the docetaxel group (7.5 months versus 4.6 months, $P<0.05$). Time to progression favored the docetaxel arm (4.6 months versus 3.1 months, $P<0.0001$), as did median overall survival (15.4 months versus 12.7 months, $P=0.03$). This result was seen despite the fact that approximately 25% of patients crossed over to the other taxane after experiencing progressive disease and that the median survival after stopping study of the drug was shorter for patients in the docetaxel arm. This improvement in overall survival came at the expense of greater toxicity. Febrile neutropenia was seen in 15% of those treated with docetaxel but in only 2% of those treated with paclitaxel ($P<0.05$). Nonhematologic toxicity was also greater in the docetaxel arm.

Additional clinical trials are needed to determine whether nanoparticle albumin-bound paclitaxel (ABI-007) represents an important clinical advance. Joyce O'Shaughnessy (US Oncology, Dallas, TX, USA) presented the results of a comparison of ABI-007 (ABRAXANE™) and conventional paclitaxel in 454 patients with metastatic breast cancer. Investigators in this multicenter trial administered ABI-007 without steroid premedication. The drug was well tolerated and patients receiving it had an improved response rate as compared with conventional paclitaxel (21% versus 10%, $P=0.002$) when assessed by independent radiologic review. The time to progression also favored the ABI-007 arm (21.9 weeks versus 16.1 weeks, $P=0.029$).

Jenny Chang (Breast Center, Baylor College of Medicine and The Methodist Hospital, Houston, TX, USA) presented the results of a neoadjuvant study in locally advanced breast cancer, designed to determine the efficacy of single-agent neoadjuvant herceptin, to explore the mechanism of action of herceptin and to determine biomarkers of response. Twenty-seven patients with palpable breast cancers were enrolled and received weekly herceptin as single-agent therapy for 3 weeks. Beginning in week 4, docetaxel was added to the regimen. Tissue specimens were available for study at the following time points: pretreatment, day 1, day 8, day 15 and day 22. None of the patients progressed during the herceptin phase of the study and 26% had a partial response. Proliferation, as assayed by Ki67, did not change with therapy and high Ki67 correlated with resistance to therapy. Apoptosis was statistically increased with therapy even after 1 week (from 2.6% to 4%). Chang believes that the synergism seen with the combination of chemotherapy and herceptin results from the fact that the two agents are targeting different populations of malignant cells.

Changing the model for breast cancer care

Umberto Veronesi presented the William L McGuire Memorial Lecture. His inspiring lecture described the revolutionary change in clinical treatment philosophy from 'maximum tolerable to minimum effective therapy'. Veronesi described the clinical trials that have proven the efficacy of breast-conserving surgery, of sentinel lymph node mapping, of chemoprevention and of her2-targeted therapy. He concluded that "we are achieving a reduction in mortality while preserving a very good quality of life". Veronesi urged patients and clinicians to continue clinical trials evaluating gene expression profiling and partial breast radiation as these techniques may further decrease the amount of therapy required by selected patients.

Advances in breast radiation therapy designed to decrease both the time required to complete treatment and the morbidity associated with it were presented in a mini-symposium. Jayant Vaidya presented preliminary results from the ongoing targeted intra-operative radiotherapy (TARGIT) trial [6]. Frank Vicini discussed the multiple ways in which partial breast radiation can be delivered, and highlighted the upcoming trial planned by the National Surgical Adjuvant Breast and Bowel Project to compare whole breast radiation and three different techniques of partial breast radiation (catheter or balloon [MammoSite] brachytherapy, or three-dimensional conformal external beam radiation).

Conclusion

The 26th San Antonio Breast Cancer Symposium continues to bring together clinical and basic investigators from all over the world. Presentations at this year's meeting expand our treatment options for those who are diagnosed with benign and/or malignant disease. The meeting provides a unique forum with integration of clinical and basic research presentations. Each attendee is challenged to translate the data presented into scientific hypotheses that will further enhance our understanding of the disease.

Competing interests

None declared.

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