ANZ BCTG Oncology Conference Review

Making Education Easy

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Welcome

to the Review of the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) 29th Annual Scientific Meeting, held in Alice Springs, Australia, last month. This is a focused summary of some of the groundbreaking clinical research presented.

This Review has been created to allow those of you who were unable to attend, who have a keen professional interest in breast cancer treatments, to access a summary of some significant clinical studies presented. Selection and review of the research has been carried out independently by Dr Richard Isaacs, Medical Oncologist, Palmerston North Hospital.

I hope you find the information interesting and I look forward to your feedback.

Kind Regards

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Improving informed consent: A randomised controlled trial of a Decision Aid for women invited to participate in IBIS-II

Presenter: Ilona Juraskova et al.

Summary: Patient-based educational interventions have a vital role to play in improving the process of informed consent and patient accrual to clinical trials. Up to 50% of patients decline entry into clinical trials, often due to difficulties in understanding the rationale for a trial from discussions with clinicians and the complexity of patient information sheets. This pilot study used a Decision Aid based on the Ottawa decision aid framework for use in certain ANZ BCTG centres participating in the International Breast Cancer Intervention Study II (IBIS-II). The Aid was used to assist postmenopausal women at high risk of developing breast cancer to decide on trial participation or standard risk management options. The Decision Aid presents evidence-based information in clear graphical form, using a variety of visual analogies e.g., pie diagrams and dot density plots. Participants felt the aids greatly assisted in decision making (97%) and did not provoke anxiety. They were much preferred to information sheets, despite their large size.

Comment: These aids were very easy to use and clearly helped decision making. A randomised trial as part of IBIS-II is under way to clarify benefits and it is hoped that on-line versions will subsequently become available.

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Lapatinib as targeted therapy: Update and the ALTTO trial

Presenter: Associate Professor Fran Boyle

Summary: Recent clinical studies have shown that Lapatinib, an oral, small molecule dual tyrosine kinase (EGFR/HER1 and HER2) inhibitor, has potential advantages over the monoclonal antibody trastuzumab, an inhibitor of HER2 and effective in the treatment of HER2-overexpressing metastatic breast cancer. Increased expression and activation of HER1 and HER2 in breast cancer are associated with a high risk for recurrence after primary treatment and consequently a poor clinical outcome. The potential advantages Lapatinib has over trastuzumab include oral delivery, CNS penetration, preclinical synergy with trastuzumab and maintained preclinical activity in some settings of trastuzumab resistance (truncated Her2p95 as seen in 10% of FISH+, and altered PTEN signalling). Some New Zealand centres have had limited access to Lapatinib in the international TEACH (Tykerb® Evaluation After CHemotherapy) breast cancer clinical trial and an expanded access programme, but it will shortly be available in the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) adjuvant trial. The ALTTO trial involves 4 treatment arms comparing 12 months of trastuzumab treatment with 12 months of Lapatinib, 12 months of the two drugs together, and 3 months of trastuzumab followed by a drug washout period and then Lapatinib to complete 12 months of therapy.

Comment: The ALTTO trial is a 12-month duration study with all 6 Cancer Treatment Centres likely to contribute. This trial offers NZ patients funded access to the international standard duration of therapy, and exposure to a new agent with potential clinical advantages.

Future role of aromatase inhibitors for treatment and prevention of early breast cancer

Presenter: Professor John Forbes

Summary: Despite remaining disease-free at periods >5 years from primary therapy, women with a history of estrogen receptor-positive breast cancer have a 5- to 10-fold increased incidence of a second breast malignancy, compared to the 'high risk' women in the North American National Surgical Adjuvant Breast and Bowel Project P1 Study (NSABP-P1) and International Breast Cancer Intervention Study I (IBIS-I) trials. In the NSABP-P1 trial (conducted between 1992 and 1997), women at increased risk of breast cancer were defined by their absolute age (60 years or older), or if they were 35 to 59 years of age and had a 5-year predicted breast cancer risk of at least 1.66% (the same risk as that of a 60-year-old woman free of any other risk factors), or if they had a history of lobular carcinoma-in-situ. The Later adjuvant Aromatase inhibitor Therapy for postmenopausal women with Endocrine Responsive tumour (LATER) trial was launched in Australia and New Zealand in April 2007. The aim was to find out whether late 'adjuvant' therapy with the aromatase inhibitor Letrozole can not only prevent recurrence of breast cancer, but also significantly reduce the high incidence of second breast cancers.

