Breast Cancer Research Review™

Making Education Easy

Issue 56 - 2023

In this issue:

Abbreviations used in this issue:

DFS = disease-free survival; **HDL** = high-density lipoprotein; **HER2** = human epidermal growth factor receptor-2; **HR** = hazard ratio; **MMSE** = Mini-Mental State Examination; **OS** = overall survival; **QOL** = quality of life; **RR** = rate ratio; **RT** = radiotherapy.

Welcome to issue 56 of Breast Cancer Research Review.

We begin this issue with research reporting that women who have had hormone receptor-positive early breast cancer can safely interrupt their adjuvant endocrine therapy when considering pregnancy without increasing their risk of recurrence. There is also a randomised trial comparing the new breast reconstruction technique of autologous fat transfer with implant-based reconstruction, reporting better QOL with the former with no evidence of safety concerns. Other included research explored the impact of adherence to cancer prevention lifestyle recommendations before, during and after breast cancer treatment on recurrence and mortality. This issue concludes with research suggesting that treatment for early breast cancer, including endocrine therapy, does not seem to affect cognitive decline in older women.

We hope you enjoy this update in breast cancer research. We look forward to comments and suggestions.

Kind Regards,

Dr Hilary Martin
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Interrupting endocrine therapy to attempt pregnancy after breast cancer

Authors: Partridge AH et al., for the International Breast Cancer Study Group, and the POSITIVE Trial Collaborators

Summary: This trial evaluated temporary interruption of adjuvant endocrine therapy to attempt pregnancy in 516 women aged ≤42 years with prior stage I–III (93.4% stage I–II) breast cancer. Among 497 women followed for pregnancy status, 368 had ≥1 pregnancy, with 317 having ≥1 live birth and a total of 365 babies. After a median 41 months of follow-up (1638 patient-years), a breast cancer event occurred in 44 of the women, which was under the prespecified safety threshold. The 3-year incidence of breast cancer events among the women in whom treatment was interrupted was 8.9%, compared with 9.2% in an external control cohort.

Comment: For many younger women, a diagnosis of breast cancer comes at a time of life when they may be considering pregnancy in the near future. These plans are generally delayed for treatment, with patients generally counselled to delay planned pregnancy for 18 months to 2 years, and that cessation of endocrine therapy for pregnancy is considered safe based on retrospective and anecdotal data; however, this recommendation was not based on prospective trial data. The POSITIVE study aimed to address the important clinical question of safety of interruption of endocrine therapy for pregnancy attempt, and enrolled patients internationally, including at Australian sites. Reassuringly, this study has shown that there was no significant difference in 3-year incidence of breast cancer events between those who ceased endocrine therapy for attempted pregnancy and matched external controls. Given hormone receptor-positive recurrences can occur many years from initial diagnosis, longer-term follow-up is required to confirm no increase in later relapses for those who have treatment interruption. However, patients at this point can be advised there is no clear signal for increased early recurrence with treatment interruption for pregnancy. It is also worth noting that the majority who had a treatment break for pregnancy had at least one successful pregnancy.

Reference: N Engl J Med 2023;388:1645–56
Abstract

Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer

Authors: Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Summary: This patient-level meta-analysis examined the benefits and risks of including anthracycline in anthracycline-taxane chemotherapy and the benefits of different anthracycline-taxane regimens using data from 15 randomised controlled trials including 18,103 women with early-stage breast cancer. Recurrence rates were 14% lower with taxane regimens that included an anthracycline versus those without (RR 0.86 [95% CI 0.79–0.93]). There were 1/700 cases of additional acute myeloid leukaemia. The greatest reduction in 10-year recurrence rate was observed with anthracycline concurrently added to docetaxel plus cyclophosphamide versus docetaxel plus cyclophosphamide (12.3% vs. 21.0%; RR 0.58 [95% CI 0.47–0.73]), with a 10-year breast cancer mortality reduction of 4.2% (p=0.0034). No reduction in recurrence risk was seen for sequential schedules of taxane plus anthracycline versus docetaxel plus cyclophosphamide (RR 0.94 [95% CI 0.83–1.06]). In 35 trials (n=52,976) of anthracycline regimens with versus without a taxane, larger recurrence reductions were seen when a taxane was added to anthracycline regimens when the cumulative anthracycline dose was the same in each group (RR 0.87 [95% CI 0.82–0.93]) than with a two-fold higher cumulative dose of non-taxane (mostly anthracycline) in controls versus taxane recipients (0.96 [0.90–1.03]).

