

SPECIAL ARTICLE ΕΙΔΙΚΟ ΑΡΘΡΟ

Advances in breast cancer management Past year review from the 2014 San Antonio Breast Cancer Symposium

It has been an exciting year for breast cancer management. From the announcement of the Suppression of Ovarian Function Trial (SOFT) results last December at the 2014 San Antonio Breast Cancer Symposium to the latest changes in screening, prophylactic mastectomy and the evaluation of new chemotherapy and targeted therapies this review aims to evaluate the advances of the past year. Emphasizing the most significant presentations at the symposium, it provides a look ahead at the changes anticipated in 2016.

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Πρόοδοι στη διαχείριση
του καρκίνου του μαστού:
Επιθεώρηση του προηγούμενου
έτους από το συμπόσιο
για τον καρκίνο του μαστού
στο San Antonio

Περίληψη στο τέλος του άρθρου

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1. INTRODUCTION

There is no doubt that the San Antonio Breast Cancer Symposium (SABCS) is the largest breast cancer meeting globally, with approximately eight and a half thousand attendances annually. More important, however, is that it is considered “an international scientific symposium for interaction and exchange among basic scientists and clinicians in breast cancer”. In this short review, the exciting strides made in the field of breast cancer research and treatment up until 2015 are described.

2. SURGERY

Controversies and trends in contralateral prophylactic mastectomy (CPM) were discussed in the first Clinic Science Forum. Increasing numbers of women are opting for “maximal surgery” – removal of both the ipsilateral and contralateral breast (fig. 1). These trends are age dependent, with dramatic increases in CPM amongst women over 40 years of age. The annual hazard rate for death from contralateral breast cancer has been decreasing since 1985 due to widespread use of adjuvant systemic treatment. Contemporary rates

for contralateral breast cancer are about 0.2% per year, and examining the impact of CPM on mortality there is currently no robust evidence that CPM reduces mortality. Factors associated with decision-making in favor of CPM

Clinical Science Forum - Controversies and trends in contralateral prophylactic mastectomy (CPM)



Figure 1. The recent increase in contralateral prophylactic mastectomy was a heavily debated issue in the 2014 San Antonio Breast Cancer Symposium.

include genetic testing, family history of breast or ovarian cancer, MRI breast imaging, higher educational attainment and greater innate fear about risk of recurrence. The latter is a major factor for younger women and significant effort should be made to dissuade women with a low likelihood of ipsilateral cancer from undergoing CPM.¹

3. HORMONAL THERAPY

In the first plenary lecture of the 2014 SABCS the potential of genome-directed therapies in estrogen receptor (ER) positive breast cancer was explored. For patients receiving neoadjuvant endocrine therapy, whole genome analysis can provide information on response to aromatase inhibition. It is important to examine both common and low frequency mutations. Translocations on the ER gene can lead to resistance to hormonal therapy and promote hormone-independent growth. This type of resistance could be overcome with ER degrading agents, such as pure anti-estrogens, and pre-clinical models show promise for this approach. Ultimately better neoadjuvant therapy for ER positive breast cancer will lead to better, i.e., less, chemotherapy.

The Perioperative Endocrine Therapy-Individualizing Care (POETIC) trial management group and trialists reported changes in gene expression profiles in response to preoperative aromatase inhibitor therapy.² Mutational profiles and subclones are reproducible between core biopsy samples despite tumor heterogeneity, with high concordance between sample pairs taken at baseline and at surgery. Mutational counts were greater for poor responders than for good responders and were generally lower in surgical than baseline samples, with most pairs of samples showing common clusters on exome sequencing. Genomic analysis of ER positive breast cancers during development of endocrine resistance in postmenopausal women revealed a dramatic fall in mutation numbers among tumors responding to neoadjuvant letrozole compared with non-responders with progressive disease.³

It was emphasized that gene expression profiles change during therapy and baseline analysis alone will not suffice. Using integration of DNA and RNA sequencing in a group of patients enriched for non-response, a 4-gene model was developed which could successfully predict response to letrozole with an overall accuracy of 94%.

