Breast Cancer Research Review™

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In this issue:

Abbreviations used in this issue:

AI = aromatase inhibitor; **DFS** = disease-free survival; **ER** = oestrogen receptor; **HER2** = human epidermal growth factor receptor 2; **HR** = hormone receptor; **LCIS** = lobular carcinoma in situ; **OS** = overall survival; **PFS** = progression-free survival.

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Welcome to issue 16 of Breast Cancer Research Review.

We are delighted to have Professor Michael Friedlander (Medical Oncologist at the Prince of Wales Cancer Centre in Sydney) as our guest reviewer for this issue.

The results of a large, prospective study that followed over 600 breast cancer patients for lymphoedema indicate that the risk of developing this well-known complication of breast cancer treatment may be smaller than is widely believed. While there was an increased risk of lymphoedema in patients with a body mass index of over 25 as well as in patients with a previous history of cellulitis, there were no significant associations between lymphoedema and ipsilateral blood draws/injections, blood pressure readings, or air travel. Interestingly, in a separate article, a systematic review of the literature and current guidelines has failed to support the contention that venepuncture precipitates breast cancer-related lymphoedema.

A large, multinational, open-label, phase 3 randomised trial that evaluated the combination of adjuvant lapatinib and trastuzumab for early HER2-positive breast cancer found there was no significant improvement in disease-free survival compared with trastuzumab alone. Moreover, lapatinib was associated with added toxicity. The paper concludes that one year of adjuvant trastuzumab remains standard of care.

We hope you find this issue stimulating reading and welcome your comments and feedback.

Kind Regards

Professor Michael Friedlander

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Trastuzumab for $HER2^+$ metastatic breast cancer in clinical practice: Cardiotoxicity and overall survival

Authors: Rossi M et al.

Summary: These researchers examined healthcare administrative data from 681 women residing in Lombardy, Italy, who were treated with trastuzumab for metastatic breast cancer in clinical settings during the period 2006–2009. The analysis assessed short- and long-term overall survival (OS) and cardiotoxicity. OS was 81.8%, 64.0%, 50.2%, 41.1% and 37.2% at 1, 2, 3, 4 and 5 years, respectively. Independent predictors of worse OS were age, brain liver or lung metastasis compared to other metastasis, use of taxanes and other chemotherapies, a cardiac adverse event after trastuzumab use, and a longer time between metastasis and breast cancer diagnoses.

Comment: There is very good evidence to show that trastuzumab improves both PFS and OS in women with metastatic HER2-positive breast cancer but that it can be associated with cardiac toxicity, necessitating regular surveillance of left ventricular function. This study reports the risk of cardiac toxicity in a large population-based cohort of women from Lombardy in Italy, which is more representative of clinical practice than clinical trials, which tend to recruit younger and fitter patients. This study included 681 patients with a median follow-up of 3 years. 32 (4.7%) women were diagnosed with cardiac events – the cumulative risks were greatest during the first (2.4%) and second (4.3%) year and went up to 7.2% by 5 years. The risk was greater in older women >70 (HR 4.3). 2.9% of patients were admitted with congestive cardiac failure. This may be an underestimate of cardiac risk, as the study only included women admitted to hospital for cardiac events, which they included as myocardial infarction, arrhythmias and congestive cardiac failure. The findings are similar to those reported by others and underscore the importance of ongoing monitoring in patients on trastuzumab for metastatic breast cancer.

Reference: Eur J Cancer. 2016;52:41-9

Abstract

Breast cancer-related lymphoedema and venepuncture: a review and evidence-based recommendations

Authors: Jakes AD, Twelves C

Summary: This systematic review of the literature and current guidelines identified 7 published articles and 15 published patient information leaflets concerning the development of lymphoedema as a complication of venepuncture in patients with breast cancer following axillary surgery. There was one small prospective study (level of evidence 2); all other articles were either case-control studies (level 3) or retrospective reviews (level 4). The contention that venepuncture can precipitate lymphoedema was not supported by good evidence. These researchers propose new, patient-centred, evidence-based recommendations for venepuncture in women with breast cancer. These guidelines advocate that whenever possible, venepuncture should be performed on the contralateral arm. In patients where this cannot be readily achieved and lymphoedema is not present, healthcare professionals should consider venepuncture in the ipsilateral arm or insertion of a central venous device as opposed to making further attempts in the contralateral arm or resorting to sites such as veins in the foot. In the absence of lymphoedema, these reviewers state that venesection in the ipsilateral arm carries little, if any, risk of additional complications.

Comment: See adjacent study.