Comment: Based on previously reported studies, anthracycline plus taxane regimens are considered more effective than either regimen, with only taxane-based or only anthracycline-based regimens, but with the combination regimen more toxic. This very large meta-analysis undertaken by the Early Breast Cancer Trialists Collaborative Group investigated whether there are differences in outcome for patients treated with anthracycline regimens compared with anthracycline plus taxane-containing regimens, and between taxane-based regimens compared with anthracycline plus taxane regimens. Not unexpectedly, the study confirmed anthracycline plus taxane regimens to be the most effective combination, with regimens with higher dose and higher dose intensity more effective. Interestingly, when compared with anthracycline regimens, concurrent anthracycline plus taxane regimens had the greatest difference in efficacy, such as the TAC regimen. These regimens had higher cumulative doses it seems. It should be noted most trials in this meta-analysis had 3-weekly regimens, rather than the dose-dense regimens. Importantly, the benefit from the addition of anthracycline-containing regimen to taxane regimen benefited both oestrogen receptor-positive and -negative breast cancer patients. There were only limited numbers of trials within the meta-analysis with HER2 status available, and therefore the study has not been able to assess the different regimens definitively for this subgroup. This study does show a higher rate of secondary acute myeloid leukaemia for taxane plus anthracycline combinations, compared with anthracycline regimens, with an additional 1/700, but did not show an increase in risk of CV-related death for the anthracycline-containing regimens. However, longer-term follow-up may be required to investigate this. Overall, the meta-analysis confirms the additional benefit of the use of anthracycline plus taxane therapy over taxane regimens, including TC, which is more commonly used than anthracycline-alone regimens in clinical practice. The findings confirm current clinical understanding and practice.

Reference: Lancet 2023;401:1277–92
Abstract

Extended adjuvant aromatase inhibition after sequential endocrine therapy in postmenopausal women with breast cancer

Authors: Tjan-Heijnen VCG et al., on behalf of the Dutch Breast Cancer Research Group (BOOG) for the DATA Investigators

Summary: These authors reported a follow-up analysis of the open-label phase 3 DATA trial from The Netherlands, which evenly randomised 1912 postmenopausal women with hormone receptor-positive breast cancer who were disease-free after 2–3 years of adjuvant tamoxifen treatment to receive oral anastrozole 1mg once daily for 3 years (n=955) or 6 years (n=957); 1660 of the participants were eligible and disease-free at 3 years after randomisation. For the respective 6-year and 3-year anastrozole groups, the 10-year adapted DFS rates (i.e. from 3 years after randomisation) were 69.2% and 66.0% (HR 0.86 [95% CI 0.72–1.01]) and the 10-year adapted OS rates were 80.9% and 79.2% (0.93 [0.75–1.16]).

Comment: This study examined the important question of the value of extension of adjuvant endocrine therapy. There have already been a number of studies reported examining this question. In this study, patients who had received 2–3 years of adjuvant tamoxifen were randomised to either 3 years of anastrazole or 6 years of anastrazole. The study utilised adapted DFS and OS. This adapted DFS meant survival was measured not from randomisation, but from 3 years after randomisation, which is the timepoint at which the arms differed in management, with those in the 3-year arm ceasing anastrazole at that time, whereas the 6-year arm continued anastrazole for a further 3 years. Thus the reported 10-year adapted DFS data are 13 years from randomisation, and 7 years from time of cessation of anastrazole for the 6-year arm. This is important to note, as this is therefore a reasonably long follow-up period. The study did not show any difference in invasive DFS or OS with the additional 3 years of anastrazole when examining the overall population. However, subgroup analysis did show a benefit of the additional 3 years anastrazole for those who were both oestrogen receptor- and progesterone receptor-positive, and for those who were both oestrogen receptor- and progesterone receptor-positive with high-risk features, including positive lymph nodes and larger tumour size. The authors have suggested in their discussion that it would be worthwhile undertaking a meta-analysis of trials examining extension of aromatase inhibitor therapy to provide greater clarity regarding subgroups that may benefit from extension of therapy.