Data were presented on potential genetic drivers for lobular cancers, looking for what distinguishes invasive lobular cancer (ILC) from invasive ductal cancer (IDC) at the molecular level. Mutations of *CDH1*, which codes for

e-cadherin, were found in 63%, and *PIK3Ca* in 48% of lobular tumors. Other mutations occurred individually in fewer than 15% of tumor samples. E-cadherin loss is the hallmark of ILC and most mutations of *CDH1* are loss of function events, which lead to reduced levels of e-cadherin protein.⁴

Analyses of gene expression profiling from the Austrian Breast Cancer Study Group 8 trial patients provided some interesting clinical correlates, with statistically significant reductions in disease-free survival (DFS) and overall survival (OS) for luminal B type lobular cancers treated with anastrozole compared with tamoxifen. Cuzik emphasized that there is continuing benefit from tamoxifen and the curves remain divergent. It is too early to conclude whether chemoprevention with tamoxifen will impact on mortality, and it remains unclear whether tamoxifen should be given for 5 years only or for 10 years, with no clear evidence that a duration of >5 years is beneficial in the chemoprevention setting.

The longer-term follow-up data were presented from the International Breast Cancer Intervention Studies (IBIS-1) trial, which randomized high risk women to either tamoxifen or placebo. During the first 5 years, the breast cancer incidence for the tamoxifen and placebo groups was 4.6% and 6.3%, respectively, with the number needed to treat (NNT) to prevent 1 breast cancer being 59. At 20 years, the respective figures were 7.8% and 12.3% for tamoxifen and ovarian function suppression (OFS) or exemestane and OFS. For low risk women, tamoxifen alone for (at least) 5 years is sufficient systemic therapy with no need for chemotherapy or OFS. Those women in the intermediate risk category are perhaps the more challenging in terms of decision-making in this area; age will influence recommendations, but Rugo considers it "reasonable" to offer tamoxifen and OFS to those women who warrant prior chemotherapy. Once again, the estimated absolute benefits from OFS must outweigh the endocrine-related side effects (fig. 2).

The eagerly awaited results of the landmark Suppression of Ovarian Function Trial (SOFT) were presented by Francis et al on behalf of the International Breast Cancer Study Group.⁵ The primary analysis, which was a comparison of tamoxifen and OFS compared with tamoxifen, revealed a small but non-statistically significant increase in disease-free survival for the combination of tamoxifen and OFS compared with tamoxifen alone (fig. 3). Subgroup analysis confirmed that patients not receiving chemotherapy had an excellent disease outcome and derived no benefit from either OFS or a combination of exemestane and OFS. For patients receiving chemotherapy, outcome was improved

16 year long term follow up of the IBIS-I breast cancer prevention trial
[Jack Cuzik – Queen Mary College, London, UK]