Reference: Breast Cancer Res Treat. 2015;154(3):455-61

Abstract

Impact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer

Authors: Ferguson CM et al.

Summary: This study recruited 632 patients diagnosed with breast cancer between 2005 and 2014 in a single institution in the US, all of whom were screened prospectively for lymphoedema using postoperative bilateral arm volume measurements at regular intervals. At each measurement, patients completed a survey that included exposure information including number of blood draws, injections, blood pressure readings, trauma and cellulitis affecting the at-risk arm, as well as number of flights and length of flight since last measurement. After a median follow-up of 24 months, data collected from a total of 3,041 measurements showed no significant association between increases in arm volume and undergoing ≥1 blood draws (p=0.62), injections (p=0.77), number of flights (1 or 2 [p=0.77] and ≥3 [p=0.91] vs none), or duration of flights (1 to 12 hours [p=0.43] and ≥12 hours [p=0.54] vs none). In multivariate analysis, factors significantly associated with increases in arm volume included body mass index (BMI) ≥25 (p=0.024) and cellulitis (p<0.001), axillary lymph node dissection (p<0.001) and regional lymph node irradiation (p=0.0364).

Comment: Approximately 20% of women will develop lymphoedema after axillary node dissection and the risk is greatest in the first 2 years after surgery. The incidence of lymphoedema is significantly less after sentinel node biopsy and is approximately 5%. There are a number of precautionary measures that have been widely advocated to prevent lymphoedema and these include avoiding blood pressure cuffs, not taking blood from the affected arm as well as wearing a compression sleeve on air travel. However, there is no good evidence to support these recommendations and these 2 papers are instructive and illuminating as they challenge the widely held dogma. Ferguson et al. report the results of a large, prospective study involving 632 women with early breast cancer who were prospectively followed and screened for lymphoedema prior to surgery. They used sophisticated measures to screen for lymphoedema, including relative arm volume change and weight-adjusted volume change using an optoelectric Perometer. At 24 months, the cumulative incidence of lymphoedema was 7.7%. Cellulitis, BMI >25 and axillary node dissection were associated with an increased risk of lymphoedema, but ipsilateral blood draws, blood pressure readings and air travel were not.

The findings of this prospective study are supported by a systematic review of venepuncture and risk of lymphoedema by Jakes and Twelves, which showed that there was no good evidence to suggest that venepuncture can increase the risk of lymphoedema and that venepuncture/venous access on the ipsilateral arm is a reasonable option, providing there is no existing lymphoedema.

The conclusions of these 2 papers are supported by an excellent commentary by Ahn and Port in the *JCO* published on line on December 28 entitled *Lymphedema precautions: Time to abandon old practices?* These papers are recommended to all oncologists, surgeons and nurses who care for women with early breast cancer.

Reference: J Clin Oncol. 2016;34(7):691-8

Abstract

Impact of age at primary breast cancer on contralateral breast cancer risk in *BRCA1/2* mutation carriers

Authors: van den Broek AJ et al.

Summary: This Dutch investigation evaluated 6,294 patients with invasive breast cancer, with and without *BRCA1/2* mutations, treated between 1970 and 2003 and diagnosed at age <50 years, to determine overall and age-specific risks for contralateral breast cancer (CBC). The median follow-up was 12.5 years. Compared with non-*BRCA* carriers, *BRCA1* and *BRCA2* mutation carriers had a 2–3-fold higher risk for CBC (HRs, 3.31 [95% CI, 2.41 to 4.55; p<0.001] and 2.17 [95% CI, 1.22 to 3.85; p=0.01], respectively). Age at first diagnosis of breast cancer was found to be a significant predictor for CBC risk in patients with *BRCA1/2* mutations.

Comment: This paper describes the 10-year cumulative risk of CBC in a large, unselected cohort of women with early breast cancer unselected by family history. This is probably more relevant to clinical practice compared to published data that include *BRCA* mutation carriers ascertained through clinical genetic centres. A more precise estimate of CBC risk would enable individualised counselling regarding surveillance versus prophylactic mastectomy in *BRCA* mutation carriers. The study included 6924 women <50 years old diagnosed with an invasive breast cancer between 1970 and 2003 in the Netherlands. Two hundred women (4.3%) were found to have a *BRCA1* or *2* mutation. The 10-year cumulative risk of CBC was 5.1 % for non-carriers; 21.1% (95% CI, 15.4 to 27.4) in *BRCA1* carriers and 10.8% (95% CI, 4.7 to 19.6) in *BRCA2* carriers. There was a higher risk of a CBC in mutation carriers aged <40 at diagnosis (*BRCA1* 25.5% <41 years and 15.6% >40 years; *BRCA2* 17.2% <41 years and 7.2% >40 years) but this was not evident in non-carriers. The greatest risk of CBC (~38%) was seen in *BRCA* mutation carriers diagnosed at <40 years and with a family history of breast cancer. This study provides unbiased risk estimates that can be used to counsel patients. There are a few important caveats to this study – relatively few patients received hormonal therapy during the time period of the study, which would be expected to significantly reduce the risk of CBC. In addition, a large proportion of patients were diagnosed before 1995 and therefore many *BRCA* carriers were unaware of their mutation status and would not have had a risk-reducing bilateral salpingectomy that would also reduce the risk of CBC by at least 50%.

