Oncology Conference Review

San Antonio Breast Cancer Symposium

Making Education Easy SABCS, December 2006

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Welcome

to a review of the SABCS conference, held in San Antonio in December 2006. We present here a summary of some of the most topical and relevant clinical research presented at the conference. Selection and review of the research has been carried out independently by Dr Richard Isaacs.

We hope you will find the information stimulating and relevant to your practice here in New Zealand. Do please contact me with your comments and feedback.

Kind regards,

Dr Shaun Holt
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Tamoxifen for chemoprevention: updated findings from the IBIS-I study

Authors: Cuzick J.

Summary: This long-term trial reports updated findings from the IBIS-1 study. 7,145 women at increased risk for breast cancer were randomised to 5 years treatment with tamoxifen (20mg/day) or matching placebo. At median follow-up of 96 months, breast cancers had occurred in 146 tamoxifen-treated women and 196 controls (OR 0.73; 95% CI 0.58-0.91; p = 0.005). A 33% reduction in ER-positive breast cancers occurred in the tamoxifen group (80 vs. 120; OR 0.65 95% CI 0.48-0.88), but there was no risk reduction for ER negative invasive cancers (34 vs. 35; OR 0.97; 95% CI 0.58-1.60). The effect of tamoxifen appeared stable over time, with results available for up to 9 years. Women who took concomitant HRT were the only group who did not appear to benefit from the preventative effect of tamoxifen. Tamoxifen-treated women had non-significantly greater all-cause mortality (66 vs. 54; p = 0.27).

Comment: Tamoxifen prevents breast cancer well beyond the 5 year period of use, with maximal effects in the second 5 years, when most side effects also resolve. This effect must thus be genuine cancer prevention, rather than treatment of early microscopic disease as previously suggested. There was a difference in incidence of invasive cancer of 1.7% at 10 years, but no survival difference. A trend towards worse outcome with concurrent HRT use was seen, indicating this combination should be used with caution.

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CEF versus dose dense EC followed by paclitaxel versus AC followed by paclitaxel in women with node positive or high risk node negative breast cancer: interim analysis

Authors: Burnell, M et al.

Summary: This trial compared the efficacy of CEF (cyclophosphamide, epirubicin, fluorouracil), EC-T (a 3-month dose dense regimen of EC followed by paclitaxel) and AC-T (doxorubicin plus cyclophosphamide followed by paclitaxel). Trial participants were 2,104 women aged < 60 with axillary node positive or high risk node negative breast cancer who underwent lumpectomy or mastectomy. Subjects randomised to CEF received 6 cycles (C 75 mg/m^2 PO on days 1-14 plus E 60 mg/m^2 and F 500 mg/m^2 IV on days 1 and 8) with concurrent antibiotic prophylaxis. The EC/T regimen comprised 6 cycles of EC (epirubicin 120 mg/m^2 and cyclophosphamide 830 mg/m^2, both IV on day 1 plus filgrastim SC 5µg/kg/day days 2-13 and epoetin alpha SC 40,000 units/once weekly) followed by 4 cycles of T (175 mg/m^2 per 21 days) with filgrastim and epoetin alpha. The AC-T regimen consisted of 4 cycles of A (60 mg/m^2 and C 600 mg/m^2 IV every 21 days) followed by 4 cycles of T (175 mg/m^2 every 21 days). Mean follow-up (survivors) was 30.4 months. Hazard ratio's for breast cancer recurrence were AC/T vs. CEF, 1.49 (p=0.005); AC/T vs. EC/T 1.68 (p = 0.0006) and EC/T vs. CEF 0.89 (p = 0.46). Three year recurrence-free survival rates were 90.1 (CEF), 89.5 (EC/T) and 85.0% (AC/T).

Comment: Both CEF and dose dense/dose intense chemotherapy showed a clear 5% absolute benefit in 3 year disease free survival, with differences being entirely due to greater efficacy in hormone receptor double negative patients. These more intense arms had significantly more immediate toxicity however, and 8 patients have already developed acute leukaemia in this group. These data indicate taxanes may not be necessary when a schedule such as CEF is used, but there remain concerns over toxicity.

Lapatinib in patients with ErbB2 positive advanced or metastatic breast cancer

Authors: Cameron D et al.