Reference: eClinicalMedicine 2023;58:101901
Abstract

Breast Cancer Research Review™

Independent commentary by Dr Hilary Martin

Dr Hilary Martin is a medical oncologist at Fiona Stanley Hospital Perth subspecialising in breast cancer. Her initial oncology training was undertaken in South Australia. She subsequently worked as a breast unit fellow at the Royal Marsden Hospital, London, and also as a clinical fellow at Royal Perth Hospital. She has a Masters of Public Health through the University of Sydney and a PhD through the University of Western Australia. Her research interests include mammographic breast density, survivorship, CTDNA, and lobular breast cancer.

Effect of total breast reconstruction with autologous fat transfer using an expansion device vs implants on quality of life among patients with breast cancer

Authors: Piatkowski AA et al., for the Breast Reconstruction With External Preexpansion & Autologous Fat Transfer vs Standard Therapy (BREAST) Trial Investigators

Summary: Patients with breast cancer who had undergone mastectomy were randomised to breast reconstruction with autologous fat transfer plus expansion (n=91) or two-phased implant-based reconstruction (n=80) in the BREAST trial from The Netherlands; six and 18 participants dropped out of the respective groups. The mean breast volumes achieved in the respective autologous fat transfer and implant groups were 300.3 and 384.1mL. Compared with the implant group, the autologous fat transfer group had statistically significantly higher scores for three domains of the BREAST-Q questionnaire, namely satisfaction with breasts, physical well-being – chest, and satisfaction with outcome. Change in QOL over time favoured the autologous fat transfer group. There were no significant between-group differences for oncological serious adverse events.

Comment: Current standard autologous breast reconstructions in Australia involve either deep inferior epigastric perforator or latissimus dorsi flap reconstructions. These operations are major surgical procedures, with extended operating times as well as recovery. Implant-based reconstructions are shorter procedures with faster recovery times. However, implant-based reconstructions have some issues, including implant-associated lymphoma and potential for subsequent implant rupture. This research investigated a new surgical technique of autologous fat reconstruction, compared with implant-based reconstruction. Importantly, patients based from postmastectomy RT were excluded. Six patients withdrew from the autologous fat transfer due to treatment being too burdensome, and 18 dropped out of the implant arm, mainly as they did not wish to proceed with implantation. QOL at 12 months after surgery was higher for those who had received the autologous fat transfer reconstruction. There were higher breast volumes in the implant reconstruction group compared with the autologous fat transfer group, but at 12 months, the difference in mean breast volume between the two options was 83.8mL, with mean volumes of 300.3mL in the autologous fat transfer group and 384.1mL in the implant reconstruction group. The authors have interpreted this finding to support the use of autologous fat transfer, interpreting the 300.3mL as a reasonable mean volume to have at 12 months with this technique. Longer-term follow-up is required to assess later outcomes with this new technique, but the results are promising.

Reference: JAMA Surg 2023;158:456–64
Abstract

Association of allostatic load with all-cause mortality in patients with breast cancer

Authors: Obeng-Gyasi S et al.

Summary: The association between allostatic load and all-cause mortality was investigated in a US cohort of 4459 patients with breast cancer. The mean allostatic load was 2.6, and it was higher in Black versus White patients (adjusted relative ratio 1.11 [95% CI 1.04–1.18]), single versus married/*de facto* patients (1.06 [1.00–1.12]) and those with government-supplied versus private insurance. Compared with the first allostatic load quartile, patients from the third and fourth quartiles had increased mortality risks (respective adjusted HRs 1.53 [95% CI 1.07–2.18] and 1.79 [1.16–2.75]), with the association between allostatic load and all-cause mortality persisting after adjusting for comorbidities.

