San Antonio Breast Cancer Symposium

Conference Review

Making Education Easy

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In this issue:

Welcome to the San Antonio Breast Cancer Symposium Review,

a locally focused summary of some high-quality papers in basic, translational, and clinical cancer research presented at this prestigious and comprehensive scientific meeting in December 2009.

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 future practice. Selection and review of the research is carried out independently by Dr Richard Isaacs, a Medical Oncologist at Palmerston North Hospital, who attended the SABCS.

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

Kind Regards,

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Five years of exemestane as initial therapy compared to 5 years of tamoxifen followed by exemestane: the TEAM trial, a prospective, randomized, phase III trial in postmenopausal women with hormone-sensitive early breast cancer

Authors: Rea D et al

Summary: Between 2001 and January 2006, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study randomised 9775 postmenopausal women with HR+ early breast cancer to receive open-label exemestane 25 mg/day (n=4898) or tamoxifen 20 mg/day (n=4868), for 5 years. In 2004, all women who were initially receiving tamoxifen were switched to exemestane after 2.5–3 years. All women had undergone surgery with curative intent for invasive breast cancer, 99% of patients were ER+ and/or PgR+, 50% were node-negative, and 36% had received chemotherapy. The trial's primary endpoint was a comparison of disease-free survival (DFS) at 5 years for women initially receiving exemestane versus those who switched from tamoxifen to exemestane. At a median 5.1-year follow-up, there were no between-group differences (HR 0.97; p=0.604). Similarly, an analysis of results by nodal status revealed a virtual overlap for the events curve between women who were node-negative and those who were node-positive.

Comment: This is the first trial adequately powered to prospectively determine whether the hormonal 'switch approach' had an advantage over an aromatase inhibitor alone, as suggested by the 2006 EBCTG Overview analysis. The TEAM trial, however, showed no difference between either approach in DFS or OS at any time, including the first two years when there was a direct comparison of tamoxifen with exemestane, while the toxicity data was as expected for either agent. Clinicians now have a strong evidence base to select either approach, with selection determined predominantly by issues of bone health and individual side effect concerns.

Session Info: General Session I, December 10, 2009. Abstract 11.

http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_1839

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Outcomes of women who were premenopausal at diagnosis of early stage breast cancer in the NCIC CTG MA17 trial

Authors: Goss PE et al

Summary: In the MA17 trial, adjuvant letrozole after 5 years of tamoxifen markedly reduced the risk of recurrence in women with ER+ early-stage breast cancer and improved overall survival in women with node-positive disease. This study discusses outcomes for those women who were premenopausal at initial diagnosis and in whom subsequent menopause, prior to randomisation, may have influenced their outcome on extended adjuvant letrozole. At primary diagnosis, 889 women were identified as premenopausal and 4277 as postmenopausal. A statistically significant interaction between treatment and menopausal status was observed for disease-free survival (DFS) (p=0.02); premenopausal status was associated with significantly better DFS (HR 0.25) on letrozole treatment than postmenopausal status (HR 0.69).

Comment: This was a subgroup analysis of women who were premenopausal at diagnosis, but who became postmenopausal after chemotherapy, elective oophorectomy, or during the five years of tamoxifen administration. The results showed an even greater benefit in this group than in women who were already postmenopausal at primary diagnosis. While numbers were small, DFS benefits continued to be seen even in women who commenced letrozole more than a year after stopping tamoxifen. This data supports women with HR+ breast cancer who were premenopausal at primary diagnosis, and have received 5 years of tamoxifen and become postmenopausal, being offered sequential letrozole for another 5 years.

Session Info: General Session I, December 10, 2009. Abstract 13.

http://tinyurl.com/y8tnu3c

Alcohol and breast cancer survival in a prospective cohort study

Authors: Kwan ML et al

Summary: This assessment of the association between alcohol consumption (overall and type) and breast cancer recurrence and overall mortality used data from 1898 early-stage breast cancer survivors participating in the Life After Cancer Epidemiology (LACE) Study. A total of 275 breast recurrences and 232 deaths were confirmed as of 21 October 2008. Compared to little or no alcohol consumption (≤0.5 g/day), consuming ≥6 g/day was associated with an increased risk of recurrence. Among the drinkers (50% of the cohort), wine was the most frequently consumed beverage (90%), followed by liquor (43%) and beer (36%). The elevated risk was primarily observed among wine drinkers who had ≥2 servings per day compared to none. Risk of overall death was also increased among women who consumed ≥6 g/day. The increased risk of recurrence was greater among postmenopausal women and women with ER- tumours.

