San Antonio Breast Cancer Symposium

Conference Review

Making Education Easy

34th Annual San Antonio Breast Cancer Symposium, 6–10 December 2011, San Antonio, Texas, USA

In this review:

Welcome to our review of the 34th Annual San Antonio Breast Cancer Symposium (SABCS), which was held in San Antonio, Texas, from 6–10 December 2011.

The SABCS has been held annually since 1977 and has evolved from a one-day clinical meeting into a five-day symposium integrating clinical, translational, and basic research, with a formal collaboration between clinicians at the Cancer Therapy & Research Center (CTRC) in San Antonio and the American Association for Cancer Research (AACR) since 2007. It now attracts over 8,000 international attendees annually and is a forum, not only for the presentation of major study results, but also for educational reviews and case-based discussions, making it a very valuable meeting for clinicians and scientists alike.

This Review has been created to allow those unable to attend, but who are keen to keep up with evidence-based information and perspectives on progress in breast cancer research, to access a summary of significant clinical studies presented that are likely to affect current practice. Selection and review of the research has been carried out independently by Dr Richard Isaacs, a Medical Oncologist at Palmerston North Hospital, who attended the SABCS.

All SABCS 2011 abstracts may be accessed from http://www.sabcs.org/UserPortal/Documents/Abstract_Book_SABCS_20111215.pdf.

I hope you find the conference review stimulating and I look forward to your feedback.

Kind regards

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Long-term follow up in ABCSG-12: Significantly improved overall survival with adjuvant zoledronic acid in premenopausal patients with endocrine receptor–positive early breast cancer

Authors: Gnant M et al

Summary: Premenopausal women with endocrine-receptor-positive early-stage breast cancer (n=1,803) were randomised to ovarian function suppression with goserelin (3.6 mg q28d) and tamoxifen (TAM; 20 mg/d) or anastrozole (ANA; 1 mg/d) ± zoledronic acid (ZOL;4 mg q6mo) for 3 years. At median follow-up of 76 months, patients receiving ZOL had a significant 27% reduction in the risk of disease-free survival (DFS) events (HR 0.73; Cox p=0.022) and a significant 41% reduction in the risk of death (HR 0.59; Cox p=0.027) vs no ZOL. Multivariate analyses showed a strong interaction between ZOL and patient age, but did not show any interactions between ZOL and ANA/TAM or any classic tumour parameter (e.g., T, N, grade, ER). Among patients >40 years of age (n=1,390) with presumed complete ovarian blockade, ZOL significantly reduced the risk of DFS events by 34% (HR 0.66; Cox p=0.014) and the risk of death by 49% (HR 0.51; Cox p=0.020); however, there were no significant DFS or OS benefits in patients <40 years of age. Currently, all patients have completed 3 years of ZOL and are in the follow-up phase with no reported cases of osteonecrosis of the jaw or renal failure.

Comment: This extended follow-up data of the ABCSG-12 trial has shown persistent benefits from the additional use of zoledronic acid (ZA) in this very good prognosis group of premenopausal ER+ women treated with endocrine manipulation alone. The use of ZA not only maintained an absolute disease-free survival (DFS) advantage of 4%, at four years after stopping all therapy, but also showed a modest overall survival advantage of 1.6%. The advantages appeared confined to patients who commenced therapy aged >40 years, in whom ovarian ablation is presumably more effective than in younger women, generating a lower hormonal environment. The 6-monthly regimen of ZA also induced minimal toxicity, with no reports of osteonecrosis of the jaw using this schedule. While the survival was already very good in this subgroup of women, the additional gains demonstrated here should be discussed in those premenopausal ER+ women not receiving chemotherapy.

Session Info: General Session I, December 6, 2011. Abstract S1-2.

