short review

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Post San Antonio: immunotherapy, chemotherapy and new combinations

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Summary This article gives a summary of several studies presented at the San Antonio Breast Cancer Symposium in 2018. In specific, the biomarker analysis of the 'IMpassion130' trial, the effects of CDK4/6 inhibitors on T-cells and tumor immunogenicity, adjuvant chemotherapy in older patients, the prognostic relevance of achieving a pathologic complete response after neoadjuvant therapy, the quality of life analysis of the 'TAILORx' trial, the prognostic impact of detecting bone marrow tumor cells at the time of primary resection and b-cell lymphoma 2 as a new possible therapeutic target in luminal breast cancer, are discussed.

Keywords B-cell-lymphoma-2 · Atezolizumab · IMpassion130 · TAILORx · PADDY

Take home messages

- Expression of PD-L1 on tumor infiltrating immune cells currently is the key biomarker for the use of atezolizumab in triple negative disease.
- Promising new therapeutic options under investigation in ER positive patients are pembrolizumab combined with abemaciclib and for those with BCL-2 overexpression venetoclax combined with endocrine therapy.

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Introduction

This article discusses studies presented at the last San Antonio Breast Cancer Symposium (SABCS) which focused on immune checkpoint inhibitors, neoadjuvant and adjuvant chemotherapy, the prognostic value of bone marrow biopsy and B-cell lymphoma (BCL) 2 as a new therapeutic target.

'IMpassion130' biomarker analysis

Since the publication of the phase 3 trial IMpassion130, immune checkpoint inhibition represents a new treatment standard in a subset of patients with triple negative advanced breast cancer. In this study, atezolizumab combined with nab–paclitaxel showed substantial superiority in terms of overall survival (OS) compared to placebo and nab–paclitaxel in patients with positive (≥1%) expression of programmed death ligand 1 (PD-L1) on tumor infiltrating immune cells (IC). The biomarker analysis presented at SABCS 2018 now showed that the level of PD-L1 expression beyond 1% is not correlated to therapeutic outcome. PD-L1 expression on tumor cells was positive in 9% of all patients and was predictive for prolonged progression-free survival (PFS) on atezolizumab. This was not the case for OS, probably due to the small number of such patients. As the majority of these patients had PD-L1 positive IC as well, it was concluded that the additional testing of tumor cell PD-L1 expression does not provide clinically relevant additional information. The detection of cluster of differentiation 8 positive (CD8+) intratumoral cells also correlated with positive PD-L1 expression of IC and, as expected, was predictive for an increased OS and PFS of atezolizumab. However, this was only confirmed in the PD-L1 positive subgroup of patients. Furthermore, evidence of stromal tumor-infiltrating

lymphocytes (sTILs) was predictive for better PFS on atezolizumab but not for OS. BRCA mutational status did not exhibit any predictive value. In conclusion, positive IC PD-L1 expression turned out to be the most robust predictive biomarker for effectiveness of atezolizumab combination therapy [1].

Combination of CDK 4/6 inhibitors with immunotherapy

Cyclin dependent kinase (CDK) 4/6 and cyclin D play a major role in the transition from the cell cycle synthesis (S) to G1 phase by activation of essential signaling pathways for cleavage. Inhibition of CDK4/6 hence hinders cell division and has become standard therapy for estrogen receptor (ER) positive disease. Several studies at SABCS elaborated the plausibility of combining CDK4/6 inhibitors with immunotherapy [2].

CDK4/6 inhibitors have diverse effects on T-cells. On the one hand, they block cyclin-dependent T-cell proliferation and thereby seemingly counteract the effect of immunotherapy. On the other hand, however, preclinical studies suggest that T-cell differentiation and effector function could be increased by CDK4/6 inhibitors, which would be expected to enhance the efficacy of immunotherapy. Moreover, nonclinical research indicates that tumor antigen presentation, which has been observed under CDK4/6 inhibitors, possibly increases tumor immunogenicity. Together this data set provides the foundation of a phase 1b trial testing the combination of abemaciclib and pembrolizumab in 28 patients who had received previous chemotherapy. After 24 weeks of therapy, the objective response rate was 29% [3]. Further studies are underway.

Chemotherapy in older patients

To evaluate the benefit of and reasons for adjuvant chemotherapy in patients older than 65 years, the US National Cancer Database was searched for patients with newly diagnosed breast cancer between the years 2004 and 2015 [4]. Around 160,000 patients were available for evaluation, of which 60% received adjuvant chemotherapy. Age was a statistically significant factor in terms of patient selection for adjuvant chemotherapy. The median age of patients receiving chemotherapy was 5 years younger than of those who did not. An increase in OS was shown independently of age, leading to the conclusion that older patients do benefit from adjuvant chemotherapy, whereby the absolute benefit depends on comorbidities and resulting competing causes of mortality. To better estimate the probability of the occurrence of higher grade adverse events in older patients undergoing adjuvant therapy, the newly developed score “Chemo Tox Risk Score for breast cancer” can be used as a simple tool in clinical practice [5].

Pathologic complete response after neoadjuvant therapy

The question whether a pathogenic complete response (pCR) post neoadjuvant chemotherapy is a prognostic factor in terms of event-free survival (EFS) and OS was addressed by a meta-analysis including 52 trials with almost 30,000 patients [6]. In the overall study population, a significant benefit was seen if a pCR was reached in terms of 5-year EFS (88% vs 67%) and OS (94% vs 75%) compared to having residual disease. Especially patients with triple negative as well as those with human epidermal growth factor receptor 2 (HER2) positive histology profited substantially. In luminal disease, a positive trend was seen which was not statistically significant.