Comment: This was a questionnaire study of the effect of alcohol intake on breast cancer recurrence and survival, rather than its better known effects on developing breast cancer, with feedback received yearly, commencing 2 years from diagnosis. There was a trend (of borderline statistical significance) for women consuming >2 glasses of wine/day to have higher recurrence rates and for women maintaining consumption of >1/2 unit of any alcohol/day having higher breast cancer mortality. Risks appeared greater (and were statistically significant) in the subgroups of postmenopausal women and those who were overweight/obese and consumed >2 glasses wine/day. While the data is not definitive, and can be confounded by other lifestyle factors, breast cancer survivors should be cautioned against maintained high alcohol consumption, particularly in the higher risk groups mentioned above.

Session Info: General Session I, December 10, 2009. Abstract 17.

http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_2214

Effect of obesity on prognosis after early breast cancer

Authors: Ewertz M et al

Summary: These researchers examined the influence of obesity on breast cancer recurrence and mortality in relation to adjuvant treatment, using health information from the Danish Breast Cancer Co-operative Group database that included age and menopausal status at diagnosis, tumour size, number of lymph nodes removed, number of positive lymph nodes, deep fascia invasion, histological type, malignancy grade, estrogen receptor status, treatment regimen, and protocol version, from 18,967 women in whom BMI data were available (35% of the women followed). Women with higher BMIs had more advanced disease at diagnosis, and were more often older and postmenopausal compared with those who had a BMI <25. On follow-up there was no difference in locoregional relapse on multivariate analysis, but the risk of distant metastases increased with increasing BMI after 3 years of follow-up. Throughout the 30-year follow-up, a high BMI was associated with an increased risk of dying from breast cancer. Adjuvant treatment appeared less effective in those with BMI >30.

Comment: This is a unique Scandinavian study with extensive data on a large number of patients treated in a very standard fashion, allowing exploration of lifestyle factors. Increasing body weight clearly has delayed adverse effects on outcome, probably due to secondary hormonal factors, and those who have a BMI >30 at diagnosis are particularly at risk. Studies of early intervention with diet and exercise programmes during adjuvant therapy are critical to see if these effects can be negated.

Session Info: General Session I, December 10, 2009. Abstract 18.

http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_937

Independent commentary by Dr Richard Isaacs, Medical Oncologist, Palmerston North Hospital.

Research Review publications are intended for New Zealand health professionals

Oral bisphosphonate and breast cancer: prospective results from the Women's Health Initiative (WHI)

Authors: Chlebowski RT et al

Summary: Data were re-analysed from 151,592 postmenopausal women enrolled in the WHI, to investigate associations between oral bisphosphonates and invasive breast cancer. To control for any potential difference in bone mineral density (BMD) between bisphosphonate users and non-users, this study used a 10-item hip fracture prediction model that did not incorporate BMD against the 10,296 WHI participants who had baseline total hip BMD measurements. A total of 2216 women were receiving oral bisphosphonates at entry (90% alendronate, 10% etidronate). After a mean 7.8 years of follow-up, the incidence of invasive breast cancer was reduced by 32% among bisphosphonate users compared to non-users (64 cases vs 5092 cases; $p<0.01$) and the incidence of ER+ breast cancer was reduced by 30% ($p=0.02$). In addition, there was a reduction in the risk of ER- breast cancer among bisphosphonate users (HR 0.66), but this was not statistically significant ($p=0.27$).

Comment: This study attempted to tease out the effects of oral bisphosphonates alone on the incidence of breast cancer in postmenopausal women. Studying the WHI database they excluded patients with prior breast cancer, tamoxifen or roloxifene use and cohorts were matched using a hip fracture prediction model, to try and remove effects of bone density alone.