Long-term survival outcomes amongst postmenopausal women with hormone receptor-positive early breast cancer receiving adjuvant letrozole and zoledronic acid: 5-year follow-up of ZO-FAST

Authors: de Boer R et al

Summary: This study involved 1,065 postmenopausal women with hormone receptor-positive early breast cancer receiving letrozole (LET; 2.5 mg qd × 5 yr) with a BMD T-score ≥–2 who were randomised to zoledronic acid (ZOL 4 mg every 6 months) either as immediate (IMZOL; n=532) or delayed treatment (DZOL; initiated for post-baseline T-score <–2 or nontraumatic/asymptomatic fracture; n=533). At 60 months' follow-up, the risk of a disease-free survival (DFS) event was significantly reduced with IMZOL by 34% versus DZOL (HR 0.66; 95% CI, 0.44 to 0.97; p=0.034). Among women who were postmenopausal for >5 years or >60 years old at study entry (n=670), IMZOL was associated with a 37% relative risk reduction in risk of recurrence (HR 0.63; 95% CI, 0.39 to 1.01; p=0.052) and significantly prolonged overall survival (HR 0.50; 95% CI, 0.27 to 0.92; p=0.022) versus DZOL. During 5 years of treatment, osteonecrosis of the jaw (ONJ) was reported in 4/669 patients (0.6%) who received ZOL, and there was no increase in renal adverse events (AEs) among ZOL recipients. The overall AE profiles were consistent with the known safety profiles of both study drugs.

Comment: This study explored the timing of zoledronic acid (ZA) in postmenopausal women receiving letrozole as adjuvant therapy with median follow-up extended to 5 years, rather than having a systemic therapy-alone control group. There were clear gains in terms of bone density using a 6-month schedule of ZA with early use, with an increase of 10% in lumbar spine measurements, and a modest DFS benefit of 3.6% was also seen for early vs later use of ZA, which was more apparent in those at least 5 years' postmenopausal. Only a small number of cases of ONJ were seen in this study with its longer duration of use.

This study suggests that if a bisphosphonate is to be used, there are clear advantages in maintaining bone health from early use and more modest advantages in preventing relapse, while the subgroup of postmenopausal women had an apparent survival advantage.

Session Info: General Session I, December 6, 2011. Abstract S1-3.

Partial breast brachytherapy is associated with inferior effectiveness and increased toxicity compared with whole breast irradiation in older patients

Authors: Smith GL et al

Summary: These researchers evaluated Medicare claims of 130,535 women aged >66 years who were diagnosed with incident-invasive breast cancer between 2000 and 2007 and were treated with conservative surgery followed by accelerated partial breast brachytherapy (APBI-brachy) alone or whole-breast irradiation (WBI). The use of APBI-brachy increased over time, from <1% of patients treated in 2000 to 13% of patients in 2007 (p<0.001 for trend). Patients treated with APBI-brachy were less likely to have axillary lymph node involvement or to have received chemotherapy, and were more likely to be older, White, and have comorbid illness. At 5 years, the risk of mastectomy was 4% in patients treated with APBI-brachy versus 2.2% in the WBI cohort (p<0.001). Multivariate analysis revealed that APBI-brachy was associated with a two-fold higher risk for subsequent mastectomy (HR 2.14; 95% CI, 1.83 to 2.52; p<0.001), with more acute complications, including a higher risk of hospitalisation (9.6% vs 5.7%; p<0.001) (adjusted OR 1.71; 95% CI, 1.58 to 1.86) and infection (8.1% vs 4.5%; p<0.001) (adjusted OR 1.85; 95% CI 1.69 to 2.02; p<0.001). In addition, APBI-brachy was associated with a higher 5-year cumulative incidence of radiation-related side effects including rib fracture (4.2% vs 3.6% in WBI), fat necrosis (9.1% vs 3.7%) and breast pain (14.9% vs 11.7%) (p<0.001 for all comparisons), but also with a lower incidence of pneumonitis (0.1% vs 0.8%; p<0.001).