Reference: J Clin Oncol. 2016;34(5):409-18
Abstract

Predictive value and clinical utility of centrally assessed ER, PgR, and Ki-67 to select adjuvant endocrine therapy for premenopausal women with hormone receptor-positive, HER2-negative early breast cancer: TEXT and SOFT trials

Authors: Regan MM et al.

Summary/Comment: The SOFT and TEXT trials were practice-changing trials that demonstrated that 5 years of adjuvant treatment with an aromatase inhibitor (AI), exemestane (E) in combination with ovarian function suppression (OFS) improved outcomes relative to OFS plus tamoxifen (T) or T alone in women who were at sufficient risk to warrant chemotherapy and who remained premenopausal after treatment. SOFT also showed that in women at low risk of recurrence, T alone is an appropriate option. It would be very helpful in clinical practice to know which women are most likely to benefit from OFS and an AI, as this would help individualise treatment recommendations. The authors investigated the predictive value and absolute magnitude of treatment benefits according to the level of oestrogen receptor (ER), progesterone receptor (PR) and Ki-67 assessed by central review in the 4115 HER2-negative patients in these 2 studies. There was no consistent evidence of heterogeneity of relative treatment effects according to PR or Ki-67 and individually they were of limited predictive value for selecting adjuvant therapy although they were both associated with reduced breast cancer-free intervals and the absolute gains from OFS + E were greater in patients with tumours with low PR and high Ki-67. TEXT and SOFT could not inform the use of ER to select treatment as the majority of tumours had ER expression >90%. The investigators went on to assess the relative treatment benefits based on the 2013 St. Gallen definition of Luminal A/B (A – PR >20% AND Ki-67 <20%; B – PR <20% AND Ki-67 >20%), which may be clinically helpful, although this was a post hoc analysis. The relative treatment benefit of AI plus OFS vs T plus OFS in TEXT and vs T alone in SOFT was evident in both Luminal A and B subgroups but the absolute benefit in Luminal A was quite small (~2%). In Luminal B patients, however, there were larger absolute benefits of E + OFS vs T with or without OFS (7.9% and 10.7% vs T + OFS at 5 years in TEXT no chemotherapy and chemotherapy cohorts, respectively, and 1.5% and 7.1% vs T in SOFT no chemotherapy and prior chemotherapy cohorts, respectively).

Reference: Breast Cancer Res Treat.2015;154(2):275-86
Abstract

Myelodysplastic syndrome and acute myeloid leukemia following adjuvant chemotherapy with and without granulocyte colony-stimulating factors for breast cancer

Authors: Calip GS et al.

Summary/Comment: This study describes the risk of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) following chemotherapy with or without granulocyte colony-stimulating factors (G-CSF) for breast cancer. Secondary treatment-related myeloid cancers are rare and the authors evaluated the risk in over 56,000 women over the age of 66 years who were treated for Stage 1–3 invasive breast cancer between 2001 and 2009 and who were included in the Surveillance, Epidemiology, and End Results (SEER) database. 1.2% of patients were diagnosed with MDS/AML with a median follow-up of 3.2 years. 14% of patients received chemotherapy. The risk of AML/MDS was 2.4% in elderly women treated with anthracycline/cyclophosphamide regimens, which was double that of women treated with surgery only. Adjusted for chemotherapy type, there was a non-significant risk in women who received G-CSF but this was exclusive to those who received 6+ cycles of filgrastim and pegfilgrastim was not found to be associated with an increased risk of AML/MDS. This study is important, as it includes a large number of older women with early breast cancer who are not typically included in clinical trials. Although the risks of AML/MDS are very low, careful consideration regarding the choice of chemotherapy agents in this population is very important.

Reference: Breast Cancer Res Treat. 2015;154(1):133-43
Abstract

Lobular carcinoma in situ: A 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk

Authors: King TA et al.