Comment: Review of this study is my first encounter with the term 'allostatic load'. Allostatic load is defined as the "*cost of chronic exposure to fluctuating or heightened neural or neuroendocrine response resulting from repeated or chronic environmental challenge(s)*". Measurement of allostatic load is undertaken by examining primary mediators of the hypothalamic-pituitary-adrenal axis and the sympathetic adrenal medullary pathway, such as cortisol, secondary outcomes of these two pathways such as C-reactive protein, and tertiary outcomes such as cancer, and using these parameters to give a composite score. For this study, allostatic load parameters were measured from the period 12 months before breast cancer and 6 months after diagnosis. The parameters used for allostatic load calculation were heart rate, blood pressure, BMI, levels of alkaline phosphatase, blood glucose, albumin, creatinine and blood urea nitrogen, and white blood cell count. Allostatic load results were assessed in quartiles. The study also collected data on sociodemographic factors. As was anticipated based on other studies, those with a high allostatic load had higher all-cause mortality. This difference in mortality persisted with adjustment for Charlson Comorbidity Index. Those of Black race, and unpartnered unmarried status had higher allostatic load. Further research to determine whether the mortality risk can be reduced for those within this high allostatic load group would be of interest.

Reference: JAMA Netw Open 2023;6:e2313989
Abstract

Adherence to cancer prevention lifestyle recommendations before, during, and 2 years after treatment for high-risk breast cancer

Authors: Cannioto RA et al.

Summary: The impact of adherence to a recommended post-treatment healthy lifestyle on breast cancer recurrence and mortality was explored in a prospective, observational cohort of 1340 women with stage I–III high-risk breast cancer in the Diet, Exercise, Lifestyles, and Cancer Prognosis study; 65.3% of the women had hormone-receptor positive breast cancer, and 71.2% had completed some education beyond high school. Using an aggregated lifestyle index score based on data on physical activity, BMI, fruit/vegetable consumption, red/processed meat intake, sugar-sweetened beverage consumption, alcohol consumption and smoking status obtained across four timepoints, it was found that patients with the highest versus lowest lifestyle index scores were significantly less likely to experience disease recurrence (HR 0.63 [95% CI 0.48–0.82]) or die (0.42 [0.30–0.59]).

Comment: Multiple lifestyle factors are associated with breast cancer outcome, including exercise, diet, alcohol consumption and smoking. In clinical practice, where much of the focus is on active prescription treatments such as endocrine therapy, the importance of these lifestyle factors should not be underestimated. This is a large study where lifestyle factors before treatment, during treatment and at 1 and 2 years after treatment were assessed. These factors were scored at each timepoint to form a lifestyle index score. There was a marked improvement in outcome for those with the highest compared with the lowest lifestyle index scores, with a reduction in disease recurrence by over one third and a remarkable 58.0% reduction in mortality. These results strongly support the importance of lifestyle factors on breast cancer outcome and patient mortality. Greater resources, education and support for patients to adhere to lifestyle guidelines is imperative.

Reference: JAMA Netw Open 2023;6:2311673
Abstract

Efficacy of alternative dose regimens of exemestane in postmenopausal women with stage 0 to II estrogen receptor-positive breast cancer

Authors: Serrano D et al.

Summary: Postmenopausal women with oestrogen receptor-positive breast cancer who were surgical candidates were randomised to receive exemestane 25mg once daily (evaluable n=55), three times per week (evaluable n=56) or once weekly (evaluable n=60) for 4–6 weeks prior to surgery in this phase 2b trial. For the respective exemestane once daily, three times weekly and once weekly arms: i) the least squares mean percentage changes of serum oestradiol level were –89%, –85% and –60%, with the difference between once daily and three times per week not meeting the noninferiority criterion, although it did when only compliant participants were evaluated (p=0.02 for noninferiority); ii) Ki-67 levels decreased by –7.5%, –5.0% and –4.0% (p=0.31 for once daily versus three times weekly; p=0.06 for once daily versus once weekly); and iii) progesterone receptors fell by –17.0%, –9.0% and –7.0%. Compared with exemestane once daily, exemestane three times per week was associated with better sex hormone-binding globulin and HDL cholesterol level profiles. Adverse events did not differ significantly among study arms.