Comment: There has been much recent interest in the use of partial breast irradiation (brachytherapy), despite a lack of prospective data comparing it to whole breast irradiation. This retrospective study is the largest cohort study to date comparing the two modalities. Due to the large numbers studied, the differences in outcome were significant for assumed local recurrence and toxicities, but the absolute differences were small at <2% for recurrence. There was a more marked difference in toxicity rates, particularly delayed fat necrosis, indicating the importance of awaiting the mature results of large randomised trials before adopting new therapies as a standard of care.

Session Info: General Session 2, December 7, 2011. Abstract S2-1.

Next generation sequencing reveals co-activating events in the MAPK and PI3K/AKT pathways in metastatic triple negative breast cancers (mTNBC)

Authors: O'Shaughnessy J et al

Summary: This group harvested tissue from 14 patients with mTNBC and analysed them with 'deep whole genome' and transcriptome sequencing to identify mutations to guide therapeutic targeting within available phase I/II clinical trials. They were able to identify point mutations, indels, and structural events including translocations. RNA sequencing was also performed to enable deep differential expression analysis, isoform expression analysis, and fusion transcript detection. All patients' cancers analysed had alterations that would activate the MAPK pathway, but through various mechanisms in different patients. These included *BRAF* amplification and overexpression, *NF1* homozygous deletion, and consistent *IQGAP3* overexpression. Furthermore, all patients' cancers also had mutations that would activate the PI3K/AKT pathway including *PTEN* homozygous deletion or down-regulation, consistent *INPP4B* downregulation, *FBXW7* homozygous deletion, and *ERAS* overexpression. They are now using the information to prioritise therapeutic targeting in their heavily pre-treated patients.

Comment: This extraordinary presentation was a look into the future, demonstrating the power of 'next generation' deep whole genome and transcriptome sequencing for individual patient tumours. The results for 14 patients were presented, in whom the technology was able to identify dominant mutations in critical signalling pathways, predominantly affecting the MAPK and PI3K/AKT pathways, but by different mechanisms. The data was used to select different targeted therapies and one patient in particular had a dramatic response to targeting of MEK and AKT. Clearly such technology will not be available for clinical use soon, but it shows not only the heterogeneity of tumour growth regulation, but also the potential to truly individualise therapy.

Session Info: General Session 3, December 7, 2011. Abstract S3-5.

Independent commentary by Dr Richard Isaacs,

a Medical Oncologist at Palmerston North Hospital and member of the ANZ Breast Cancer Trials Group, Chair of the NZ Association of Cancer Specialists Breast Cancer Special Interest Group from 2007 to 2011 and an invited member on the New Zealand Breast Cancer Guideline Implementation Group. He is also Vice President of the Palmerston North Medical Research Foundation.

Update of International Breast Cancer Study Group trial 23-01 to compare axillary dissection versus no axillary dissection in patients with clinically node negative breast cancer and micrometastases in the sentinel node

Authors: Galimberti V et al

Summary: Outcomes from a median 57-month follow-up were presented for the IBCSG Trial 23-01, which was designed to determine whether axillary dissection (AD) is necessary in patients with minimal sentinel node (SN) involvement (defined as one or more micrometastatic [≤2 mm] SNs) and tumours ≤5 cm. This trial randomised 934 such patients to axillary dissection or no further axillary surgery. At study entry, mean patient age was 54 years, 56% of the patients were postmenopausal, 67% had tumours <2 cm, 7% had tumours ≥3 cm, and 26% had grade 3 disease. Five-year disease-free survival (DFS) rates were 87.3% for AD vs 88.4% for the no-dissection group; regional relapse rates were 0.2% vs 1.1%, respectively; 5-year overall survival (OS) rates were 98% in each arm. Lymphoedema was observed in 13% of the AD group and in 4% of the no-dissection group; corresponding rates for motor neuropathy were 8% and 4%, respectively.