Summary: The authors reported initial data from 213 patients recruited to this randomised, controlled trial which evaluated the time to progression (TTP) in patients with ErbB2+ refractory advanced or metastatic breast cancers. Particiapants had received prior treatment with at least anthracycline, taxane, and trastuzumab. Treatments consisted of lapatinib (1250 mg/day) plus capecitabine (2000 mg/m^2/d days 1-14, q 21d) or capecitabine alone (2500 mg/m^2/d days 1-14, q 21d). Mean TTP was significantly improved in the lapatinib treatment arm (36.9 wks) compared to capecitabine monotherapy (19.7 wks; HR 0.51; 95% CI 0.35-0.74; p = 0.00016). Adverse events for the combination therapy and monotherapy groups respectively included diarrhea (58 vs 39%), hand foot syndrome (43 vs 34%), rash (30 vs 18%), asymptomatic ≥ 20% relative decrease in ejection fraction (2.5 vs <1%). NB All patients recovered normal ejection fraction. The authors concluded the addition of lapatinib to capecitabine provided a "clinically meaningful and statistically significant prolongation in median TTP."

Comment: Lapatinib targets the receptor tyrosine kinases of both EGFR and Her2 and shows significant clinical activity in Herceptin-resistant disease. The drug appears well tolerated with only mild diarrhoea and rash seen in this trial, although longer term follow up will be needed to assess cardiotoxicity. New Zealand patients should have access to trials using this drug in the near future.

The impact of LHRH agonists on breast cancer recurrence and mortality

Authors: Cuzick J et al.

Summary: The authors present interim data from a review of trials involving LHRH agonists (both adjunctive and as monotherapy) for the treatment of ER receptor positive breast cancers. Data from a total of 13 trials involving 6,437 patients were included. Overall, the hazard ratio reduction of an LHRH agonist (with or without tamoxifen) compared to chemotherapy was 12.2% (95% CI; 23.8% reduction to 1.3% increase; p = 0.075) for breast cancer deaths and 4.9% (14.3% reduction to 5.6% increase; p = 0.347) for recurrence. The authors found "the addition of an LHRH agonist to chemotherapy significantly reduced the rate of cancer recurrences, although deaths from breast cancer were reduced less and were not significant". Further, "an LHRH agonist was as effective as chemotherapy for both breast cancer recurrence and deaths after recurrence".

Comment: This meta-analysis showed a clear reduction in the rate of relapse and death when LHRH analogs were used in combination with chemotherapy+/- tamoxifen and trends for benefit in comparison to CMF chemotherapy alone and when used as single agent therapy. The critical issue of any additional gains from its use in combination with optimal combination chemotherapy and hormonal therapy is yet to be addressed, but is being assessed in current trials such as SOFT, to which New Zealand centres are recruiting.

Fulvestrant versus exemestane in post-menopausal women with advanced breast cancer: first results from EFECT, a randomized, phase III trial

Authors: Gradishar WJ et al.

Summary: This randomised, double-blind, double-dummy trial was used to evaluate the efficacy of fulvestrant in women with advanced, hormone receptor positive breast cancer, who progress or relapse following treatment with third-generation non-steroidal aromatase inhibitors (AI's). 693 subjects were randomised to treatment with fulvestrant IM (500 mg on day 0, 250 mg on days 14 & 28, and 250 mg every 28 ± 3 days thereafter) or exemestane PO (25 mg/day). At the time of analysis, progression had occurred in 82.1% of fulvestrant-treated patients and 87.4% of those who received exemestane. Median time to progression (3.7 months) was not different between groups (HR: 0.963; 95% CI 0.819-1.133; p = 0.6531). Median duration of response (13.5 vs 9.8 months) favoured fulvestrant but the difference was not significant. Both treatments were well tolerated with no significant differences in the rates of adverse events.

Comment: Fulvestrant (Faslodex) has recently become available, if unfunded as yet in New Zealand. In this trial it had modest activity in patients with metastatic disease previously treated with non-steroidal aromatase inhibitors. Fulvestrant was well tolerated and may have a role in delaying the initiation of chemotherapy in those patients with prior responses to tamoxifen and aromatase inhibitors

A sharp decrease in breast cancer incidence in the United States in 2003

Authors: Ravdin PM et al.

Summary: The authors present trends in breast cancer incidence in the United States from 1990-2003 calculated from SEER public use data. From 1990 to 98 there was a gradual increase in breast cancer incidence of 1.7% per year. Incidence fell at the rate of 1% per year from 1998 to 2003. In 2003, breast cancer incidence fell by a further 7%. Incidence of both in situ and malignant cancers fell (5.5 and 7.3% respectively). Age appeared to affect the rate of decline. A decrease of 1% was observed in women in their 40's, 11% in women aged 50-69, and 7% in those 70 or over. ER positive breast cancers declined more than ER negative tumours (8 vs 4%). In women aged 50-69 there was a 12% decline in ER positive tumours, and a 4% decline in incidence of ER negative tumours. These findings may be linked to a sharp decrease in the use of hormone replacement therapy beginning in late 2002.

