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-positve/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 (TAC) 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.

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Table 1 – Different neoadjuvant approaches according to breast cancer subtypes.

Subtype	Neoadjuvant treatment	Reference
HR-positive disease	EC–Pw TAC × 2 → response-guided chemotherapy	Meta-analyses of several neoadjuvant studies[2–4] GeparTrio[5]
HER2-positive disease	EC(H)–TH FECHP–TH or TCH (plus P if available)	Meta-analyses of several neoadjuvant studies[2–4] Tryphaena[6]
TNBC	TAC EC–Pw Role of bevacizumab is uncertain Role of carboplatin is uncertain	Meta-analysis of seven German neoadjuvant studies[7] Meta-analyses of several neoadjuvant studies [2–4] GeparQuinto[8] and NSABP 40[9]Waiting for GeparSixto[10] and CALGB 40603[11] Waiting for GeparSixto[10] and CALGB 40603[11]

E, epirubicin; C, cyclophosphamide; Pw, paclitaxel weekly; T, docetaxel; A, doxorubicin; F, 5-fluorouracil; H, trastuzumab; P, pertuzumab; TNBC, triple-negative breast cancer.

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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REFERENCES

[1] Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf [assessed 14.05.13].

[2] von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012 May 20;30(15):1796–804.

[3] Houssami N, Macaskill P, von Minckwitz G, Marinovich ML, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. Eur J Cancer 2012;48(18):3342–54.

[4] von Minckwitz G, Untch M, Nüesch E, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011;125(1):145–56.

[5] von Minckwitz G, Kümmel S, Vogel P, et al. German Breast Group. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008;100(8):552–62.

[6] Schneeweiss A, Chia S, Hickish T, et al. Neoadjuvant pertuzumab and trastuzumab concurrent or sequential with an anthracycline-containing or concurrent with an anthracycline-free standard regimen: a randomized phase II study (TRYPHAENA). Cancer Res 2011;71(24 Suppl. 3).

[7] von Minckwitz G, Mamouhdian-Dekordi C, Loibl S, et al. Response characteristics and overall survival of 781 patients with triple-negative breast cancer – a meta-analysis on 7 German neoadjuvant studies. AACR Annual Meeting 2013.

[8] von Minckwitz G, Eidtmann H, Rezai M, et al. German Breast Group; Arbeitsgemeinschaft Gynäkologische Onkologie–Breast Study Groups. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012;366(4):299–309.

[9] Bear HD, Tang G, Rastogi P, Geyer Jr CE, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med 2012;366(4):310–20.

[10] Available from: http://clinicaltrials.gov/show/NCT01426880 [accessed 14.05.13].

[11] Available from: http://clinicaltrials.gov/show/NCT00861705 [accessed 14.05.13].