There was a lower rate of breast cancer seen in bisphosphonates in users, although DCIS was more common in this group. Vitamin D levels were accounted for on multivariate analysis, but other factors including actual incidence and type of HRT use were more difficult to analyse and the study must be considered as hypothesis-generating only at this stage.

Session Info: General Session II, December 10, 2009. Abstract 21.

http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_443

A comparison of denosumab versus zoledronic acid for the prevention of skeletal-related events in breast cancer patients with bone metastases

Authors: Stopeck A et al

Summary: This trial included 2046 patients with breast cancer and bone metastases who were randomised to either subcutaneous denosumab 120 mg or intravenous zoledronic acid 4 mg every 4 weeks. Compared with zoledronic acid, denosumab significantly delayed the time to first on-study skeletal-related event (SRE), defined as pathological fracture, radiation to bone, surgery to bone, or spinal cord compression (HR 0.82; $p<0.0001$ noninferiority; $p=0.01$ superiority) and the time to first and subsequent on-study SRE (rate ratio 0.77; $p=0.001$). Denosumab also significantly delayed the time to first radiation to bone (HR 0.74; $p=0.01$) and the time to first on-study SRE or hypocalcaemia of malignancy (HR 0.82; $p=0.007$). Denosumab reduced the mean skeletal morbidity rate compared with ZA (0.45 vs 0.58; $p=0.004$). The total number of SREs was 491 events for denosumab and 623 events for ZA. At 34 months, there were fewer patients with at least 1 on-study SRE in the denosumab arm than in the zoledronic acid arm (30.7% vs 36.5%).

Comment: Denosumab is a novel compound interacting via RANK ligand to block bone resorption. Its use showed an improvement in all parameters analysed and it appeared better tolerated than zoledronic acid, but there was no difference in survival or disease progression. Importantly, osteonecrosis of the jaw was seen with both zoledronic acid and denosumab (1.4 and 2.0% respectively), but all those affected did have risk factors for ONJ. The optimal frequency of administration has yet to be determined and it is not yet available in New Zealand, but it may well become an important agent in maintaining bone health in breast cancer patients.

Session Info: General Session II, December 10, 2009. Abstract 22.

http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_1966

Adjuvant tamoxifen treatment outcome according to cytochrome P450 2D6 (CYP2D6) phenotype in early stage breast cancer: findings from the International Tamoxifen Pharmacogenomics Consortium

Authors: Goetz MP et al

Summary: This report details the ongoing data collection of the International Tamoxifen Pharmacogenomics Consortium concerning the relationship between CYP2D6 phenotype (combined genotype and medication) and clinical outcomes of women with early-stage ER+ invasive breast cancer treated with adjuvant tamoxifen. Individual patient data including tumour characteristics, genotype, medication data, and recurrence information were requested from all published and non-published reports of clinical outcomes related to CYP2D6 and deposited at PharmGKB. CYP2D6 genotype was available for the following null (*3, 4, 5 and 6) and IM (*10, 17 and 41) alleles. This report presents data on 2880 patients from 6 centres. In these patients there was no correlation between CYP2D6 phenotype and disease outcome in this study.

Comment: There has been much concern recently about possible lack of benefit of tamoxifen in those with CYP2D6 mutations. This study group obtained individual patient data from a disappointingly small proportion of tamoxifen studies, ultimately with only 6 sites contributing. There was no significant effect of CYP2D6 phenotype seen on relapse or survival in the patients studied, but lack of covariate data (e.g. size, grade) and a lack of complete information on the use of CYP2D6 inhibitors limits the conclusions. The group continues to attempt to accumulate a more complete, global analysis.

