State of the art in neoadjuvant therapy of breast cancer

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1. Introduction

Neoadjuvant therapy is no longer an option just for locally advanced operable cancers in order to facilitate breast-conserving surgery, but also for all early breast cancers when an indication for chemotherapy is given [1]. Pathological complete response (pCR) – defined as the absence of residual invasive or sometimes even in-situ cancer on breast and lymph nodes after preoperative therapy – has been shown to predict long-term outcome in patient-based analyses of several randomised clinical trials [2–4]. Achieving pCR is important mainly for those patients with an unfavourable initial prognosis, such as HER2-positive/hormone-receptor- (HR-)negative, triple-negative breast cancer (TNBC) and some luminal-B-like tumours. In contrast, the survival benefit of patients with pCR was less pronounced in luminal-A-like tumours (HR-positive, HER2-negative, grade 1–2) [2,4].

Because of the different behaviours of breast cancer subtypes, a neoadjuvant strategy tailored on clinicopathological criteria should be considered the optimal option (Table 1).

2. HR-positive disease

The GeparTrio trial [5] investigated a response-guided approach based on early response assessment; the treatment was either intensified with two additional cycles in the case of an early response, or changed to a different chemotherapy in the case of no response. Response-guided strategy led to a higher pCR rate in patients with HR-positive tumours, without a significant improvement in disease-free survival. These discordant results might be explained by the established weak prognostic impact of pCR in HR-positive disease [2,4].

3. HER2-positive disease

In studies adding trastuzumab to neoadjuvant chemotherapy, patients with HER2-positive/HR-negative tumours achieved the highest pCR rate across subtypes [3]. Otherwise, in the German neoadjuvant trial experience, an increasing number of chemotherapy cycles might be related to a higher pCR rate in patient with HER2-positive/HR-positive disease [4]. Moreover, results from the Tryphaena study showed that six to eight cycles of a taxane-based chemotherapy, including either an anthracycline or carboplatin, plus trastuzumab and pertuzumab lead to an increased pCR rate of >60% [6].

Currently, a sequential chemotherapy approach containing anthracycline–cyclophosphamide and a taxane plus trastuzumab is the better choice for patients with HER2-positive disease. The addition of pertuzumab to this sequence, or to a taxane–carboplatin combination, could be a future option when it becomes available.

4. TNBC

The simultaneous application of docetaxel, doxorubicin and cyclophosphamide (TAG) for six cycles accounts for the highest pCR rates in TNBC patients in the German neoadjuvant studies, particularly for patients with an early response after only two cycles [7].

As shown in the GeparQuinto study, the treatment effect might be further improved by adding bevacizumab to neoadjuvant chemotherapy [8]. However, even considering the non-confirmatory results of the NSABP B40 trial [9], the use of this anti-angiogenic drug in the neoadjuvant setting should be further investigated.

In the near future the role of bevacizumab and carboplatin will be better defined by the GeparSixto study [10] which is investigating bevacizumab given simultaneously to weekly carboplatin, paclitaxel, and pegylated doxorubicin in TNBC and HER2-positive patients; and by the CALGB 40603 study [11] which is evaluating three weekly carboplatin and bevacizumab in a 2 by 2 factorial design in patients treated with weekly paclitaxel followed by dose-dense doxorubicin/cyclophosphamide.
5. Conclusion

In conclusion, considering that HER2-positive/HR-negative and TNBC patients who achieve pCR showed a prognosis comparable to that of patients with luminal-A-like tumours [2], a neoadjuvant strategy tailored to different breast cancer subtypes can completely change the natural history of some cancers.

**Conflict of interest statement**

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