Comment: This trial accrued patients slowly over almost 10 years and had a lower than expected event rate, so was closed early. Patients were predominantly postmenopausal and had hormone receptor-positive disease, with most tumours <2 cm in size. As expected there was greater morbidity in those having axillary node dissection (AND) and, like the Z0011 trial, there was absolutely no evidence of a DFS advantage for an axillary dissection in these patients with minimal known axillary disease. These results add further weight to the move to avoid AND in better risk patients with limited axillary involvement. The number receiving mastectomy was small in this study (and not allowed in Z0011), making conclusions on management in this group premature. In the setting of wide local excision, it is seen as critical that patients have tangential breast radiotherapy and systemic adjuvant therapy to minimise risks of loco-regional relapse.

Session Info: General Session 3, December 7, 2011. Abstract S3-1.

Everolimus for postmenopausal women with advanced breast cancer: updated results of the BOLERO-2 phase III trial

Authors: Hortobagyi GN et al

Summary: Study outcomes from an additional 5 months' follow-up were presented for the BOLERO-2 trial, in which 724 patients with estrogen receptor-positive (ER+) advanced breast cancer refractory to letrozole or anastrozole were randomised to receive exemestane 25 mg/day with or without everolimus 10 mg/day. According to local investigator assessment, progression-free survival (PFS) was more than doubled in the everolimus treatment group to a median 7.4 months versus 3.2 months in the exemestane-alone group (HR 0.44; 95% CI, 0.36 to 0.53; $p<1 \times 10^{-16}$), 12-month estimates of PFS were 31% and 10%, respectively. When assessed by a central radiology review, everolimus prolonged PFS to a median 11.0 months versus 4.1 months with exemestane alone (HR 0.36; 95% CI, 0.28 to 0.45; $p<1 \times 10^{-16}$), 12-month estimates were 48% and 18%, respectively. Response rates and clinical benefit rates were also higher for the everolimus arm (12.0% vs 1.3% and 50.5% vs 25.5%, respectively). More adverse events occurred in the everolimus arm, but the increased toxicities did not affect quality of life.

Comment: It is clear that the development of hormone resistance is linked to activation of the PI3K pathway with subsequent activation of mTOR signalling. These data show the effects of adding the mTOR inhibitor everolimus to exemestane in patients with prior aromatase inhibitor therapy for ER+ metastatic disease, with a median follow-up of 12.5 months. There was a profound improvement in PFS increasing from 4.1 to 11 months on central review, despite the objective response rate being relatively low at 12 vs 1.3%. There was also some evidence of a bone-protective effect from everolimus and there was no compromise of quality of life using combination therapy. This class of drugs offers great potential for improving management of this patient group.

Session Info: General Session 3, December 7, 2011. Abstract S3-7.

Results of a randomized, double blind, multi-centre, placebo-controlled study of adjuvant lapatinib in women with early-stage ErbB2-over-expressing breast cancer

Authors: Goss P et al

Summary: The TEACH (Tykerb® Evaluation After Chemotherapy) trial randomised 3,161 patients who completed neoadjuvant chemotherapy without trastuzumab for HER2-positive stage I-IIIc breast cancer without evidence of recurrence to receive lapatinib 1,500 mg/day or placebo for 1 year, without restriction of time after chemotherapy. At a median 4-year follow-up, the hazard ratio for disease-free survival (DFS) in lapatinib compared with placebo was 0.83 (95% CI, 0.70 to 1.00; p=0.053; events lapatinib=210, placebo=264). In pre-planned Cox regression subgroup analyses, a significant benefit was seen in favour of lapatinib in the HR-negative disease cohort (n=1,288; HR 0.68; 95% CI, 0.52 to 0.89) and in patients randomised within 1 year of diagnosis (n=647; HR 0.70; 95% CI, 0.50 to 0.99). Symptomatic CNS recurrences were delayed and fewer with lapatinib (13 patients) versus placebo (21 patients) (HR 0.65; 95% CI, 0.33 to 1.28). With 6% of deaths reported (92 lapatinib, 97 placebo), no trend in an overall survival difference was noted but analysis remains immature. In an exploratory analysis of 2,490 centrally confirmed FISH+ patients, DFS significantly favoured lapatinib (HR 0.82; 95% CI, 0.67 to 1.00; p=0.04). Adverse events were more common with lapatinib than placebo (92% vs 76%); diarrhoea (61% vs 16%) and rash (59% vs 15%).