Session Info: General Session III, December 11, 2009. Abstract 33.

http://tinyurl.com/y9eh4ys

Final overall survival (OS) results from the randomised, double-blind, placebo-controlled, phase III AVADO study of bevacizumab (BV) plus docetaxel (D) compared with placebo (PL) plus D for the first-line treatment of locally recurrent (LR) or metastatic breast cancer (mBC)

Authors: Miles DW et al

Summary: Final overall survival results are presented from the phase III multinational AVADO trial, which included 736 patients with HER2-negative locally recurrent or metastatic breast cancer and no central nervous system metastases to first-line treatment with either docetaxel 100 mg/m^2 plus placebo, docetaxel plus bevacizumab 7.5 mg/kg or docetaxel plus bevacizumab 15 mg/kg. Docetaxel was administered once every 3 weeks for ≤9 cycles. Bevacizumab or placebo was given once every 3 weeks until disease progression or unacceptable toxicity. Primary analysis results after a median 10.2 months of follow-up showed that adding bevacizumab to docetaxel significantly improved progression-free survival without affecting toxicity. However, there was no between-group difference in median survival (range 30–32 months).

Comment: This trial produced a modest benefit in progression-free survival for patients treated with docetaxel and high-dose bevacizumab. The treated patient group had 80% ER+ disease and thus a relatively long predicted survival, with multiple subsequent lines of therapy available for this group. Crossover was allowed and 37% of the placebo group received bevacizumab as second-line therapy. As might be expected, overall survival was not affected, possibly due to these factors. A greater benefit from bevacizumab at lower expense would be needed to incorporate this drug into standard first-line therapy at this stage.

Session Info: General Session IV, December 11, 2009. Abstract 41.

http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_893

SOLTI-0701: a multinational double-blind, randomized phase 2b study evaluating the efficacy and safety of sorafenib compared to placebo when administered in combination with capecitabine in patients with locally advanced or metastatic breast cancer (BC)

Authors: Baselga J et al

Summary: Results are presented from the SOLTI-0701 phase IIb trial investigating the efficacy and safety of sorafenib in combination with capecitabine for HER2-negative locally advanced or metastatic breast cancer (mBC). A total of 229 such patients were randomised to capecitabine (1000 mg/m^2, orally, twice daily for 14 of every 21 days) with placebo or in combination with sorafenib (400 mg, orally, twice daily, continuously). When used as a first-line therapy, median progression-free survival was 7.4 months in the combination treatment group, compared with 4.1 months for capecitabine alone (HR 0.498; p=0.0032). In second-line therapy, sorafenib plus capecitabine remained significantly superior to capecitabine alone (5.7 vs 4.1 months, HR 0.65; p=0.0339). Combination treatment was not associated with any new toxicities.

Comment: The combination of sorafenib with capecitabine produced modest improvements as both first- and second-line therapy in breast cancer. The incidence and severity of hand-foot syndrome (HFS), however, was breathtaking! In the combination arm 45% had >Grade III HFS compared to 13% in the capecitabine arm. The incidence of HFS was additive, rather than there being a synergistic interaction and resulted in 90% of patients having dose changes. Importantly, this study did not assess quality of life. It would seem that lower doses of both drugs will need to be used if these drugs are used in combination and QOL studies are mandatory before the combination is introduced.

Session Info: General Session IV, December 11, 2009. Abstract 45.

http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_27

Updated survival analysis of a randomized study of lapatinib alone or in combination with trastuzumab in women with HER2-positive metastatic breast cancer progressing on trastuzumab therapy

Authors: Blackwell KL et al

Summary: Updated overall survival (OS) analyses are reported for study EGF104900, which showed a trend in OS favouring the combination of lapatinib plus trastuzumab over lapatinib alone in women with HER2-positive metastatic breast cancer (mBC) progressing on prior trastuzumab- containing regimens (median number of 3). The women were randomised to receive either lapatinib 1500 mg once daily (n=148) or lapatinib 1000 mg once daily in combination with trastuzumab 2 mg/kg (after a 4-mg/kg loading dose) (n=148). If objective disease progression occurred on or after 4 weeks of lapatinib alone, crossover to the combination arm was permitted. Of the women randomised to lapatinib alone, 52% crossed over to the combination arm. At data cut-off for updated OS, 218 deaths (74%) had occurred. A statistically significant OS benefit was observed for combination treatment compared with lapatinib alone (60.7 weeks vs 41.4 weeks; HR 0.74; p=0.026) and this survival benefit was maintained after adjusting for baseline prognostic factors (HR 0.71; p=0.012). A trend toward a clinically relevant 25% reduction in risk of death (p=0.080) was also observed after adjusting for crossover.

