San Antonio 2019: interesting topics for daily clinical practice in breast cancer

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Summary The San Antonio Breast Cancer Summit is one of the most important meetings worldwide for physicians who treat breast cancer. As traveling there is always somewhat of an adventure due to the distance and the time of the year (winter) and access is not easy for all physicians, the goal of this article is to provide an overview of the presentations dealing with hormone-receptor-positive breast cancer, capecitabine, prevention, and hormone replacement therapy. Data and results should positively influence daily practice.

Keywords San Antonio · Clinical practice · Relevant 2019 · Guidance

SABCS 2019: hormone-receptor-positive breast cancer, adjuvant chemotherapy, and prevention

Preventing breast cancer (BC) is still one of the most important goals for those physicians working with women who are at higher risk to suffer from BC. Trials such as the IBIS-I [1], the STAR Trial [2], the Royal Marsden Prevention Trial [3] and the NSABP-P1 [4] showed that women treated with SERMs (Selective Estrogen Receptor Modulator) like tamoxifen (TAM) and raloxifen do not develop invasive BC. Two presentations at the SABCS 2019 dealt with this topic.

Randomized trial of low-dose tamoxifen to prevent recurrence of breast intraepithelial neoplasia. Study TAM01 [5]

Women with premalignant diseases (ADH, LCIS, DCIS), increased risk (Gail, BCSC), gene mutation carriers, prior radiation and hormone replacement therapy (HRT) users or obese women should be treated in order to prevent BC. TAM lowers overdiagnosis by 30% in high-risk women undergoing screening mammography [6]. Reduction in breast density during intake of TAM could present one potential predictive marker for prevention [7]. If women show more than 10% of reduction in mammographic density after 1 year they should continue with therapy.

As we already saw in the past, there was no disadvantage of using low-dose TAM in presurgical trials in order to reduce Ki-67. The presented trial randomized women aged less than 75 years and at higher risk for breast cancer into two arms comparing TAM 5 mg/day (babytam) vs. placebo. The primary endpoint was the incidence of invasive BC or DCIS.

All breast events decreased by 50% (28 vs. 14) in the babytam group and contralateral breast cancer decreased by 75% (12 vs. 3) with almost identical treatment adherence in both arms (TAM 64.8% vs. placebo 60.7%).

Conclusion: Babytam is safe and cost effective in preinvasive disease and likely to increase uptake also in unaffected women at risk. The benefit of babytam may be greater in postmenopausal women and those with baseline hot flashes. Screening and prevention should go hand in hand when women are already engaged in health-modifying behaviors.

Recent guidelines suggest increasing the minimal 5-year risk threshold to 3%.

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As already mentioned in the 2019 ASCO Clinical Practice Guideline Update low-dose TAM may be an alternative in women with intraepithelial neoplasia as concern about adverse effects is a major reason for poor continuation of endocrine therapy in those women.

Long-term results of the International Breast Cancer Intervention Study II (IBIS-II) using anastrozole [8]

As the IBIS-II and MAP3 trials have already shown an impact of aromatase inhibitors (AI) on breast cancer incidence in high-risk postmenopausal women, Cuzick et al. gave a 60 month update with a special focus on the posttreatment period.

Postmenopausal women aged 40–70 years at increased risk for BC received either anastrozole (ANA) or placebo for 5 years and had a median follow-up of almost 11 years.

The BC incidence after 5 years was 4.6% for placebo vs 1.8% for ANA (HR 0.39) and 8.8% for placebo vs. 5.3% for ANA after 12 years (HR 0.51). These results were even more impressive than in the IBIS-I trial (TAM vs placebo HR 0.72). Adherence to treatment was similar (77.0% placebo vs. 74.6% ANA; HR 0.89).

Conclusion: ANA significantly reduces breast cancer by 49% in postmenopausal women at increased risk after a 12-year follow-up particularly for ER-positive disease (54%). There was also a substantial reduction of 36% in the posttreatment period. The number needed to treat to prevent one breast cancer after 12 years is 29. No increase in fractures with ANA was observed and there was no difference in major adverse events between groups. These data provide further clear support for use of ANA for BC prevention in high-risk postmenopausal women.

NSABP B-42: extended adjuvant endocrine treatment with letrozole [9]

The 10-year results demonstrate a statistically significant improvement in DFS with extended letrozole (LET): 16% reduction in DFS events and 4% absolute improvement. There was no significant difference in OS with LET vs. placebo. Extended LET provided statistically significant improvement in BCFI. LET did not significantly increase the risk of osteoporotic fractures or thrombotic events.

Conclusion: These findings suggest that careful assessment of potential candidates for extended LET should be performed considering age, nodal status, comorbidities, information on BMD, and tolerance of therapy in the initial 5 years. Genomic classifiers may further assist with the decision to recommend extended AI therapy.

Validation of the clinical treatment score post 5 years (CTS5) in women with HR positive, HER2 negative, node negative disease from the TAILORx study [10]

As there is a known continued risk of late recurrence in HR positive disease, the CTS5 score was developed to predict late distant recurrence by involving nodal status, tumor size, tumor grade, and age. Women aged 18–75 years with luminal A breast cancer who were distant recurrence free after 5 years were investigated.

