short review

memo (2019) 12:312–314
https://doi.org/10.1007/s12254-019-00530-x

memo
magazine of european medical oncology

Adjuvant breast cancer: (neo)adjuvant therapy for HER2-positive breast cancer

The best of ASCO 2019

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Received: 18 August 2019 / Accepted: 19 September 2019 / Published online: 15 October 2019

Summary Early stage HER2-positive cancer outcomes have been substantially improved over the last two decades, but there is still some potential for improvement. Several studies on the preoperative/postoperative treatment of HER2-positive breast cancer were presented at the American Society of Clinical Oncology (ASCO) 2019 annual meeting.

Keywords Breast cancer · Her2-positive · Adjuvant treatment · Trastuzumab · T-DM1

Role of trastuzumab emtansine

The KATHERINE trial on trastuzumab emtansine (T-DM1) superiority over trastuzumab for patients with residual disease after neoadjuvant therapy were presented last year, providing a new standard therapy. After the ASCO 2019, this antibody drug conjugate might also have an additional effect in the neoadjuvant stage and offer an option to selected patients. Patient-reported outcomes of the phase III KATHERINE trial were now presented: the mean scores showed only a small deterioration from the baseline in treatment-related symptoms in both of the studied arms. More patients in the T-DM1 group reported clinically deterioration of a number of symptoms at any given point of the study; the baselines in global health status and functioning were, however, maintained in both arms during the treatment [1, 2].

Achieving pathologically complete response (pCR) is a surrogate for an improved long-term outcome, especially in high-risk breast cancer types [3]. The standard care for HER2-positive breast cancer in the preoperative setting is chemotherapy along with dual HER2-blockade with pertuzumab and trastuzumab, leading to pCR rates ranging from 46 to 62% [4, 5]. Due to the toxicity of systemic chemotherapy, de-escalated therapy strategies are still a matter of debate.

Hurvitz et al. presented the final results of the phase III KRISTINE trial. A total of 444 patients were randomly assigned to receive either six cycles of neoadjuvant therapy with carboplatin, docetaxel, trastuzumab and pertuzumab, or six cycles of T-DM1 and pertuzumab. The combination of chemotherapy and dual blockade resulted in a better pCR rate compared to pertuzumab plus T-DM1 (56% versus 44%; $p = 0.155$), while the latter regimen showed a better safety profile (≥grade 3 adverse events 64% versus 13%). The event-free survival (EFS) rate after 3 years was 94.2% with chemotherapy, trastuzumab, and pertuzumab, compared to 85.3% in the T-DM1 arm. Interestingly, there was a higher number of preoperative locoregional recurrences, with 15 in the T-DM1 arm versus none in the arm treated with the chemotherapy and dual blockade combination. However, invasive disease-free survival (IDFS) rate after 3 years was 92% in the chemotherapy group versus 93% in the T-DM1 group [6, 7]. This suggests that there is a group of patients that might benefit from a de-escalated therapy strategy and that identifying such a group would be helpful.

The phase II trial PREDIX randomly assigned 202 patients with operable HER2-positive breast cancer with a tumor size >20 mm and/or verified lymph node metastasis to neoadjuvant therapy with either six cycles of T-DM1 or docetaxel in combination with trastuzumab and pertuzumab. Adjuvant therapy consisted of two to four cycles of epirubicin/cyclophosphamide, followed by radiotherapy and en-

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docrine therapy in hormone receptor positive (HR+) disease. The pCR rates were 47% and 45% for patients receiving T-DM1 and chemotherapy as well as dual blockade ($p = 0.359$). In HR+ patients, pCR rates were lower, with 36% in both arms; in HR– tumors, the pCR rates were 67% in patients with docetaxel/trastuzumab/pertuzumab and 57% in the T-DM1 arm ($p = 0.502$). Not surprisingly, grade 3/4 adverse events were more common in the chemotherapy arm [8].

