short review

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(Neo)adjuvant approaches: pavement on the road to cure—breast cancer

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Summary During the past few decades, major advances have been achieved in the treatment of early breast cancer (BC) resulting in improvements of invasive disease free survival and overall survival. New treatment substances have been established in neoadjuvant and adjuvant settings. On the other hand, deescalation strategies are studied to get more tailored treatment concepts.

Keywords Early breast cancer · Treatment · Neoadjuvant and adjuvant strategies

During the past few decades, major advances have been achieved in the treatment of early breast cancer (BC). The role of neoadjuvant and "post-neoadjuvant" strategies is gaining increasing relevance. The main types of BC, i.e., hormone receptor-positive (HR+), HER2-positive (HER2+), and triple-negative (TN) types, require different treatment approaches.

Hormone receptor-positive breast cancer

In HR+ BC, neoadjuvant or adjuvant chemotherapy is given depending on several clinical risk factors, such as tumor size, positive lymph nodes, proliferation index, hormonal status, and age. In adjuvant settings, these risk factors play an important role for decision-making regarding whether chemotherapy should be administered or not. Gene signatures such as Oncotype DX, MammaPrint, or PAM50 can be used in situations with unclear benefit [1].

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In adjuvant-treatment patients with four or more positive lymph nodes or one–three positive nodes and G3 or tumor size ≥ 5 cm, the CDK4/6 inhibitor abemaciclib in addition to standard antihormonal treatment should be given for 2 years. In the MonarchE trial, the 4-year invasive disease-free survival (iDFS) was increased from 79.4 to 85.5% (hazard ratio: 0.664; $p < 0.0001$) [2]. Also, ribociclib, another CDK4/6 inhibitor was tested in the adjuvant setting for lower-risk patients. In the NATALEE trial, ribociclib showed promising results with an increase in 3-year iDFS from 87.1 to 90.4% in the first interim analysis [3]. Patients with stage II–III BC and, moreover, patients with node-negative disease were included in this trial.

For high-risk patients harboring a germline *BRCA 1* or *BRCA 2* mutation, olaparib given for 1 year beyond antihormonal treatment should be given. The OlympiAD trial randomized patients with HR+ BC and at least four positive lymph nodes or a CPS + EG score ≥ 3 after neoadjuvant chemotherapy [4]. Olaparib improved the 3-year DFS for 7.1% and the 4-year overall survival (OS) from 86.4 to 89.9% [4, 5].

In the KEYNOTE 756 trial, which was presented at ESMO 2023, adding pembrolizumab to neoadjuvant chemotherapy for patients with high-risk HR+, HER2– BC led to a significant increase in pathological complete response (pCR; [6]). However, long-term follow-up data are needed in this population.

Triple-negative breast cancer

The main aim of neoadjuvant treatment is to reach a pCR. Cortazar et al. showed that patients with pCR, especially with TNBC, had the best event-free survival and overall survival [7].

In stage II and stage III TNBC, combination treatment of chemotherapy with the immune checkpoint-inhibitor (ICI) pembrolizumab should be given [8].

A significant improvement in pCR was reached (51.2 to 64.8%, $p<0.001$). The event-free survival after 3 years was 84.5% in the pembrolizumab arm versus 76.8% in the placebo arm [9]. The highest benefit seemed to be in patients with residual cancer burden (RCB) II with a hazard ratio of 0.52 (0.32–0.82; [10]). The benefit of continuation of pembrolizumab in patients with pCR after neoadjuvant combination treatment is unknown. In the GEPAR Nuevo Trial, durvalumab was used as ICI combination. Despite the fact that no significant improvement in pCR was shown, all patients had a benefit from adding durvalumab independently from reaching a pCR [11]. In stage I TNBC, chemotherapy combination without ICI remains the standard of care. These patients were excluded from the KEYNOTE 522 trial.

Patients without pCR after neoadjuvant treatment benefit from adjuvant treatment. Currently, there seem to be some possibilities. In the CREATE X trial, capecitabine was given for six up to eight cycles and showed an improvement in DFS from 56.1 to 69.8% after 5 years and an OS benefit of 8.3% was reached [12].