Conclusion: Low rates of late DR were observed in the TAILORx cohort. CTS5 is highly prognostic for the prediction of late DR specifically for patients older than 50 years and much less prognostic for younger ones. The most prognostic value of CTS5 was observed in women at intermediate or higher risk for recurrence classified by Oncotype Dx. Further evaluation in premenopausal cohorts is needed before CTS5 can be applied in younger patients.

Menopausal hormone therapy and breast cancer: long-term findings from the Women's Health Initiative randomized clinical trials [11]

After more than 50 years, the influence of hormone therapy on breast cancer remains controversial with discordant findings from observational studies to randomized clinical trials. Patients with or without hysterectomy were randomized either to receive CEE (conjugated equine estrogen) with or without progestrone (MPA) vs. placebo.

Conclusion: The use of CEE-alone and CEE plus MPA (for those without hysterectomy) have opposite effects on breast cancer. CEE-alone significantly decreases breast cancer incidence and deaths from breast cancer, which persist over decades after discontinuing use. CEE plus MPA significantly increases breast cancer incidence and associated mortality, which also persist over a decade after discontinuing use. These findings, in conjunction with other hormone therapy effects on clinical outcomes, should influence clinical decision making.

Adjuvant endocrine therapy in 2020: it's complicated [12]

This presentation summarized all essential topics concerning treatment of hormone receptor positive BC.

Conclusion:

- The use of AI is associated with improved outcomes in postmenopausal women.
- The addition of bone remodeling agents further decreases recurrence in postmenopausal patients.

- Premenopausal women with “high-risk” cancers should be treated with ovarian suppression and exemestane.
- Longer tamoxifen is superior to shorter durations but data is much less clear on extending AI therapy.
- Ongoing trials are evaluating the addition of CDK inhibition and mTOR inhibition to standard endocrine therapy.

Addition of S-1 to endocrine adjuvant treatment—Potent trial [13]

S-1 is a combination drug based on biochemical modification of fluorouracil, containing tegafur, gimeracil, and oteracil. S-1 is administered twice a day for 14 days and 7 days off for 1 year. Patients at intermediate or higher risk of recurrence who would be candidates for additional adjuvant chemotherapy or who already had neoadjuvant treatment were randomized after surgery either to receive S-1 + endocrine therapy vs. endocrine therapy alone.

Primary endpoint was iDFS. Secondary endpoints were OS, DFS, and safety.

Conclusion: The 5-year invasive disease-free survival was significantly better in the treatment group with a HR 0.63 compared to endocrine treatment alone. Therefore, the authors concluded that the oral formulation of S-1 should be added to endocrine therapy and would be an important treatment option for ER+ and HER2 negative patients at intermediate or high risk of recurrence. Overall the safety profile of S-1 was manageable.

Effects of capecitabine as part of neo/adjuvant chemotherapy

A meta-analysis of individual patient data from 12 randomized trials including 15,457 patients [14]

The primary objective of this analysis was to examine the effect of capecitabine (CAP) on DFS. Secondary objectives were the effect on OS and to test if there is an interaction of occurrence of capecitabine-specific toxicity and treatment effects. Median follow-up of this examination was 79 months.

Overall CAP did not alter DFS in this meta-analysis, but when it was administered in addition to other systemic treatment an improvement in DFS was observed. OS was improved by CAP treatment in the overall cohort and when given in addition. Only patients with triple negative breast cancer (TNBC) benefited from treatment with CAP overall and in addition to other systemic therapy in terms of DFS and OS. All effects were small; the largest was observed for OS in patients with TNBC who received capecitabine in addition (HR 0.78). There was no evidence supporting a predictive value of capecitabine-specific adverse events on patient outcome.

Conclusion: The addition of capecitabine to other systemic treatment may be recommended for TNBC patients. The two trials driving the results are CreateX [15] and FinXX [16] although different CAP doses were applied. The effect of the addition of CAP to other systemic treatment including carboplatin in TNBC remains to be investigated.

CBCSG-10

Adjuvant capecitabine in combination with docetaxel and cyclophosphamide plus epirubicin for TNBC [17]

Patients with TNBC received three cycles of docetaxel with or without CAP and were then switched to either receive FEC or EC in combination with CAP (1000mg/m² bid).

Conclusion: Capecitabine concomitantly administered with taxane/anthracycline significantly improved DFS rates in early TNBC (5-year DFS with capecitabine vs control 86.3% vs 80.4%, HR 0.66). XT-XEC is an alternative adjuvant regimen for TNBC with clinically meaningful improvement in survival and safety data in line with the known capecitabine safety profile.

Take home message

Like every year, data presented at the SABCS influences the treatment of breast cancer patients in our daily practice. Prevention can be offered more easily with low doses of tamoxifen for those patients at higher risk to suffer from breast cancer. In clinical routine we are searching for tools to evaluate patients at higher risk for a late recurrence. CTS5 offers such a tool. Patients with luminal A tumors who would profit from adjuvant chemotherapy can be treated alternatively with S-1 as recent data have shown. We tend to offer capecitabine after neoadjuvant chemotherapy for patients with TNBC: one meta-analysis and one trial have had a closer look at its role. Hormone replacement therapy is less dangerous than thought and can be offered to a selected group of patients. The WHI study guides us to the use in our daily routine.

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