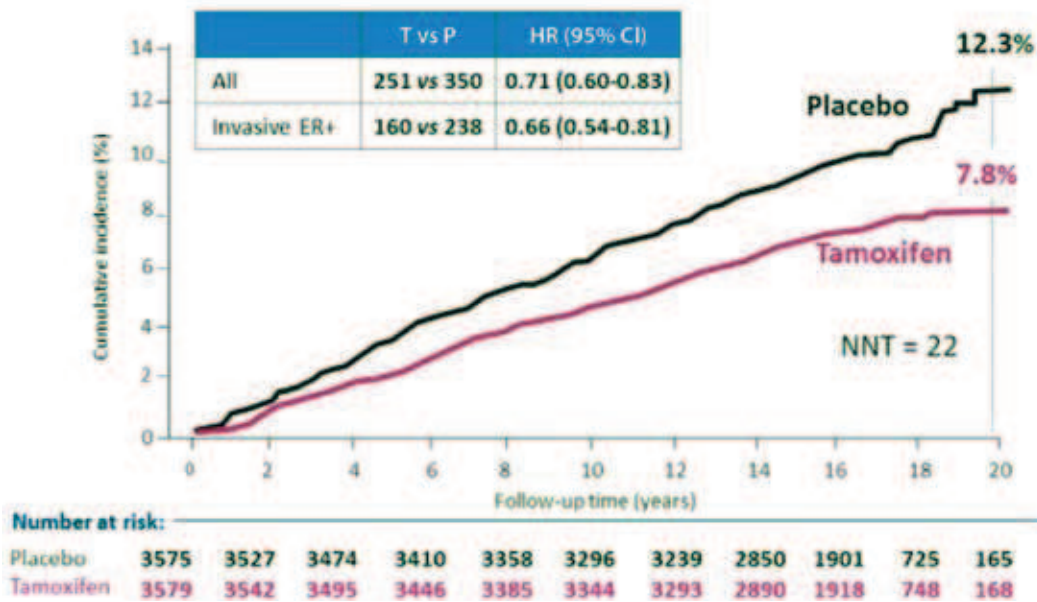


Figure 2. Long-term follow-up: Slide from Jack Cuzik’s presentation at the 2014 San Antonio Breast Cancer Symposium on the long-term risk of tamoxifen administration, from the International Breast Cancer Intervention Studies (IBIS) trial (NNT: Number needed to treat).

Analysis of the Suppression of Ovarian Function Trial (SOFT) [Prudence Francis on behalf of SOFT Investigators – Bern Switzerland (International Breast Cancer Study Group)]

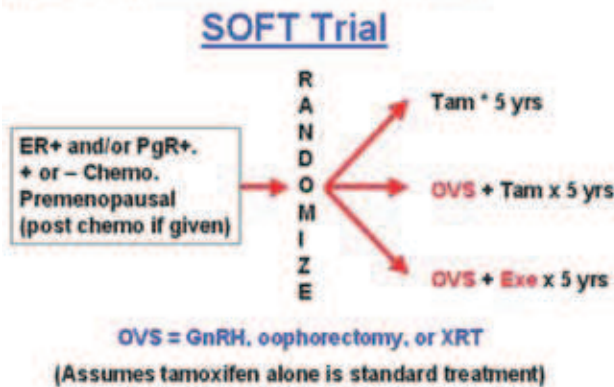


Figure 3. The basic design of the Suppression of Ovarian Function (SOFT) trial: Slide from the SOFT trial group presentation at the 2014 San Antonio Breast Cancer Symposium.

with OFS with 5-year breast cancer-free survival rates of 78% (tamoxifen), 82.5% (tamoxifen+OFS) and 85.7% (exemestane+OFS). Furthermore, prolonged DFS was better for the tamoxifen and OFS group and greater primary outcome effects were evident for all women aged over 35 years.⁶ Women who maintained premenopausal estrogen levels benefited most from tamoxifen and OFS and this was most evident for women aged over 35 years.

4. CHEMOTHERAPY

The results were reported of the phase III Triple Negative breast cancer Trial (TNT), which randomized patients with metastatic or recurrent locally advanced triple negative breast cancer (TNBC) (or *BRCA1/2* mutation) to carboplatin or docetaxol, with NNT=22. There was no evidence of a superior response to carboplatin in unselected TNBC, and progression-free survival was the same in both groups based on a restricted mean survival analysis, with no significant difference in OS. However, response rates were higher for *BRCA 1/2* tumors (68% versus 33%), which may benefit from carboplatin and arguably *BRCA1/2* mutation status should be known for metastatic disease. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B36 trial aimed to determine whether 5-fluorouracil, epirubicin and cyclophosphamide treatment (FEC-100) was superior to standard chemotherapy for patients with node negative breast cancer.⁷ At a median follow-up of 8 years there was no difference between FEC-100 and AC in terms of either DFS or OS. Of note, there were 5 deaths in the FEC-100 group, with higher overall levels of toxicity, which raises the question of whether FEC-100 can be justified for (younger) node negative patients, many of whom will do well without any form of chemotherapy. The addition of adjuvant capecitabine to ibandronate in older women does not improve disease-free survival.