In TNBC patients with germline *BRCA 1* or *BRCA 2* mutation, adjuvant treatment with olaparib should be given. In the OlympiA trial, TNBC patients with residual disease after neoadjuvant chemotherapy and patients receiving adjuvant chemotherapy with positive lymph nodes or tumor size of at least 2 cm were included.

Currently, the optimal post-neoadjuvant approach in patients with residual disease remains unclear. In principle, options consist of pembrolizumab continuation, single-agent capecitabine or olaparib, or off-label combinations.

The ongoing SASCIA trial, randomizing sacituzumab-govitecan versus standard of care in patients with residual disease in TNBC and in HR+ BC with a CPS + EG score ≥ 2, might provide another treatment option. In the ASCENT 05 trial, the combination of sacituzumab-govitecan and pembrolizumab in TNBC patients with residual disease is studied [13].

The ongoing ABCSG 45 trial randomizes patients with TNBC and homologous recombination deficiency to neoadjuvant treatment with carboplatin and olaparib versus standard chemotherapy [14].

HER2-positive breast cancer

In HER2+ BC, a neoadjuvant chemotherapy regime in combination with dual HER2 blockade is the preferred strategy [15–17]. Several trials have shown its cardiac safety with pCR rates over 50% [16, 17]. In patients with residual disease, post-neoadjuvant treatment with trastuzumab-emtansine (T-Dm1) for 14 cycles is standard of care [18]. In the KATHERINE trial the risk of recurrence or death was reduced for 50% of cases compared to trastuzumab alone in these patients [18]. Data show that also patients with HER2-negative residual BC benefit from T-Dm1 [19]. The DESTINY-Breast 05 trial compares standard post-neoadjuvant treatment with T-Dm1 versus trastuzumab-deruxtecan in patients with HER2+ disease [20].

The pan-tyrosine kinase inhibitor neratinib is recommended for high-risk patients after completion of neoadjuvant or adjuvant treatment. Patients after neoadjuvant treatment were only included in the ExteNET trial if they had residual disease [21]. Patients with HR+ disease had an improvement in DFS, but no improvement in OS could be reached after 8 years [22]. In a subgroup analysis the highest benefit could be seen in patients with residual disease or positive lymph nodes [23]. The ongoing COMPASHer RD trial analyzes the combination of T-Dm1 and tucatinib in high-risk patients as post-neoadjuvant treatment in order to reduce the occurrence of brain metastases [24].

Nonetheless, in some patients less treatment could be sufficient. The phase II APT trial showed that in patients with small (max. 3 cm), node-negative HER2+ BC, the combination of adjuvant paclitaxel with trastuzumab alone is a reasonable and safe treatment [25]. The WSG-ADAPT-HER2+/HR– trial compared 12 weeks of neoadjuvant dual blockade with paclitaxel versus dual blockade alone. Epirubicin and cyclophosphamide were given after surgery, and for patients with pCR adjuvant chemotherapy could be omitted. However, the WSG-ADAPT-HER2+/HR– trial was a small phase II trial. The phase III trial TRAIN 2 aimed to omit anthracyclines in the neoadjuvant treatment of HER2+ BC [27]. Rates of pathological response were comparable between an anthracycline-containing regime and one without anthracyclines. Both subgroups received carboplatin in combination with paclitaxel and dual HER2 blockade; in the anthracycline-free arm, taxane-based treatment cycles were escalated [27]. The combination of pertuzumab and trastuzumab without anthracycline was not inferior in pCR, DFS, and OS rates with differing toxicity [26]. In the PHERGain phase II trial, a PET-based pathologic complete response strategy to omit chemotherapy in HER2+ tumors under dual HER2 blockade showed promising results [28].

However, further trials including large numbers of patients are needed. Another obstacle is to distinguish between patients who need more treatment and those who need less treatment. Liquid biopsy could help to monitor response to neoadjuvant treatment. Magbanua et al. showed that positive ctDNA can predict remaining residual disease in neoadjuvant treatment [29].

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