Neoadjuvant therapy with T-DM1 might therefore be a valid option for at least selected patients with comorbidities, older age or contraindications for standard chemotherapy plus dual blockade.

Heterogeneity in HER2-positive breast cancer

Although high pCR rates can be achieved in HER2-positive breast cancer, there is still a group of patients that do not respond at all or do not respond well to the standard treatment. One of the obstacles for treatment may be the heterogeneity in HER2 gene amplification or HER2 protein expression. A total of 163 patients were enrolled in a phase II single-arm study presented at ASCO 2019 by Metzger et al. Patients received six cycles of neoadjuvant therapy with T-DM1 plus pertuzumab. The primary endpoint of the study was the association between pCR rate with the level of HER2 genetic and/or regional intratumor heterogeneity. Intratumor heterogeneity was defined as HER2-positivity by fluorescence in situ hybridization (FISH) in more than 5% and less than 50% of tumor cells and/or an area of tumor with HER2-negativity. In all, 10% of the patients met the definition of HER2 intratumor heterogeneity. The pCR rate in the HER2 non-heterogeneous group was 55%, whereas none of the patients in the HER2 intratumor heterogeneity group achieved a pCR ($p = 0.001$). The effect was independent from a patient's hormone receptor status, and represents a distinct subset of patients with HER2-positive breast cancer who may need more than standard anti-HER2 therapy [9].

De-escalated therapy strategies

In the adjuvant phase, for most patients with stage I HER2-positive breast cancer, taxane treatment and 12 months of trastuzumab may be sufficient, with a 7-year disease-free survival rate of 93% [10]. In stage II and III HER2-positive breast cancer, patients with initially node-positive disease, dual blockade with trastuzumab and pertuzumab is now standard. In the case of residual disease after neoadjuvant therapy, T-DM1 has become a new standard treatment. For patients with low-risk HER2-positive breast cancer, where 12 months of trastuzumab is still the standard of care, discussions on de-escalating strategies with a shorter duration of trastuzumab are ongoing. The PERSEPHONE trial, which explored whether 6 months of trastuzumab are as effective as 12 months, suggests that the shorter treatment regimen is non-inferior to the standard duration (4-year DFS 89.8% for 12 months versus 89.4% for 6 months) [11]. On the other hand, there are also two negative trials with 6-month durations of trastuzumab—PHARE and HORG—which underline the need of biomarkers to help us identify the subgroup of patients who might benefit from de-escalation of treatment [12, 13].

Dose-dense chemotherapy and trastuzumab

A meta-analysis on over 37,000 patients with early breast cancer showed that adjuvant dose-dense (DD) chemotherapy improves the outcome. However, there are less data on the combination of DD chemotherapy and trastuzumab [14, 15]. A secondary analysis of the phase 3 PANTHER trial was presented at ASCO 2019. Women with node-positive breast cancer or high-risk node-negative breast cancer received either 4 cycles DD epirubicin/cyclophosphamide followed by 4 cycles of DD docetaxel or standard 3-weekly 5-fluorouracil/epirubicin/cyclophosphamide followed by 3 cycles of docetaxel. HER2-positive patients received one year of adjuvant trastuzumab. There was no significant difference between cardiac outcomes after 4 and 6 years of follow-up between HER2-positive and HER2-negative patients, nor between the DD treatment and the standard treatment. The breast cancer relapse-free survival as the primary endpoint was not statistically significant, the risk of breast cancer relapse was decreased by 32% in the DD therapy arm [16].

Conclusion

While studies in the (neo)adjuvant phase in the subgroup of HER2-postive disease presented at ASCO2019 were not immediately practice-changing, the data presented will help to differentiate treatment and define further clinical and biomarker study approaches in order to optimize treatment in a more individualized manner.

Funding Open access funding provided by Medical University of Graz.

Conflict of interest C. Suppan and M. Balic declare that they have no competing interests.

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