This study formally proofed a direct positive correlation between a change in pCR rate and a change in EFS. Administration of postoperative chemotherapy after pCR showed no advantage and also does not correspond to current clinical practice.

In residual disease after HER2-directed therapy, postoperative administered trastuzumab emtansine markedly lowered the risk of recurrence compared to trastuzumab, which was shown in the KATHERINE trial. [7] The GEICAM trial tested the addition of adjuvant capecitabine after standard (neo)adjuvant chemotherapy in triple-negative disease [8]. While there was a significant benefit in the subgroup of non-basal like histology, this trial alone does not suffice for defining a new treatment standard because superiority was not shown in the intent to treat population.

Quality of life analysis of TAILORx

The TAILORx trial randomized ER positive and node negative patients with an intermediate risk score (11–25 points) by the gene expression test Oncotype DX© to chemotherapy followed by endocrine therapy versus endocrine therapy alone. There was no difference in distant disease-free survival (DDFS) for this intermediate-risk population. However, patients younger than 50 years were at higher risk for developing metastases with increasing Oncotype DX© risk score within the intermediate risk group. This elevated risk was slightly but statistically significantly reduced by chemotherapy in the subgroup of patients with a risk score greater or equal to 16 points. In contrast, patients older than 50 years did not benefit from chemotherapy if they were in the intermediate-risk group.

At SABCS 2018, the quality of life (QOL) evaluation of TAILORx was presented [9]. Of about 6600 patients with intermediate Oncotype DX© score, 454 participated in the QOL questionnaire. Interestingly, no significant difference in the overall QOL evaluation was found between the chemotherapy plus endocrine therapy group versus the endocrine ther-

apy alone group. Analysis by category showed worse fatigue during and to a lesser extent after chemotherapy (follow up 36 months). However, evaluation by menopausal status yielded important differences in two categories: Postmenopausal women experienced substantial cognitive impairment and worsened endocrine symptoms with chemotherapy. On the other hand, premenopausal patients had markedly higher cognitive impairment 3 months after the start of chemotherapy; this difference however completely disappeared after 6–9 months. In almost the same manner, endocrine symptoms were initially elevated by chemotherapy but without a difference to endocrine therapy alone after 1 year. Apparently the leading cause of QOL deterioration in younger patients are symptoms induced by early menopause which were experienced in both treatment arms. In conclusion, while older or postmenopausal patients with an intermediate risk score receiving chemotherapy suffer significantly from side effects without any benefit, younger or premenopausal patients gain a small benefit from chemotherapy with acceptable tolerability if the risk score exceeds 16 points. A possible limitation of this study is that fewer than 10% of all patients participated in the QOL questionnaire thereby reducing its validity.

Prognostic impact of detection of bone marrow tumor cells

The PADDY trial investigated the prognostic implication of detectable tumor cells in a bone marrow biopsy performed during primary breast cancer resection [10]. Eleven centers participated in this study including more than 10,000 patients. Tumor cells were found in 27.3% of all patients with an unexplainable heterogeneity between the centers (differences as high as 20%). As already known, proof of tumor cells in the marrow correlates with a worse prognosis; in this study, PFS was reduced by around 20% with an HR of 1.23 for OS if disseminated tumor cells were found. Bone marrow tumor cells were more likely to be detected in patients with a higher grading, higher T stage, positive nodes, negative ER status, positive HER2 status and triple negative disease. Subgroup analyses revealed a noticeable prognostic benefit in terms of DDFS for the luminal B subtype and to a lesser extent for HER2 positive disease if no tumor cells were found in the marrow. In patients with luminal A and triple negative histology, a positive trend was seen for longer DDFS which was not statistically significant. As no predictive value has as yet been shown for bone marrow tumor cells, routine bone marrow biopsy at the time of primary resection will likely not be implemented in routine clinical practice.

B-cell lymphoma 2: a new possible therapeutic target

Proteins of the BCL family regulate cell apoptosis with some inhibiting and others promoting apoptosis. BCL-2 acts anti-apoptotic and thereby possibly serves as a therapeutic target if overexpressed. At present, venetoclax, a BCL-2 inhibitor, is approved for the treatment of chronic lymphatic leukemia. It is known that luminal breast cancer exhibits overexpression of BCL-2 quite often (~70%) and that the extent of expression is of prognostic relevance. Preclinical trials with venetoclax combined with endocrine therapy have shown anti-tumorigenic effects in breast cancer cell lines. In a phase 1b trial with the combination of tamoxifen and venetoclax in pretreated patients with ER and BCL-2 positive breast cancer, an ORR of 54% and a clinical benefit rate of 75% were reached in those 24 patients receiving the full dose of 800 mg venetoclax [11]. An impressive duration of response was achieved with a median of 42 weeks. Treatment was well tolerated with no toxicity-associated discontinuation, the leading side effects were lymphopenia in 88% of patients (30% grade 3–4), neutropenia in 73% of patients (mostly grade 1–2) and nausea in 67% of patients (all ≤grade 2). Because of this promising early data, the phase 2 trial VERONICA has been launched investigating venetoclax in combination with fulvestrant.

Conflict of interest K. Mayrhofer and K. Strasser-Weippl declare that they have no competing interests.

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