Comment: The TEACH study had an unusual design with adjuvant lapatinib or placebo offered to patients who had not received prior adjuvant trastuzumab, at any time after primary therapy for HER2-positive breast cancer. Only 647 patients received lapatinib within 12 months of primary therapy, but the placebo arm showed a relatively constant rate of relapse at 3%/year over a 10-year period, which supported the concept of later use. Benefit was only seen on subgroup analysis of those who commenced lapatinib early, in those confirmed as HER2-positive on central testing and in hormone receptor-negative disease. Given this modest result, and considering the data from metastatic studies, the preferred place of lapatinib may be as combination HER2-directed therapy. This will become apparent as results of the ALTTO trial are released.

Session Info: General Session 4, December 8, S4-7.

A quantitative multigene RT-PCR assay for predicting recurrence risk after surgical excision alone without irradiation for ductal carcinoma in situ (DCIS): A prospective valdiation study of the DCIS score from ECOG E5194

Authors: Solin LJ et al

Summary: These authors developed a modification of the Onco*type* DX® assay to look specifically at the risks of an ipsilateral breast event (IBE) after surgical treatment alone of DCIS. They used the data from ECOG E5194, which reported the 5-year rates of local recurrence in 670 eligible patients with DCIS treated with surgical excision (≥3 mm negative margins) without irradiation, 228 of whom received tamoxifen. They had shown on standard analysis that risk varied with age, grade, and lesion size (Hughes et al. J Clin Oncol 2009;27:5319).They performed the Onco*type* DX® assay on specimens from 327 patients (49% of the parent study). Recurrence Score® (RS) was calculated using the published algorithm, while a new, prespecified DCIS Score™ was designed to predict recurrence using an optimised gene expression algorithm. 46 patients had an IBE (as either DCIS [n=20] or invasive cancer [n=26]). Median follow-up was 8.8 years. The 10-year IBE rates were 15.4% for low/intermediate grade DCIS and 15.1% for high-grade DCIS (as determined by central pathology review), and for invasive IBE, 5.6% and 9.8%, respectively. Comparison between local and expert grading showed substantial disagreement. Continuous DCIS Score was significantly associated with IBE (HR 2.34 per 50 units; 95% CI, 1.15 to 4.59; p=0.02) when adjusted for tamoxifen use (prespecified primary analysis) and with invasive IBE (HR 3.73; 95% CI, 1.34 to 9.82; p=0.01). DCIS Score was significantly associated with outcome when evaluated by the prespecified risk groups. Similar results were observed with and without adjustment for tamoxifen use or for negative margin width. Features associated with IBE in multivariate models included menopausal status (HR 0.49; 95% CI, 0.27 to 0.90; p=0.02), tumour size (HR 1.52 per 5 mm; 95% CI, 1.11 to 2.01; p=0.01), and continuous DCIS Score (HR 2.41; 95% CI, 1.15 to 4.89; p=0.02). The standard RS, which is calculated using thresholding of many genes unlike the DCIS Score, was not associated with IBE or invasive IBE (p>0.6).

Comment: This assay is modified from the Onco*type* DX platform, selecting 12 genes to predict local recurrence risk in women who have local excision of DCIS without radiotherapy. The stated intention of the test is to identify those women who might avoid local radiotherapy. It appeared to predict more accurately for IBE than standard clinical factors, but it does not predict the extent of benefit from radiotherapy in an individual patient, including those at low risk and will cost US$4,175 per test when available from early 2012. It is an option to discuss in patients anxious to avoid radiotherapy, but is unlikely to change New Zealand practice in the short term.