Comment: Many patients experience significant toxicities with endocrine therapy, often resulting in early cessation of adjuvant endocrine therapy and poorer breast cancer outcomes as a result. Each of the four oral adjuvant endocrine therapy treatments have only one dose and one dosing schedule that has evidence for use in the adjuvant setting: 20mg daily tamoxifen, 1mg daily anastrazole, 25mg daily exemestane and 2.5mg daily letrozole. The mechanism of action of aromatase inhibitors in the adjuvant setting is to lower oestrogen production, such that circulating oestradiol should be undetectable via sensitive oestradiol assay. In this study, patients with early-stage breast cancer who were postmenopausal were randomised to one of three differing dosing schedules of exemestane, 25mg daily, 25mg three times per week or 25mg weekly, for the 4- to 6-week time period while awaiting surgery, and oestradiol levels were measured at baseline and at the final visit. Tissue biomarkers were also assessed as well as HDL and sex hormone-binding globulin, and adverse events. Weekly treatment was inferior to daily exemestane in lowering serum oestradiol level; however, three times per week was noninferior to daily exemestane. While this result is somewhat reassuring, it is possible that there was additional fluctuation of oestradiol levels with the three times per week dosing, which was not captured in this study, with only one subsequent timepoint of blood testing for oestradiol. Daily exemestane should remain the standard of care. For patients who are unable to tolerate exemestane, or an alternative endocrine therapy as per standard treatment schedule, it is possible a reduced schedule of three times per week exemestane may be preferable to no treatment at all; however, additional data would be required to confirm if this is a suitable option.

Reference: JAMA Oncol 2023;9:664–72
Abstract

Long-term survival of breast cancer patients with brain metastases

Authors: Riecke K et al.

Summary: This subanalysis of the German registry for brain metastases in breast cancer sought to identify factors associated with long-term survival among 2889 enrolees, 887 of whom were categorised as long-term survivors (≥15 months). Compared with the other patients, long-term survivors were of younger median age at breast cancer and brain metastases diagnosis (48 vs. 54 years and 53 vs. 59 years, respectively), were more likely to have HER2-positive tumours (59.1% vs. 36.3%) and Eastern Cooperative Oncology Group performance status 0–1 at the time of brain metastases diagnosis (76.9% vs. 51.0%), were less likely to have luminal-like or triple-negative breast cancer (29.1% vs. 35.7% and 11.9% vs. 28.1%), and they had higher pathological complete remission rates after neoadjuvant chemotherapy (21.6% vs. 13.7%) and fewer brain metastases, with 40.9% vs. 25.4% having one, 26.5% vs. 26.7% having 2–3, and 32.6% vs. 47.9% having ≥4. Long-term survivors were also less likely to have leptomeningeal and extracranial metastases than other patients (10.4% vs. 17.5% and 73.6% vs. 82.5%, respectively) and were significantly more likely to have asymptomatic brain metastases at the time they were diagnosed (26.5% vs. 20.1%). Long-term survivors had a median OS duration of 30.9 months (33.9, 26.9 and 26.5 months for HER2-positive, luminal-like and triple-negative breast cancer, respectively).

Comment: This is a large study examining data from the German registry for patients with breast cancer-related brain metastases, examining patient survival and factors associated with survival. For analysis of factors associated with survival, patients were categorised into either long-term survivors, defined as those surviving for over 15 months, which formed approximately one-fifth of the cohort, and non-long-term survivors. Not surprisingly, HER2-positive disease, younger age, lower number of brain lesions and better performance status were all associated with long-term survival, as was less visceral burden. The authors conclude that the findings of this study can be used to guide decisions regarding which patients may be more likely to benefit from additional local and systemic treatment. The study does not, however, report on what interventions the patients received in this prospectively collected dataset. These data would have been useful for interpreting the study findings. The factors identified generally as potentially associated with improved outcome are those that are currently used for determining whether a patient is suitable for additional therapy. It may be that we are undertreating CNS metastases in those with poorer prognostic factors, and that these patients may have an improved outcome with a more aggressive approach.

