St. Gallen Conference Review

Primary Therapy of Early Breast Cancer

Making Education Easy St Gallen, Switzerland, March 2007

In this issue:

Welcome

to a review of the 10th International Conference in St. Gallen, Switzerland held in March. 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 David Porter. 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

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Extracorporeal elimination of liposomal doxorubicin by therapeutic apheresis technique

Authors: Pütz, G et al

Summary: This study investigated the elimination of liposomal doxorubicin (DOXIL®/CAELYX®) by a standard membrane differential filtration (MDF) treatment originally designed for low-density lipoprotein (LDL)-apheresis. No liposomal doxorubicin was released during any apheresis step. Liposomal doxorubicin in buffer passed the plasma separating filter unit without loss and was completely detained in the plasma filter unit. Although the plasma separator unit was slightly less effective when reconstituted whole human blood was used, the liposomes were still completely detained in the plasma filter unit. Similarly, there was no release of liposomal doxorubicin when liposomes were incubated with human plasma for 24 hours prior to apheresis. The authors concluded that the safe and effective elimination of liposomal doxorubicin by MDF may lead to more efficient treatment protocols with less adverse effects. They added that the neoadjuvant and adjuvant treatment settings must focus on a balance between therapeutic benefit and severe side effects. Shifting the balance in favour of therapeutic benefit may allow new treatment options for highly potent chemotherapeutic agents, suggest the authors.

Comment: This is an interesting concept with proof of principle. But I do wonder if reducing systemic concentrations of liposomal doxorubicin may have some impact on intratumoural drug concentration. If so, the impact of this study may reside more in the management of accidental overdose of liposomal doxorubicin or in those who have significant systemic side effects from conventional doses, where it may be desirable to eliminate the residual drug from the system.

Reference: *The Breast, Volume 16, Supplement 1, page S42: Abstract P105*

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Performing sentinel lymph node biopsy is associated with a significantly improved survival compared to level I & II axillary lymph node dissection in node negative breast cancer patients

Authors: Langer I et al

Summary: This study analysed disease-free survival and overall survival rates in 355 node-negative patients with early stage breast cancer (pT1 and pT2 ≤3 cm, pNO/pNSNO), 177 of whom underwent sentinel lymph node (SLN) biopsy in the years 1998–2004 and 178 underwent axillary lymph node dissection (ALND) in 1990–1997. Median follow-up durations were 48.2 months for the SLN group and 120.0 months for the ALND group. Disease-free and overall survival rates were significantly better for the SLN group than for the ALND group. Cox proportional hazard regression analysis revealed that the performed procedure (SLN versus ALND) was a significant independent predictor for improved disease-free survival (hazard ratio 0.28, 95% confidence interval 0.11–0.75) and overall survival (0.36, 0.14–0.89). The authors concluded that the significant survival benefit associated with a negative SLN biopsy is most likely due to more accurate histopathological staging; this concept therefore offers an important advantage in breast cancer.

Comment: This study draws a startlingly strong conclusion given that the sentinel node biopsy group is compared to historical controls over a time span when great advances have been made in the adjuvant treatment of breast cancer. It is a great shame that the method of sentinel node biopsy is not described. Logically, SLN biopsy could only result in improved survival if it had a lower false negative rate than axillary dissection. This might be possible if the detection of internal mammary sentinel nodes was feasible (and biologically important) with the technique used.

Reference: The Breast, Volume 16, Supplement 1, page S31: Abstract P67

HER-2 overexpressed breast cancer and brain metastases

Authors: Lichinitser, M et al

Summary: This study analysed brain metastases (BM) development in 41 patients with stage I–IIIa breast cancer with HER-2 overexpression (IGH-3+ or 2+ and FISH+), who were followed-up after their operations for a median of 60.6 months. Seven patients received adjuvant trastuzumab (Herceptin), 34 did not. BM developed in 15/41 patients (36.5%); BM were the first manifestation of progressive disease in 8/41 patients (19.5%) and in 3 patients, BM were the only manifestation of progression. The median time to BM from the operation was 15.4 months. Three patients with an IGH assessment of HER-2/neu 3+ underwent BM removal. BM developed in 2/7 patients (28.6%) who received adjuvant trastuzumab and in 13/34 patients not given trastuzumab (38.2%); the mean times from the operation to BM development were 29.9 months and 28.5 months, respectively. The median overall survival of patients with BM was 34.9 months; a log-rank test demonstrated significantly improved survival in patients treated with trastuzumab, compared with those who were not (60.6 months vs 19.8 months). No overall survival median was achieved in pts without BM. The authors recommended routine CT/MRI assessment of brain, in consideration of the high risk of BM development in breast cancer with HER-2 overexpression.