Session Info: General Session 4, December 8, S4-6.

A phase III, randomized, double blind, placebo-controlled trial to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in patients with previously untreated HER2-positive metastatic breast cancer (CLEOPATRA)

Authors: Baselga J et al

Summary: This study randomised 808 patients with previously untreated HER2-positive metastatic breast cancer to receive docetaxel 75–100 mg/m^2 every 3 weeks for 5 cycles or until progression plus trastuzumab 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks with or without pertuzumab 840 mg loading dose followed by 420 mg every 3 weeks. A total of only 46% had received chemotherapy and 10% trastuzumab as prior adjuvant therapy. Independently assessed progression-free survival (PFS) improved from 12.4 to 18.5 months for the pertuzumab arm (HR 0.62; 95% CI, 0.51 to 0.75; p≤0.0001). Similar benefits were seen in all subgroups, with the possible exception of those with non-visceral metastases. Response rates also increased from 69 to 80%. Rates of overall survival also appeared to be increased but statistically the results did not cross the prespecified level for interim analysis.

Comment: These results were heralded as a further major breakthrough in the management of metastatic HER2-positive breast cancer, with the PFS benefits being the largest reported in this population, with an additional likely overall survival benefit. The only caveats of such profound results are that they were obtained from a population with a low incidence of exposure to prior adjuvant trastuzumab and chemotherapy, factors which may influenced the tumour sensitivity and which would have been received by most New Zealand women now presenting with metastatic disease. The cost of supplying the drug, when it is available, is likely to be large and apart from the less marked benefits seen in those with non-visceral metastases, there are no obvious subgroups for whom treatment could be restricted to on the basis of these results, which might allow selective funding.

Session Info: General Session 5, December 9, S5-5.

Patient-reported predictors of early treatment discontinuation: NCIC JMA.27/E1Z03 quality of life study of postmenopausal women with primary breast cancer randomized to exemestane or anastrozole

Authors: Wagner LI, Zhao F

Summary: This study aimed to identify predictors of treatment discontinuation. The researchers assessed patient-reported outcomes from a sample of 371 women randomised to anastrozole and 315 randomised to exemestane as adjuvant hormonal therapy. Participants completed the 56-item Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES) pre-treatment and at months 3, 6, 12 and 24 to assess breast cancer-specific concerns, side effects of hormonal treatments and health-related quality of life (HRQL). Treatment-related symptoms, as assessed by 23 items from the FACT-ES, did not differ between treatment arms at months 3, 6, 12 and 24 and the timeline change of treatment-related symptoms was similar between treatment arms (p=ns). HRQL was significantly impacted by decreased libido, weight gain, feeling bloated, breast sensitivity, mood swings, irritability, joint pain, nausea and feeling bothered by treatment side effects (p<0.001). A total of 248 participants were off-treatment by 4.1 years. In an analysis adjusted for other symptoms, demographic and disease characteristics, the likelihood of discontinuing treatment early increased by 29% when the severity of being bothered by side effects at baseline increased by 1 point (HR 1.29; 95% CI, 1.09 to 1.54). At baseline, patients with prior treatments or taking more medicines reported being more bothered by side effects (p<0.001). Increased joint pain in the first 3 months after treatment was also associated with an increased likelihood of discontinuing treatment early (HR 1.13; 95% CI, 1.01 to 1.28).

Comment: This patient group reported a high incidence of side effects on both aromatase inhibitors, leading to an early drug discontinuation in a significant proportion and potentially compromising clinical outcome. Patient-reported symptoms in this study were 5-fold higher than those reported by clinicians in the same patients, indicating a major under-assessment of drug toxicity by clinicians. Those who presented with side effects from prior treatment were at particular risk of discontinuation. This emphasises the need for careful assessment of symptoms at treatment commencement, attempts to improve any side effects and the need for close monitoring to allow optimal therapy.

Session Info: General Session 6, December 9, S6-2.

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