Summary: These researchers from the Memorial Sloan Kettering Cancer Center reviewed their experience with lobular carcinoma in situ (LCIS) to evaluate factors associated with breast cancer risk. Their prospectively maintained database contained 1060 patients participating in surveillance after an LCIS diagnosis. Comparisons were made among women choosing surveillance, with or without chemoprevention, and those undergoing bilateral prophylactic mastectomies between 1980 and 2009.

Comment: Women with LCIS have been reported to have up to a 10-fold increase in breast cancer risk and the absolute risks of developing ductal carcinoma in situ (DCIS) or invasive carcinoma range from 11% to 28% at 15 years with a persistent risk over time. The investigators report the results of a very large, single institution study that included just over 1,000 patients treated at the Memorial Sloan Kettering Cancer Center after an LCIS diagnosis between 1980 and 2009. The median follow-up for the surveillance cohort was 81 months. The median age at LCIS diagnosis was 50 years. Surveillance alone was the most common management option, chosen by 831 patients (78%); 173 patients (17%) received chemoprevention and 56 patients (5%) chose bilateral prophylactic mastectomy. Occult cancer was identified in six (11%) of 56 prophylactic mastectomy specimens (3 invasive carcinomas <1 cm and 3 with DCIS). The rate of cancer development was approximately 2% per year, which translated into a cumulative long-term rate of 26% at 15 years with no evidence of a plateau out to 150 months of follow-up. The median time to cancer diagnosis was 50 months (6 to 194 months). Of 150 patients who developed cancer, 63% developed cancer in the ipsilateral breast, 25% developed cancer in the contralateral breast, and 12% developed bilateral breast cancer. They reported a very significant decrease in breast cancer incidence in women with LCIS who opted for chemoprevention, with an annual cancer rate of less than 1%, supporting the recommendation for chemoprevention in this patient population. The findings of this large, single institution study are helpful in counselling patients who are diagnosed with LCIS and the risk of breast cancer is similar to that reported in historical studies. Only a small proportion of women with LCIS have chemoprevention and the results of this study and the large randomised trials of chemoprevention reinforce the importance of discussing chemoprevention options with women with LCIS.

Reference: J Clin Oncol. 2015;33(33):3945-52
Abstract

Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: Results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial

Authors: Piccart-Gebhart M et al.

Summary: In the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial, 8,381 patients with HER2-positive early breast cancer were enrolled between June 2007 and July 2011 and randomly assigned to 1 year of adjuvant therapy with trastuzumab, lapatinib, their sequence (trastuzumab→lapatinib), or their combination (lapatinib+trastuzumab). The primary end point was disease-free survival (DFS).

Comment: The ALTTO trial was a very large study designed to test the hypothesis that dual anti-HER2 blockade would improve survival outcomes of patients with HER2-positive early breast cancer compared with adjuvant trastuzumab. It was expected that this would be a positive trial based on the almost doubling of the pathological complete response rates reported in the neoadjuvant trial NeoALTTO, which tested the combination of lapatinib plus trastuzumab with paclitaxel. However, this was a negative trial and there was no significant improvement in DFS with dual blockade of HER2. ALTTO also tested the hypothesis that lapatinib would decrease CNS relapses, have a better cardiac toxicity profile and that the oral medication would be more convenient for patients than intravenous trastuzumab every 3 weeks for 1 year. The lapatinib-alone arm was closed early at interim analysis because a demonstration of noninferiority to trastuzumab was unlikely, and results later showed that patients assigned to lapatinib alone had a worse DFS than those treated with trastuzumab alone. In addition, there were more adverse events with lapatinib and the degree of diarrhoea in particular was unexpected by the investigators who designed the trial. This trial underscores the importance of carrying out large randomised trials before changing practice based on pathological complete response rates in the neoadjuvant setting. There remains significant interest in further exploring the role of dual anti-HER2 blockade and the Breast International Group has carried out the APHINITY (A Study of Pertuzumab in Addition to Chemotherapy and Herceptin [Trastuzumab] as Adjuvant Therapy in Patients With HER2-Positive Primary Breast Cancer) trial based on the positive results of this combination in the metastatic setting. ALTTO also illustrates the improvement in clinical outcomes in patients with HER2-positive early breast cancer, with 4-year overall survival rates of approximately 95%.