Comment: The apparent increase in cerebral metastases in women treated with adjuvant trastuzumab probably reflects better systemic disease control, without a similar reduction in CNS metastases due to the limited penetration of this drug through the blood brain barrier. The conclusion that all women with HER-2 positive breast cancer should have regular head CT scans or MRIs in the absence of symptoms is highly arguable.

Reference: The Breast, Volume 16, Supplement 1, page S19: Abstract P26

Adherence to tamoxifen therapy

Authors: Barron, TI et al

Summary: This study assessed rates of tamoxifen non-persistence (early discontinuation) in 3216 women aged 35 years commencing tamoxifen as initial hormonal therapy between January 2001 and July 2004, using prescription refill data from the Irish HSE-PCRS pharmacy database. By the end of follow-up (all patients were followed for between 1 and 4.5 years), the non-persistence rate was 29.0%, 25.6% had switched hormonal therapy, 15.8% were lost to follow up and 29.6% of women had persisted with treatment to the end of follow-up. Non-adherence was defined as a Medication Possession Ratio (MPR) of <90%. In 1901 women who received tamoxifen for 1 year, MPRs were: 26.5% MPR <90%, 11.9% MPR <80%, 5.3% MPR <70%. Non-adherence to tamoxifen was associated with subsequent non-persistence when compared with the reference group of persistent patients, and patients between the ages of 35 and 44 years were more likely to discontinue tamoxifen when compared with the reference group of women aged 45–54 years. The risk of non-adherence was lower in patients receiving higher numbers of concomitant medications. The authors concluded that low adherence rates predict subsequent discontinuation of treatment and that oncologists should be concerned about the 28.2% of patients who discontinued tamoxifen without receiving other hormonal therapies.

Comment: That only 73.5% of women took more than 90% of their planned dose of tamoxifen highlights an opportunity to improve matters with better attention to side effect management, support and encouragement. Poor compliance heralds early discontinuation of therapy, and limits the benefits that can be achieved through treatment. Although aromatase inhibitors are widely considered to be better tolerated than tamoxifen, several adjuvant trials directly comparing these drugs have reported higher treatment drop out rates in the AI arm.

Reference: The Breast, Volume 16, Supplement 1, page S44: Abstract P111

Independent commentary by Dr David Porter, Medical Oncologist, Oncology Dept, Auckland Hospital

Research Review publications are intended for New Zealand health professionals

The neoadjuvant endocrinetherapy vs chemotherapy in postmenopausal women with ER-positive breast cancer

Authors: Semiglazov, VF et al

Summary: This study reported similar clinical outcomes in postmenopausal women with estrogen receptor (ER)- and/or progesterone receptor (PgR)-positive tumours who were administered neoadjuvant endocrine treatment with aromatase inhibitors (once-daily anastrozole 1 mg or exemestane 25 mg) for 3 months or neoadjuvant chemotherapy (doxorubicin 60 mg/m2 plus paclitaxel 200 mg/m2 every 3 weeks, 4 cycles); the clinical objective response rate was 64% for both endocrine therapy and chemotherapy. The median time to clinical response was 57 days for aromatase inhibitor recipients and 51 days for chemotherapy recipients. No significant between-group differences were observed in rates of pathological complete response (3% vs 6%) and disease progression (9% vs 9%) in the endocrine therapy and chemotherapy treatment groups, respectively. Most commonly observed toxicities after chemotherapy included alopecia (79%), grade 3/4 neutropenia (33%), and grade 2 neuropathy (30%). Endocrine treatment was well tolerated. No deaths occurred during the preoperative treatment. The authors concluded that preoperative neoadjuvant endocrine therapy with aromatase inhibitors offers good tolerability and the same benefits as chemotherapy in postmenopausal women with ER- and/or PgR-positive tumours.

Comment: A surprising message from this study is that for postmenopausal women with receptor-positive breast cancer, neoadjuvant therapy with an aromatase inhibitor results in identical response rates to those achieved by chemotherapy with a taxane or anthracycline. Moreover, responses occur equally rapidly whichever treatment modality is chosen. All there is to choose between them is the side effect profile. It should not be forgotten that it is not an either-or choice: many women may be best served to have both chemotherapy and hormonal manipulation.