5. TARGETED THERAPIES

The results were presented of the initial Breast cancer trials of Oral Everolimus (BOLERO-1), a phase III randomized controlled multicentre trial of daily everolimus plus weekly trastuzumab and paclitaxel as first line therapy in women with HER2-positive advanced breast cancer. Median progression free survival (PFS) in the everolimus group was not significantly different to that in the placebo group, and on-treatment deaths were recorded in the everolimus group.⁸ Mo Rimawi (Houston) discussed the targeting of ER escape pathways as a strategy for overcoming endocrine resistance. The hypothetical benefits of co-targeting ER and HER2 pathways with longer duration of treatment was investigated in the TBCRC023 trial which randomized women with HER2-positive breast cancer to either 12 or 24 weeks of dual HER2 inhibition with lapatinib and trastuzumab. A significantly increased rate of pCR was observed in the 24 weeks group compared with the 12 weeks of therapy group (28% versus 12%). This increase in pCR was almost entirely confined to the ER positive group and therefore it appears that more prolonged dual anti-HER2 and endocrine therapy (without chemotherapy) could offer a promising research strategy for ER positive and HER2-positive tumors. The results were presented of the phase III Ibandronate with or without Capecitabine in Elderly patients with early breast cancer (ICE) study, which randomized women aged ≥ 65 years to treatment with either ibandronate alone or ibandronate combined with capecitabine. The three year DFS was similar in the two groups but there were more side effects in the capecitabine group. The outcome for moderate or high risk patients receiving ibandronate alone was favorable, with 5-year DFS and OS rates of 77% and 85%, respectively. The immunotherapy approach is progressing rapidly, with improved understanding of immunogenic tumors and immunological characterization of TNBC. The potential application of HER2 T cell-dependent bi-specific antibodies (HER2-TDB) for the treatment of

chemo-resistant HER2 positive breast cancer was discussed. HER2-TDB induces T-cell proliferation with anti-tumor effects conditional upon activation of T-cells. The immune gene PD-L1 is found on tumor cells, and a combination of HER2-TDB with anti-PD-L1 enhances growth inhibitory effects in genetically engineered mouse models. Evidence is accumulating of a molecular distinction between ILC and IDC, which could have relevance for treatment strategies.

6. SCREENING

A particularly controversial topic at the 2014 SABCS was supplementary screening for women with dense breasts. Legislation has now been enacted in the United States, with a mandate that radiologists make women aware of the potential benefits of supplementary screening for those with dense breast tissue on conventional screening with mammography. The state of Connecticut was the first to adopt this legislation and data were presented suggesting that supplementary screening with breast ultrasound can detect an additional 3.2 cancers per 1,000 high risk women. All these additional cancers were detected in women with a normal mammogram but dense breast tissue. Discussant Jafi Lipson conceded, however, that the clinical impact of finding these additional cancers is unknown and some of them might be detected at the next screening round (and still remain impalpable).⁹ No data are available on the effects of supplementary screening on mortality, and the increase in false positive results (5–10%) with ultrasound screening represents a particular problem. A recent analysis concluded that supplemental ultrasound would increase costs with little benefit.¹⁰ Tomosynthesis may offer better prospects for supplemental screening, with an increase in the cancer detection rate but reduction of false positive cases by as much as 15–30%. Several presentations in the final session of the meeting addressed advances in targeted therapies with a focus on biological and endocrine agents.

ΠΕΡΙΛΗΨΗ

Πρόοδοι στη διαχείριση του καρκίνου του μαστού: Επιθεώρηση του προηγούμενου έτους από το συμπόσιο για τον καρκίνο του μαστού στο San Antonio

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Το παρόν έτος ήταν εντυπωσιακό για τη θεραπευτική αντιμετώπιση του καρκίνου του μαστού. Αυτή η ανασκόπηση έχει σκοπό την αξιολόγηση των εξελίξεων του εν λόγω έτους, αρχίζοντας από την ανακοίνωση των αποτελεσμάτων της μελέτης SOFT τον περασμένο Δεκέμβριο στο συμπόσιο για τον καρκίνο του μαστού στο San Antonio έως τις

τελευταίες εξελίξεις αναφορικά με τον προληπτικό έλεγχο, την προληπτική μαστεκτομή και την αξιολόγηση των νέων μορφών χημειοθεραπείας και στοχευμένων θεραπειών. Δίνοντας έμφαση στις πλέον σημαντικές παρουσιάσεις του συμποσίου του προηγούμενου έτους, προδιαγράφονται οι εξελίξεις του έτους που ακολουθεί.

Λέξεις ευρητηρίου: Καρκίνος μαστού, Ογκολογία καρκίνου μαστού, Συμπόσιο San Antonio

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