Comment: These data suggest a linkage between a sudden decline in breast cancer incidence in 2003 and a prior fall in HRT use. If the 50% reduction in HRT use seen in 2002 did contribute, a role in cancer promotion rather than initiation for HRT is most likely, due to the short lag time before incidence changes. Reduced use of screening mammography at that time may also have contributed. Subsequent SEER reports will clarify if these trends are maintained.

Micrometastases in the sentinel node: take it or leave it?

Authors: Rutgers EJ et al.

Summary: Micrometastases (0.2-2.0 mm) are found in about 30% of all tumour-positive sentinel nodes (SN). Examination techniques including multiple slicing of the SN, staining with immunohistochemistry or RT-PCR techniques can increase detection by around 10% in each case. However there may be limited clinical value in detecting micrometastases. After an average follow-up of 3 years, analysis of data from 9,000 published patients with negative SN and untreated axilla found the clinical occurrence of metastasis was 0.4%. In addition, there is a false negative rate of 2-11% following back-up ALND in SN negative patients. Studies suggest that the presence of SN micrometastases does not have an independent effect on survival prognosis in comparison to the size and grade of the primary tumour. The authors conclude that although the presence of SN micrometastasis would indicate further axillary treatment, clinicians "should not look too hard for micrometastasis in the sentinel node".

Comment: This plenary gave a pragmatic review of the significance of nodal micrometastases (0.2-2mm) identified on sentinel node biopsy. Micrometastases are not independent prognostic factors on meta-analysis, but do predict for macroscopic involvement of non-sentinel nodes in >15% and mandate axillary dissection. Nanometastases (<0.2mm) are currently of unproven significance, with a proportion being displaced epithelial cells at biopsy. Unless ongoing studies change this view, their identification should not alter management.

Evaluating dietary fat reduction and breast cancer outcome: data from WINS

Authors: Chlebowski RT et al.

Summary: 2,437 women with resected early-stage breast cancer who were receiving conventional cancer management were randomised to dietary interventions designed to reduce fat intake, or control. At 12 months, women in the intervention group had significantly lower fat intake than controls (33.3 vs 51.3 g/day: $p < 0.001$). Body weight was also significantly lower in the intervention group ($p = 0.005$). Interim data reported after 60 months found breast cancer recurrence or new contralateral breast cancer in 96/975 women in the intervention group compared to 181/1462 controls (HR 0.76; 95% CI 0.60- 0.98; $p = 0.077$ [stratified log rank]; $p = 0.034$ [adjusted Cox model analysis]). Follow-up data with a mean length of 95 months (surviving patients) will be available at a future date.

Comment: Reducing dietary fat intake from 30% to an achieved 21% was associated with a concordant, minor reduction in BMI. These changes produced a trend towards benefit in the group overall, but a profound improvement in hormone receptor double negative patients, with an overall survival benefit in that group of 11% at 5 years. This trial provides strong support to advocate lifestyle change in such patients, although it is not clear whether the effect is from fat or dietary caloric reduction.

Independent commentary by Dr Richard Isaacs

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Impact of boost radiation after breast conserving treatment: 10 year results of the EORTC trial

Authors: Bartelink H et al.

Summary: 10-year follow-up data from 5,318 patients who underwent lumpectomy for stage I and II breast cancer was reported. Patients were randomised to receive whole breast irradiation (50 Gy) with or without boost radiation of 16 Gy. 10-year survival was 82% in both treatment groups and was not significantly different ($p = 0.93$). The 10-year cumulative incidence of local recurrence was significantly greater in the no boost vs the boost group (10.2 vs 6.2%; $p < 0.0001$). Boost radiation was associated with significant reductions in absolute risk at 10-years; from 23.9% to 13.5% ($p = 0.0014$) for women aged ≤ 40; from 12.5% to 8.7% ($p = 0.0099$) for women aged 41-50; from 7.8% to 4.9% ($p = 0.0157$) for women aged 51-60; and from 7.3% to 3.8% for women >60 years old ($p = 0.0008$). Boost radiation was associated with a significantly greater incidence of severe fibrosis 4.4% vs 1.6% ($p < 0.0001$). Boost radiation improved local control at 10-year follow-up by approximately 10% in patients aged < 40, 4% in patients aged 41-50, and 3% in patients over 50 years.