Reference: The Breast, Volume 16, Supplement 1, page S50: Abstract P131

Rechallenge of patients previously treated with adjuvant anthracyclines using pegylated liposomal doxorubicin (PLD) with cyclo phosphamide (C) as first-line chemotherapy for metastatic breast cancer (MBC)

Authors: Trudeau, M et al

Summary: This study investigated the substitution of anthracycline with pegylated liposomal doxorubicin (PLD; Caelyx/Doxil) in 73 patients with measurable metastatic breast cancer previously treated with an anthracycline-containing adjuvant regimen >12 months prior to diagnosis of metastatic disease. PLD 35 mg/m2 was given in combination with cyclophosphamide 600 mg/m2 every 3 weeks as first-line chemotherapy. The median prior dose of anthracycline was 240 mg/m2 and 576 mg/m2 for doxorubicin and epirubicin, respectively. Patients received a median of 6 cycles of PLD and cyclophosphamide. Major toxicities comprised grade 3/4 neutropenia (7.5%), asymptomatic >10% declines in left ventricular ejection fraction (9%) (reversed after discontinuation of PLD) and grade 3/4 hand foot syndrome (6%). No grade 3/4 cardiac toxicities were observed, despite overall cumulative doses of anthracycline reaching 450 mg/m2 and 700 mg/m2 for doxorubicin and epirubicin, respectively. The objective response rate (ORR) was 38% (3% complete responses, 35% partial responses) and an additional 30% achieved stable disease >6 months, resulting in a clinical benefit rate of 69%. The ORR was similar for patients previously treated with adjuvant taxanes. The Kaplan-Meier estimate for progression was 6.6 months. The authors concluded that rechallenge with PLD and cyclophosphamide demonstrates good tolerability and cardiac safety following previous adjuvant anthracycline exposure.

Comment: This study shows that retreatment with doxorubicin and cyclophosphamide is feasible, effective and safe so long as doxorubicin is packaged in a liposome. This is a definite advantage for those women with disease considered potentially sensitive to an anthracycline who have reached their cardiac safety limits with conventionally administered drugs. In New Zealand this advantage will be limited to those few with deep enough pockets to purchase the drug. Instances such as this highlight the need for more comprehensive health insurance options that cover non surgical aspects of cancer care in NZ.

Reference: The Breast, Volume 16, Supplement 1, page S54: Abstract P142

Fewer gynaecological adverse events (AEs), gynaecological interventions, endometrial changes and abnormalities with anastrozole than with tamoxifen: findings from the ATAC (`Arimidex', Tamoxifen, Alone or in Combination) trial

Authors: Distler, W et al

Summary: This study reported outcomes of a new analysis of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study, which compared the aromatase inhibitor anastrozole with tamoxifen in 9366 postmenopausal women with early breast cancer. Data were analysed of all gynaecological adverse events (AEs) and interventions recorded on the main ATAC trial database (after 2.5 and 5 years' treatment and at the time of data cutoff) in all 6186 monotherapy recipients, 4465 of whom had an intact uterus at baseline. Anastrozole was associated with a significantly lower incidence of gynaecological AEs than tamoxifen (20.5% vs 34.2%), mostly because of lower rates of vaginal haemorrhage, leucorrhoea, and endometrial hyperplasia. Anastrozole recipients were less likely than tamoxifen recipients to undergo either diagnostic (21.8% vs 29.4%) or therapeutic (8.4% vs 15.4%) interventions. They were also significantly less likely to undergo a hysterectomy (1.3% vs 5.1%). The ATAC endometrial subprotocol analysis (n = 285) showed that anastrozole was associated with fewer endometrial abnormalities than tamoxifen (27.3% vs 43.9%). Endometrial thickness was unchanged during follow-up in the anastrozole group (3.0 mm) but increased in tamoxifen-treated patients (5.0 mm). The authors concluded that the superior tolerability of anastrozole over tamoxifen in women with early breast cancer is likely to translate into benefits to their psychological well being, quality of life, and economic well being.

Comment: This report selectively targets one of the areas where adjuvant tamoxifen was already known to fare less well than anastrozole, and leads to the usual single minded conclusion from the ATAC investigators. Nonetheless, the higher gynaecological intervention rate with tamoxifen within the first 2.5 years has implications for proponents of switch strategies, but has to be balanced against the greater skeletal morbidity with anastrozole. Neither is trivial. Importantly, no endometrial cancers are described in this report.

Reference: The Breast, Volume 16, Supplement 1, page S45: Abstract P115

Premenopausal women diagnosed with good prognosis breast cancer need not wait two years to become pregnant

Authors: Ives, A et al

Summary: A total of 123 breast cancer survivors aged less than 45 years who subsequently conceived were identified in the Western Australian population between 1982 and 2003. Sixty two (54%) of women diagnosed with breast cancer who subsequently conceived did so less than two years after their diagnosis and 29 of them had pregnancy terminations (27 live births, 6 miscarriages). Cox proportional hazard regression analysis revealed significantly improved overall survival among women with a subsequent pregnancy (hazard ratio 0.59, 95% confidence interval 0.37–0.95; p = 0.03); a stratified analysis adjusting for time from diagnosis to subsequent pregnancy revealed an improvement in overall survival in women who waited 24 months to conceive (0.48, 0.27–0.83; p = 0.009) and a non-significant protective effect for women who waited at least 6 months to become pregnant. The authors concluded that their analysis did not support current medical advice to premenopausal women diagnosed with breast cancer to wait two years to become pregnant; early conception is unlikely to adversely affect survival of breast cancer survivors.

