Breast Cancer Online
www.bco.org

Breast Cancer Online (www.bco.org) 2004; **7**(11),
doi:10.1017/S1470903104001191

ISSN 1470-9031

Focus On

Principles of preoperative chemotherapy

G. von Minckwitz

German Breast Group, Neu-Isenburg/Frankfurt, Germany.

Abstract Efficacy of preoperative (primary, neoadjuvant) systemic chemotherapy significantly improved over the last two decades. Only about 3% of patients reached a pathological complete remission after preoperative treatment with cyclophosphamide, methotrexate and 5-fluorouracil in the late 1980s, whereas today up to 18% have no viable tumour cell detected at histological examination when taxane-containing regimens, for example adriamycin/cyclophosphamide followed by docetaxel or docetaxel/adriamycin/cyclophosphamide, are being used. This improvement has implications on current treatment recommendations and should be considered when this approach gains a broader use in routine practice.

Keywords: Breast cancer; Neoadjuvant; Primary; Preoperative; Chemotherapy

Who should receive preoperative chemotherapy?

Primary systemic therapy is considered the standard treatment for patients with inoperable primary breast cancer. These are patients with locally advanced tumours for whom it is expected that by surgery only insufficient local control can be reached and includes tumour stages IIIA/IIIB or T3/T4, classic inflammatory breast cancer or involvement of ipsilateral supra- or infraclavicular lymph nodes (N3). Even if this approach has never been tested against a primary surgical approach in large randomized clinical trials, there is general agreement about this recommendation.

In operable breast cancer, preoperative chemotherapy may be considered as an alternative to adjuvant systemic treatment as all large randomized trials of primary systemic therapy vs. adjuvant systemic therapy have shown that these therapies offer patients equivalent disease-free survival and overall survival benefit to the patients. However, in most of these trials, the rate of breast conservation was significantly increased after primary systemic therapy. In the largest trial reported to date, in which patients had a median follow-up time of 8 years, no statistically significant difference was found in local recurrence-free survival between patients treated with primary systemic therapy (four cycles of adriamycin/cyclophosphamide (AC)) and those treated with adjuvant systemic therapy (four cycles of AC) [1].

Therefore, it is increasingly considered as a reasonable alternative for patients:

- With operable breast cancer who are deemed to be appropriate candidates for mastectomy but who desire less extensive surgery (e.g. breast conservation surgery).
- Who can technically have a lumpectomy up-front but whose physical appearance will be less damaged if primary systemic therapy is given first.
- Who wants to take advantage of the response assessment of the primary tumour before it is removed. A demonstrable response to primary systemic therapy may have a positive effect on the patient's compliance with further treatment and on the patient's willingness to accept some adverse events.
- Who may have medical contraindications to surgery or may simply wish to delay surgery. For example, primary systemic therapy can be used in the second or third trimester in pregnant patients diagnosed

Correspondence to: PD Dr Gunter von Minckwitz, German Breast Group, GBG Forschungs GmbH, Schleussnerstraße 42, 63263 Neu-Isenburg/Frankfurt, Germany. E-mail: minckwitz@germanbreastgroup.de; Tel: +49 6102 79874-0; Fax: +49 6102 7987440

Publication date 16/11/04
BCO/119/2002/FO

with breast cancer; this is followed by surgery and radiotherapy after delivery [2].

Preoperative chemotherapy with the aim to make breast conservation possible seems to be less appropriate in multicentric tumours, in the presence of microcalcifications in all quadrants or if radiotherapy to the remaining breast is not possible.

What regimen should be used?

Today, a sequential administration of anthracyclines and taxanes for more than four cycles in total can be considered as the best option when operability of the tumour should be improved. The AC followed by docetaxel regimen has been assessed in two large randomized trials and showed superiority against four cycles of AC or four cycles of a dose–dense combination of adriamycin and docetaxel [3,4]. In both trials tamoxifen was given simultaneously to chemotherapy; however, this is not recommended today as it may deteriorate the effectivity of the cytotoxic agents [5]. It still remains an open question, if the supplementation of the taxane or the duration of treatment is more important. Other sequential treatments that have been explored in large phase III trials are the adriamycin/paclitaxel (AT) followed by cyclophosphamide, methotrexate and 5-fluorouracil (CMF) [6] or a dose–dense sequence of epirubicin and paclitaxel [7].