Comment: This study is more of a secondary prevention study, than a late adjuvant study. It intervenes in a group of women at particularly high risk of second malignancy who have not previously been offered active therapy.

PARP inhibitors for BRCA 1 and 2 deficient breast cancer: Treatment and prevention

Presenter: Dr Clare Scott

Summary: Recent studies have demonstrated that PARP [poly (ADP-ribose) polymerase] inhibitors can effectively kill breast cancer-associated gene-1 and –2 (BRCA 1/2) deficient cells, heralding a new approach to targeted cancer therapy. BRCA 1/2 proteins are involved in homologous recombination to repair dsDNA breaks, while PARP-1 is another important DNA repair protein involved in base excision repair (BER). Those with BRCA mutations have impaired homologous recombination and using PARP inhibitors generates a second hit on BER, potentially causing cell death in derived cancers. PARP inhibitors have now shown significant activity in Phase I studies in those with BRCA mutations. Notably, PARP inhibitors may prove useful in combination with standard chemotherapeutic agents.

Comment: Phase II studies with these promising new agents are now commencing. It is hoped they may also have activity in those with silenced and not mutated BRCA function (e.g. 63% of metaplastic carcinomas) and they may have a role in combination targeted therapy.

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

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Updated combined analysis of adjuvant trastuzumab trials: NSABP B-31 and NCCTG N9831

Presenter: Professor Nancy Davidson

Summary: This was an update of the results of the combined US studies of trastuzumab, given concurrently with a taxane, and followed by trastuzumab to 12 months, now with a median follow-up of 63.8 months. The National Surgical Adjuvant Breast Project (NSABP) B-31 and the North Central Cancer Treatment Group (NCCTG) N9831 were both designed for women with HER2-positive breast cancer. The four-year data show a persistent benefit compared to what was seen at two years, with trastuzumab combined with chemotherapy continuing to outperform chemotherapy treatment alone. The disease-free survival (DFS) benefits continue to expand, with four-year DFS being 85.9% vs 73.1% in the control arm, despite 21% of the control arm crossing over to receive trastuzumab after the initial study report. Recurrence was most frequent in years 2 and 3 and then reduced. Benefits were significant in all groups, except those very small sized groups of node-negative and low-grade tumours. The overall survival differences are now 3.2%. Despite these studies showing an increased incidence of cardiac failure in the first year, importantly there has been no late increase in cardiac events.

Comment: The benefits of adjuvant trastuzumab in this setting are maintained with longer follow-up and there is no sign of later cardiac toxicity. The results of the sequential arm are awaited with interest, but there still too few events to allow reporting.

Is Trastuzumab benefit confined to IHC3+ and/or FISH positive tumours? Central testing in NSABP B-31

Presenter: Professor Soonmyung Paik

Summary: Central laboratory review was performed on tumour blocks from all patients in the NSABP B-31 study using fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) testing. Professor Paik's group found that 10% of tumours did not meet their criteria for amplified HER2. However, this group of 174 women with HER2 'negative' tumours, including tumours that were both IHC- and FISH-negative, nevertheless derived benefits from adjuvant therapy with Trastuzumab ($p<0.05$). Hazard ratios for benefit from Trastuzumab were similar for tumours that were HER2-positive by IHC or FISH, or that were HER2-negative. Assays showed a continuous variable of protein and mRNA expression for HER2, rather than a defined cutoff and it appears that up to 25% of cancers have FISH ratios of 1–2.

Comment: Breast tumours with HER2 ratios of 1–2 typically have focal amplified cells or clusters of such cells on immunohistochemistry. It is postulated these may be the cells with most metastatic potential, while the tumour bulk remains HER2-negative. The current ratio cutoff of 2.2 may preclude certain patients who would benefit from HER2-directed therapy.