Comment: A reiteration of the message that pregnancy does not appear to worsen the risk of relapse in breast cancer survivors. The higher annual risk of relapse in the first two years after a breast cancer diagnosis and the tendency of early relapses to be biologically aggressive means that advice to avoid pregnancy in the first two years after diagnosis is not entirely misplaced. Aggressive breast cancer relapses in pregnant women can place the wellbeing of both mother and baby in direct conflict and foreshorten the lives of both. Neither this nor the many other studies addressing this issue do not support any mandate towards termination of pregnancy in women after breast cancer.

Reference: The Breast, Volume 16, Supplement 1, page S61: Abstract P168

Hormone therapy followed by chemotherapy are not enough for hormone receptor positive young age breast cancer: Nationwide overall survival data in Korea

Authors: Han, W et al

Summary: This study used data from 9885 breast cancer patients aged >50 years enrolled between 1992 and 2001 in the Korean Breast Cancer Society Registration Program to compare the clinicopathological characteristics and overall survival between younger (<35) and older (35-50) age groups. A total of 1444 (14.6%) patients were aged <35. Compared with older age, younger age was associated with significantly higher T-stage, higher lymph node positivity, and lower estrogen receptor and progesterone receptor expression. The probability of death was higher in younger patients than in older patients; five-year overall survival rates were 81.5% and 89.4%, respectively (log-rank p < 0.0001). A subgroup analysis revealed significantly worse outcome for younger patients, regardless of tumour size or lymph node status. The younger age group showed significantly worse outcome if hormone receptor status was positive or unknown. In contrast, for hormone receptor-negative disease, the between-group survival difference was not significant. For patients with positive or unknown hormone receptor status, hormone therapy significantly improved overall survival after chemotherapy in patients aged between 35 and 50, whereas no such advantage was seen in patients aged younger than 35. The authors concluded that chemotherapy and subsequent hormone therapy might not improve outcomes in patients aged <35.

Comment: An oft-repeated message from such studies is that oestrogen-sensitive tumours in young women paradoxically have a poorer prognosis. It is hypothesised to be the consequence of the greater persistence of normal menstruation in younger women treated with chemotherapy. Our attention should be drawn to the need for meticulous care in optimising hormonal manipulations in the young. Further research that targets this group of women to elucidate the true cause of this observation is desirable.

Reference: The Breast, Volume 16, Supplement 1, page S61: Abstract P169

Cardiac safety guidelines for the adjuvant use of trastuzumab (Herceptin®) in HER2-positive early breast cancer

Authors: Suter, TM et al

Summary: This paper summarised the Consensus Committee (CC) cardiac guidelines for adjuvant trastuzumab (Herceptin) in HER2-positive early breast cancer. Baseline assessment of left ventricular ejection fraction (EF) is recommended prior to trastuzumab initiation. Trastuzumab is acceptable in normal EF (50%), regardless of prior therapy status. Firm data are lacking regarding mildly abnormal EF (>45 to <50%); anecdotal evidence suggests that trastuzumab is tolerated in such cases, with consideration of the risk-benefit ratio. Patients with mildly depressed EF should receive trastuzumab with non-anthracycline-based regimens and undergo more frequent cardiac monitoring. Adjuvant trastuzumab is not recommended for moderately or severely depressed baseline EF (<40%). Trastuzumab may continue with increased monitoring in asymptomatic patients whose EF decreases to within 40–50%, but discontinue if EF fall to <40%. Regarding significant falls in EF (a >15% decrease during trastuzumab or a >10% fall to an abnormal value), the guidelines recommend 3-monthly monitoring of EF until restoration of normal values, with yearly assessments thereafter. Assessment is advised for symptomatic patients with significant EF falls, and trastuzumab should be discontinued in cases of New York Heart Association class III/IV heart failure. Following trastuzumab, three annual EF assessments are advised for patients without cardiac dysfunction. The CC concluded that this management strategy is useful in the adjuvant use of trastuzumab.

Comment: The important take home message is that mild degrees of cardiac failure should be considered to be a relative rather than an absolute contraindication to the use of adjuvant trastuzumab. The risks of inducing heart failure in this group could well be less than the benefits achieved in reducing breast cancer recurrence risk. However, the current proposition is that trastuzumab will only be provided in New Zealand with normal cardiac function.

Reference: The Breast, Volume 16, Supplement 1, page S63: Abstract P176

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