Comment: These mature data confirm that the risk of local recurrence after breast conserving surgery and whole breast irradiation alone is highest in younger women. Boost radiotherapy to the tumour bed gives a constant relative reduction in the risk of local failure regardless of age, while survival is not affected. The small absolute benefits of boost radiotherapy in older women need to be balanced against the similarly small increased risks of severe local fibrosis.

BCIRG 006: interim analysis of trastuzumab regimens for Her2neu positive early breast cancer patients

Authors: Slaman D et al.

Summary: 3,222 HER-2 positive breast cancer patients with axillary lymph node positive or high risk negative were randomised to one of three treatment regimens. The standard treatment group (AC→T) received doxorubicin and cyclophosphamide (AC) (60/600 mg/m^2 q3wk x4) followed by docetaxel (T) (100 mg/m^2 q3wk x4). Patients in the AC→TH group received AC followed by T with trastuzumab (H) for 1 year, and those in the TCH group received T plus carboplatin (Carbo) (75 mg/m^2 / AUC6 q3wk x 6) with trastuzumab for 1 year. Subjects were stratified by the number of positive nodes and their hormone receptor status. Hormone-directed therapy was given for 5 years for subjects with ER and/or PR positive tumours. Disease-free survival was the primary endpoint, with secondary endpoints including overall survival and safety. Cardiac toxicity including symptomatic events and asymptomatic LVEF decline were also reported.

NB the commentary relates to study data presented at SABCS which is not available via the conference abstract.

Comment: This updated 36 month analysis, in line with other large studies, confirms the overall survival benefits seen for Herceptin-based therapy at a very early stage. The trial also validates the use of non-anthracycline containing TCH chemotherapy, which is not only as effective as the AC-TH arm, but appears better tolerated and less cardiotoxic. Both Herceptin combinations were more effective than chemotherapy alone, further emphasizing the need to have this drug funded in New Zealand.

Interactions between HER-2 expression and response to adjuvant chemotherapy

Authors: Gennari A et al.

Summary: This systematic review reported on randomised studies of adjuvant chemotherapy with anthracycline-based regimens where outcomes were reported according to HER-2 expression. 7 studies were eligible for inclusion, providing data according to HER-2 status for 5,099 of 6,296 (80.9%) patients. The HER-2 overexpression rate was 27.8%. Disease free survival for anthracycline vs non-anthracycline based regimens was 0.71 (CI 0.61-0.8; p = 0.0001) in HER-2 positive, and 0.98 (CI 0.88-1.09; p = 0.75) in HER-2-negative cancers. Overall survival was 0.73 (CI 0.62-0.85; p = 0.0001) and 1.03 (CI 0.92-1.16; p = 0.59) in HER-2 positive and negative patients respectively. There were highly significant interactions for treatment and HER-2 expression for both disease free survival ($p < 0.001$) and overall survival ($p < 0.001$).

Comment: This pooled data meta-analysis demonstrated that anthracycline use improved disease free and overall survival solely in HER-2 positive patients, none of whom received trastuzumab. While additional benefits to trastuzumab are now being questioned, this study and others indicate that at least until trastuzumab is available in New Zealand, anthracyclines remain a critical component of therapy for HER-2 positive disease.

ER and PgR expression and HER2 status: relationship with breast cancer recurrence

Authors: Dowsett M et al.

Summary: This study used tumour tissue from patients recruited to the ATAC trial to examine the relationship between oestrogen and progesterone receptor expression and HER-2 status with relation to disease recurrence. 9,366 patients with primary oestrogen and or progesterone receptor positive breast cancer were randomised to treatment with adjuvant anastrozole (A) or tamoxifen (T) or both. Retrospective consent was gained in order to collect tumour blocks from patients in the A and T treatment arms for biomarker analysis. Interim analysis was presented at SABCS with the data from 1,792 tumour blocks. Ultimately data should be available from > 2,000 blocks.

Comment: Only a modest proportion of tumour blocks from the ATAC trial could be reviewed, but the findings were intriguing. As expected, high ER expression predicted longer disease free survival and high PR expression a good prognosis. The mantra that aromatase inhibitors were optimal therapy for HER-2 positive disease was challenged however by the finding of an equivalent outcome between these drugs and tamoxifen – indicating that either agent is a reasonable choice in such patients.

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