A randomised trial of Capecitabine given intermittently versus continuously versus classical CMF as first-line chemotherapy for advanced breast cancer

Presenter: M Stockler et al., ANZ Breast Cancer Trials Group

Summary: Intensive treatment may not be indicated for many women having first-line chemotherapy for advanced breast cancer. Between June 2001 and July 2005, this study randomised 325 such women to either intermittent Capecitabine (2000 mg/m2/d for 14 of every 21 days), or continuously (1300 mg/m2/d for 21 of every 21 days), or CMF (cyclophosphamide 100 mg/m2/d orally on days 1–14; methotrexate 40 mg/m2 and 5-FU 600 mg/m2, IV days 1 and 8, every 28 days). Analyses revealed identical response rates between the treatment arms (20%), but the combined Capecitabine arms resulted in improved overall survival and quality of life, as remissions were maintained for longer (chemotherapy was continued beyond 6 months in 40% of Capecitabine recipients, but in only 22% of CMF recipients). Neutropenia and infection were less common with Capecitabine, but hand-foot syndrome was more frequent.

Comment: This has implications for practice in New Zealand, where many stop therapy after six cycles of Capecitabine. Providing treatment is well tolerated, continuing therapy with Capecitabine may provide a survival advantage.

The future of gene expression array: Is FFPET sufficient?

Presenter: Professor Soonmyung Paik

Summary: Analysing RNA from formalin-fixed and paraffin-embedded (FFPE) tissues has been limited by RNA degradation to fragments of about 200bp in size. Gene expression studies have thus tended to focus on fresh frozen tissues, which are more difficult to collect and to study in non-selected series. The US National Surgical Adjuvant Breast and Bowel Project (NSABP) group developed primers to amplify 100bp fragments and, using reference genes to compensate for degradation, reproducibly quantified RNA expression in FFPE tissues which had been stored for many years. Using this technology, the NSABP have now developed a predictive tool for recurrence using a 21-gene expression assay of such tissues.

Comment: This new technology offers the potential to more accurately assess gene expression profiles in large series. The assay can be performed on just 2 x 5µm (micrometre) sections from paraffin blocks, but is only likely to be available in major academic centres in the near future.

New genes for breast cancer and other diseases: Are they important?

Presenter: Dr Clare Scott

Summary: While BRCA mutations indicate a high risk of developing breast cancer, they are relatively uncommon and only account for 2–3% of breast cancers. In the majority of cases of familial breast cancer, women are at risk due to mutations in lower penetrance genes e.g. PTEN, STK II, e-cadherin, ATM and CHK II. Research groups are now screening very large series for Single Nucleotide Polymorphisms (SNPs) and have identified new candidate genes such as the FGFR2 (Fibroblast Growth Factor Receptor 2) gene, which is frequently mutated and may account for up to 16% of the population-attributable risk of developing breast cancer. The precise mechanism by which these gene variants act requires further research.

Comment: Further understanding of the biology by identifying gene mutations which carry risk will not only improve screening technology, but may lead to new therapies.

Postoperative radiotherapy duration after breast preservation for early breast cancer: How short is shorter?

Presenter: Professor David Joseph

Summary: A survival advantage has now been established for adjuvant radiotherapy, but there are concerns about limited access to the resource. Several approaches have been considered, including hypofractionation, where similar total treatment doses are given in fewer fractions, or over a shorter time. A Canadian study of hypofractionation found similar local control rates to conventional therapy, but excluded young patients, those with large breasts, patients with significant pulmonary or cardiovascular disease, and patients with postoperative infection. Another UK study, exploring the use of hypofractionation, has reported increased risks of cardiac toxicity with this approach. While hypofractionation appears to be an acceptable alternative over more traditional dosing regimens, critical long-term follow-up data are needed.

Comment: Hypofractionation would enable more women to be treated, but patient selection is critical and more information is needed on long-term non-cancer morbidities, which may occur late in cancer survivors.

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