Reference: J Clin Oncol.J Clin Oncol. 2015;34(10):1034-42
Abstract

Breast Cancer Research Review™

Independent commentary by Professor Michael Friedlander
AM, PhD, FRACP

Professor Friedlander is a medical oncologist at the Prince of Wales Hospital and Royal Hospital for Women in Sydney conjoint Professor of Medicine at the University of NSW, specialising in the treatment of women with breast and gynaecological cancers. He has published over 250 papers in peer-reviewed publications. His work has been recognised by many awards.

Dose-response effects of aerobic exercise on estrogen among women at high risk for breast cancer: a randomized controlled trial

Authors: Schmitz KH et al.

Summary: This trial randomised 139 eumenorrhoeic, non-smoking women (mean age 34 years, mean BMI 26.8 kg/m^2) to weekly treadmill exercise for either 150 or 300 min over 5 menstrual cycles, or to a control condition that required the women to maintain exercise <75 min/week. A linear dose-response relationship was observed; every 100 min of exercise was associated with a 3.6% lower oestrogen area under the curve in the follicular phase (linear trend test, p=0.03). Levels of luteal phase oestrogen and progesterone were unchanged. There was also a dose-response effect: for every 100 min of exercise, there was a 9.7% decrease in background parenchymal enhancement as assessed by quantitative digitised breast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) (linear trend test, p=0.009).

Comment: The best evidence to reduce the risk of breast cancer in women at high risk is by reducing oestrogen levels either by bilateral oophorectomy or selective oestrogen receptor modulators (SERMs) such as tamoxifen or AIs. However, the uptake of these interventions is relatively low and the investigators in this trial randomised women at increased risk of breast cancer to 2 different exercise regimens (150 minutes or 300 minutes of aerobic exercise on a stationary bicycle weekly) compared to control. This was a very well carried out study and the first dose-response exercise intervention trial to assess effects on endogenous sex hormone exposure among premenopausal women. They were able to demonstrate a dose-response effect with a reduction in follicular phase oestrogen with the high dose of exercise as well as a decrease in background parenchymal uptake on DCE-MRI. It is not known whether this will lower the risk of breast cancer, but the amount of exercise required to slightly lower oestrogen levels may be a disincentive to many, as 300 minutes a week of aerobic exercise is hard to sustain long-term.

Reference: Breast Cancer Res Treat. 2015;154(2):309-18
Abstract

Self-evaluation of adjuvant chemotherapy-related adverse effects by patients with breast cancer

Authors: Montemurro F et al.

Summary: These Italian investigators evaluated a 10-item written questionnaire derived from the US National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for patient-reported chemotherapy-related adverse effects. Their study enrolled 604 women with breast cancer receiving standard adjuvant chemotherapy conducted at 11 outpatient oncology clinics at Italian hospitals between January 2011 and October 2013. Patients were asked to complete the questionnaires after cycles 1 and 3 of chemotherapy. Information on adverse effects was extracted from the patients' medical records for comparison with the patient self-reports. 596 patient questionnaires were collected after cycle 1 and 581 patient questionnaires after cycle 3. Corresponding questionnaire results were extracted from the medical records of 594 and 573 patients, respectively, at the same time point. The percentage of completed questionnaire fields was 80% to 88% (median 82%) for the 2 patient questionnaires. A comparison of the results of the 2 patient-completed questionnaires showed reductions in severity of vomiting, incidence and severity of diarrhoea, incidence and severity of pain, and a statistically significant increase in incidence and severity of both dysgeusia and dyspnoea from the first patient-completed questionnaire to the second. Frequency and severity of chemotherapy-related adverse effects were consistently greater in patient-reported data than physician-reported data. A strong, significantly positive correlation was observed between the magnitude of discrepancy between physician reports and patient reports for each site and the number of patients enrolled at each site.

Comment: There is increasing recognition of the importance of patient-reported outcomes in clinical trials and the need for patients to report the frequency and severity of adverse effects rather than rely on clinicians alone. There are a number of studies that show a "disconnect" between patients and clinicians in reporting of adverse events. The investigators report the results of a large clinic-based study that evaluated whether patients with early breast cancer could grade and report adverse events according to CTCAE version 4.0. Compliance was very high and not surprisingly there was a significant discordance between patients and clinicians for many of the adverse events. One of the reasons for the discordance according to the investigators could be due to heavy physician workloads and inadequate time to spend addressing adverse effects. To the best of my knowledge this is the first study that has been carried out addressing this question in women receiving adjuvant chemotherapy for early breast cancer and arguably patient-reported toxicities should be included in clinical trials in this population of patients.

Reference: JAMA Oncol. 2015 Dec 23:1-8. [Epub ahead of print]
Abstract

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