Recently, high pathological complete remission (pCR) rates have been reported by weekly application of paclitaxel [8] or the addition of trastuzumab to cytotoxic treatment [9]; however, these results have to be confirmed by larger, multicenter trials.

Are there predictors for achieving a response?

Tumour size and clinical signs for lymph node involvement do not have an impact on the effect of preoperative chemotherapy. There is increasing evidence that the absence of oestrogen and progesterone receptors lead to a higher sensitivity towards preoperative chemotherapy [3,4,6,7,10]. Early response to treatment, for example after the first two cycles of aggressive chemotherapy with docetaxel/adriamycin/cyclophosphamide (TAC), can be considered as an *in vivo* chemosensitivity test and predicts a high chance for a pCR. In patients with hormone insensitivity tumours and early response results pCR rates of up to 50% have been reported [10]. On the other hand, hormone receptor positive, well-differentiated tumours without nodal involvement in postmenopausal patients have only a very low chance for a complete remission and are better candidates for (adjuvant) endocrine treatment.

There are strong efforts made to predict outcome to chemotherapy by multiple gene expression profiling. However, the results up to now are very inconsistent and the methods are not validated [11]. They cannot be recommended outside of scientific projects so far.

How should surgery be performed?

Precise localization of the primary tumour site is crucial for proper surgery. This should be started before the initiation of chemotherapy; for example, by a photograph of a sketch painted on the skin of the patient showing the exact localization and size of the tumour as well as the proposed surgical skin incision. The tumour should be followed carefully during chemotherapy by repeated physical and sonographical examinations involving both, the medical and surgical oncologist. Different marking procedures have been recommended in clinical trials (e.g. inserting clips or coils in the centre of the lesion or placing a tattoo on the skin); however, due to our experience stereotactic location of the remaining tumour by sonography, mammography or magnetic resonance tomography appeared to be most feasible. If no residual tumour can be detected by either method, the initial tumour area can be located by mammography, guided by the baseline film. The complete disappearance of the tumour on clinical examination and imaging methods has been a rare event until recently, but with the increasing rate of pCR, this may become more frequent, and standardized location procedures need to be developed.

Surgery is an obligatory part in the multidisciplinary approach to treat breast cancer. Patients have to be informed that even in the event of a complete disappearance of the tumour there remains significant uncertainty upon the histological result and sufficient local control cannot be reassured. No increased risk for local failure can be deducted from the current available data if the extend of excision is adapted to the actual tumour size at the end of surgery. A reduced tissue removal is linked with an increased rate of re-excisions (up to 20%) of which the patient should be informed. Up to now, only limited information is available of the use of sentinel node biopsies after preoperative chemotherapy. This method seems to be more difficult in this setting due to scar like changes of the axillary tissue.

Today primary systemic therapy offers an optimal test situation for the evaluation of new compounds and the detection of new biological or molecular markers of either response or resistance. Pathological complete remission may be used as a surrogate endpoint to substitute for survival and potentially provides a possibility of avoiding the arduous process