Comment: The continued use of trastuzumab in combination with lapatinib after disease progression on trastuzumab-based therapy is supported by laboratory data showing the two agents are synergistic and provide optimal Her2 inhibition. Crossover from single-agent lapatinib to combination therapy was allowed in this study, but despite this, a significant increase in PFS and OS were seen in the primary combination arm, with a 26% reduction in the relative risk of dying, equating to a 4.5-month median increase in survival. These results support use of the combination in the ALTTO adjuvant study, but a positive funding decision for the use of these expensive agents in New Zealand will no doubt require additional data.

Session Info: General Session V, December 12, 2009. Abstract 61.

http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_2086

Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients: BCIRG 006 study

Authors: Slamon D et al

Summary: Results are reported for 3222 HER2-positive breast cancer patients who received standard anthracycline-based chemotherapy (doxorubicin, cyclophosphamide, docetaxel; n=1072) or the same combination with trastuzumab (n=1076), or docetaxel, carboplatin and trastuzumab (n=1074). At 65 months' follow-up, disease-free survival (DFS) was 84% with the anthracycline-based arm with trastuzumab versus 81% with the nonanthracycline arm (p=0.21); both trastuzumab arms were significant compared with the DFS of 75% for the nontrastuzumab group (HR 0.64; p<0.001, and HR 0.75; p=0.04, respectively).

Comment: This is the 3rd planned BCIRG 006 analysis and will soon be followed by the much awaited publication. Compared to other large studies only 2.3% crossed over to receive Herceptin after the 2005 study data was released, allowing a more direct comparison of the full treatment arms. The AC-TH arm shows maintained DFS and OS benefits over AC-T, while the anthracycline-free TCH appears equivalent to AC-TH, even in those with greater nodal involvement. There was a greater incidence, although still very low, of both leukaemia and cardiac events in the anthracycline-containing regimens. This study strongly supports either of these regimens using 12 months of trastuzumab.

Session Info: General Session V, December 12, 2009. Abstract 62.

http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_1752

Results of chemotherapy alone, with sequential or concurrent addition of 52 weeks of trastuzumab in the NCCTG N9831 HER2-positive adjuvant breast cancer trial

Authors: Perez EA et al

Summary: Long-term follow-up data are reported from the phase III North Central Cancer Treatment Group trial N9831 that was initiated in 2000 and compared three regimens: doxorubicin and cyclophosphamide followed by weekly paclitaxel (group A), the same regimen followed by 52 weeks of trastuzumab after paclitaxel (group B), and the same regimen plus 52 weeks of trastuzumab initiated concomitantly with paclitaxel (group C), in women with resected stage I-III invasive HER2+ breast cancer. In the first comparison, at a median 5.5-year follow-up, women in group B had a 30% reduction in the risk of breast cancer recurrence compared to those in group A (HR 0.70; p=0.0005). After adjusting for age, tumour size, number of positive nodes, and estrogen receptor (ER) status, the HR was 0.67. Five-year disease-free survival (DFS) was 72% for group A and 80% for group B. The second comparison assessed the effects of sequence of trastuzumab delivery. At a median follow-up of 5.3 years, 84.2% of patients in group C achieved DFS compared with 79.8% of those in group B (p=0.019). After adjusting for tumour size, number of positive nodes, and ER, the risk of breast cancer recurrence was reduced by 25% with concurrent trastuzumab versus sequential administration (HR 0.75).

Comment: This was the much awaited release of the sequential arm of N9831, which occurred later than the concurrent arms due to fewer initial events with DFS curves not separating for 18 months. The presented analysis was censored to exclude patients who had crossed over to receive trastuzumab. While additional presentation of the intention-to-treat data would have strengthened the conclusions, the presented results strongly support the findings of the HERA study with a clear benefit seen from 12 months of sequential trastuzumab after chemotherapy. A further analysis of the concurrent versus sequential arm suggested a benefit for concurrent over sequential therapy with a p-value of 0.019, but this did not meet the preset level of 0.0016 and can be taken only as a trend at this stage.

Session Info: General Session VI, December 12, 2009. Abstract 80.

http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_992332

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