Reference: ESMO Open 2023;8:101213
Abstract

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer

Authors: Bartels SAL et al.

Summary: These authors reported 10-year results for the phase 3 EORTC 10981-22023 AMAROS trial of axillary lymph node dissection (n=744) versus axillary RT (n=681) in patients with cT1–2, node-negative breast cancer with a positive sentinel node biopsy; 5-year outcomes revealed excellent and comparable axillary control with both modalities and significantly less morbidity after axillary RT. Axillary lymph node dissection did not differ significantly to axillary RT for the 10-year cumulative incidence of axillary recurrence (0.93% vs. 1.82%; HR 1.71 [95% CI 0.67–4.39]), OS (HR 1.17 [0.89–1.52]) or DFS (1.19 [0.97–1.46]). Updated 5-year analyses revealed that axillary lymph node dissection was associated with a higher lymphoedema rate compared with axillary RT (24.5% vs. 11.9% [p<0.001]), but no significant difference in QOL scores. An exploratory analysis revealed that the 10-year cumulative incidences of second primary cancers in the respective axillary lymph node dissection and axillary RT arms were 8.3% and 12.1%.

Comment: This paper reported on the 10-year updated analysis of the AMOROS study, a large study of patients with early breast cancer with sentinel lymph nodes positive, examining outcomes for those treated with axillary RT compared with those who underwent axillary dissection. The study has confirmed no difference in OS, DFS or locoregional control between the two treatment arms, similar QOL and a significantly higher lymphoedema rate in the axillary lymph node dissection arm of 24.5% compared with only 11.9% in the RT alone arm. Clearly given less morbidity from treatment, the data support axillary RT. For a patient with positive lymph nodes, failure to undergo axillary clearance does mean the full pathology information is unknown. The number of lymph nodes involved does inform systemic therapy recommendations, as well as whether additional regional RT is undertaken. We now have the Oncotype DX data where if low-risk score and postmenopausal, chemotherapy can be omitted for patients with hormone receptor-positive breast cancer and 1–3 lymph nodes involved. Without clearance the true nodal burden is unknown, and so a decision needs to be made without the full pathological information. At a patient level, the additional risk of lymphoedema with the additional surgery needs to be weighed against the risk of less well-tailored additional adjuvant therapy. The study was undertaken prior to the Oncotype DX data availability.

Reference: J Clin Oncol 2023;41:2159–65
Abstract

Association between endocrine therapy and cognitive decline in older women with early breast cancer

Authors: Baltussen JC et al.

Summary: These researchers reported on cognitive functioning over time and predictors for cognitive decline in 273 women aged ≥70 years who received treatment (48% endocrine therapy) for stage I–III breast cancer in the prospective, observational CLIMB study. Assessments before treatment and after 9, 15 and 27 months revealed no clinically meaningful decline in MMSE score from baseline (mean 28.2), irrespective of endocrine therapy, and there were slight improvements in MMSE score for women with cognitive impairment prior to treatment across the entire cohort and for the endocrine therapy subgroup. Factors independently associated with declining MMSE scores over time were advanced age, low educational level and impaired mobility, although such declines were not considered to be clinically meaningful.

Comment: 'Chemo brain' is a commonly reported and well described phenomenon. Patients also separately report issues with cognition related to adjuvant endocrine therapy. Declining cognition in the elderly has major implications for function and health burden. This study examined cognitive function in elderly patients treated with adjuvant endocrine therapy. The study measured cognition using the MMSE at 9, 15 and 27 months. Adjuvant chemotherapy was received by 7.3% of the cohort. Twenty-two percent of the cohort received an aromatase inhibitor as adjuvant endocrine therapy, and 21.6% received tamoxifen as endocrine therapy. No significant change was found with adjuvant endocrine therapy. It should be noted that the MMSE is a reasonably blunt screening tool for cognitive impairment. While these findings are somewhat reassuring, there may be aspects of cognitive decline that have been missed with this testing approach. A more extensive cognitive testing battery would be required to definitively assess for cognitive deterioration.

Reference: Eur J Cancer 2023;185:1–10
Abstract