doi:10.1017/S1470903104001191

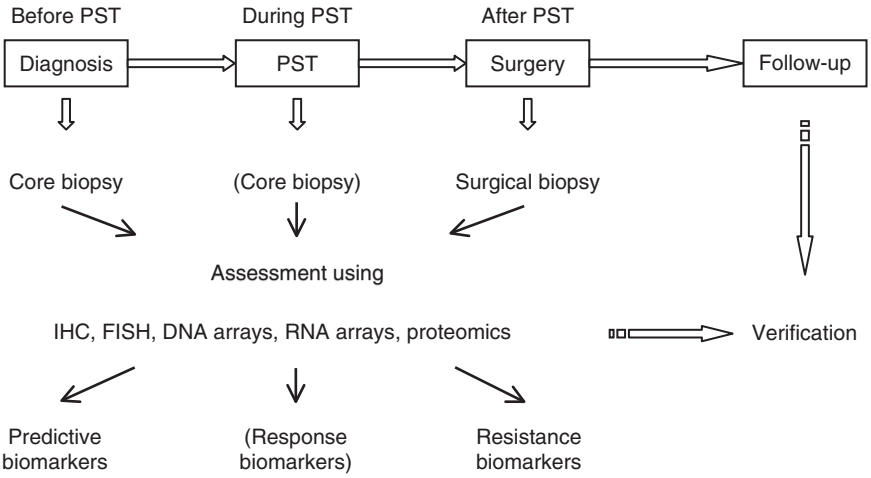

Figure 1.
Assessment of markers for prediction, response, and resistance in the primary systemic therapy (PST) setting. (IHC: immunohistochemistry; FISH: fluorescence in situ *hybridization.)*

of large randomized trials. In addition, tissue banking before, during, and after primary systemic therapy may permit the identification of undiscovered patterns of presentation of biological or molecular discriminants that could help exclude ineffective treatments and optimize systemic regimens (Fig. 1).

References

1. Wolmark N, Wang J, Mamounas E, *et al*. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr* 2001; **30**: 96–102.
2. Kaufmann M, von Minckwitz G, Smith R, *et al*. International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. *J Clin Oncol* 2003; **21**: 2600–2608.
3. von Minckwitz G, Raab G, Schütte M, *et al*. Dose–dense versus sequential adriamcycin/docetaxel combination as preoperative chemotherapy (pCHT) in operable breast cancer (T_{2-3}, N_{0-2}, M0) – Primary Endpoint Analysis of the GEPARDUO-Study. *Proc ASCO* 2002.
4. Bear HD, Anderson S, Brown A, *et al*. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2003; **21**: 4165–4174.
5. von Minckwitz G, Costa SD, Raab G, *et al*. Dose–dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb Study. *J Clin Oncol* 2001; **19**: 3506–3515.
6. Gianni L, Baselga J, Eiermann W, *et al*. First report of the European Cooperative Trial in operable breast cancer (ECTO): effects of primary systemic therapy (PST) on local-regional disease. *Proc ASCO* 2002.
7. Untch M, Konency G, Ditsch N, *et al*. Dose–dense sequential epirubicin–paclitaxel as preoperative treatment of breast cancer: results of a randomised AGO Study. *Proc ASCO* 2002.
8. Green MC, Buzdar AU, Smith T, *et al*. Weekly (wkly) paclitaxel (P) followed by FAC as primary systemic chemotherapy (PSC) of operable breast cancer improves pathologic complete remission (pCR) rates when compared to every 3-week (Q 3 wk) P therapy (tx) followed by FAC – final results of a prospective phase III randomized trial. *Proc ASCO* 2002.
9. Buzdar AU, Hunt K, Smith T, *et al*. Significantly higher pathological complete remission (PCR) rate following neoadjuvant therapy with trastuzumab (H), paclitaxel (P), and anthracycline-containing chemotherapy (CT): initial results of a randomized trial in operable breast cancer (BC) with HER/2 positive disease. *Proc ASCO* 2004.
10. von Minckwitz G, Blohmer JU, Raab G, *et al*. *In-vivo*-chemosensitivity adapted preoperative chemotherapy in patients with early stage breast cancer. The GEPARTRIO Pilot Study. *Ann Oncol* [in press].
11. Pusztai L, Wang J, Coombes K, *et al*. Cross platform comparison of multigene predictors of response to neoadjuvant paclitaxel/FAC chemotherapy in breast cancer generated by cDNA arrays and Affymetrix GeneChips. *Proc ASCO* 2004.