State of the art of neoadjuvant chemotherapy in breast cancer: rationale, results and recent developments

Aktueller Stand der neoadjuvanten Chemotherapie des Mammakarzinoms: Gründe, Resultate und neuere Entwicklungen

Abstract

Aims, results, advantages and possible disadvantages of preoperative chemotherapy (pCHT) for breast cancer are discussed in this review. Established chemotherapeutic regimens are described with respect to new drugs that are added to combinations now and in the future. Illustrating the potential of new components, trastuzumab and cytotoxic chemotherapy, were combined in neoadjuvant trials for the first time. This approach yielded impressing and unprecedented high pathological response rates. An overview regarding current neoadjuvant cytostatic and immunotherapy trials is given. Established prognostic factors like axillary lymph-nodal status are altered during pCHT, which causes the need for new prognostic markers. The consequences of these changes for clinical decision making are demonstrated. It seems possible that the advances of gene array and protein expression profile technologies will lead to improved prognostic and predictive statements. Tumor tissue can be analyzed before during and after treatment in this regard recent studies investigating the response to specific, chemotherapeutics in correlation to molecular markers are reviewed. These approaches might enable us to identify chemo resistance of specific tumors. Furthermore pCHT allows testing of chemosensitivity in vivo in an early stage, which might lead to a more individualized cancer therapy.

We discuss radiotherapy after neoadjuvant therapy and the risk of local relapse after breast conserving surgery, which was made feasible by pCHT. It is shown how the evaluation of efficacy of new cancer drugs, using the neoadjuvant situation, can be done more rapidly than in the metastatic and adjuvant setting.

Keywords: preoperative/neoadjuvant chemotherapy, breast cancer, local recurrence, prognostic factors, cancer biology

Zusammenfassung

Diese Übersichtsarbeit beschäftigt sich mit Zielen, Resultaten, Vorteilen, Kontraindikationen und möglichen Nachteilen der präoperativen Chemotherapie (pCHT) des Mammakarzinoms. Etablierte chemotherapeutische Kombinationen werden mit neuen Pharmaka verglichen, welche momentan und zukünftig in neoadjuvante Regime integriert werden. Das Potential neuerer Komponenten illustrieren erstmals unternommene neoadjuvante Studien, in welchen Trastuzumab und konventionelle Chemotherapeutika kombiniert wurden. Die Raten an pathohistologischen Ansprechraten waren beeindruckend und unerwartet hoch. Ein Überblick über aktuelle präoperative chemotherapeutische und immunotherapeutische klinische Studien wird in dieser Übersichtsarbeit vermittelt.

Aufgezeigt werden die therapeutisch bedingten Veränderungen etablierter Prognosefaktoren wie der des axillären Lymphknotenstatus während der pCHT, die sich daraus ergebende Notwendigkeit neue Prognosema-

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ker zu finden und die hieraus erwachsenden Konsequenzen für die klinische Entscheidungsfindung. Es erscheint möglich, dass die Fortschritte der Gene Array und Protein Expressionsprofil Technologie verbesserte prognostische und prädiktive Aussagen ermöglichen. Tumorgewebe kann vor, während und nach der Therapie analysiert werden. Diesbezüglich werden aktuelle Arbeiten, die das Ansprechen der Tumoren auf bestimmte Chemotherapeutika mit molekularen Markern korrelieren, diskutiert. Diese Ansätze könnten uns die frühzeitige Identifikation chemoresistenter Tumoren ermöglichen. Darüber hinaus handelt es sich bei der pCHT um einen in vivo Chemosensitivitätstest, der in Zukunft zu einer individuelleren und maßgeschneiderten Krebsbehandlung führen könnte.

Wir diskutieren die Strahlentherapie nach neoadjuvanter Therapie und das Risiko eines Lokalrezidivs nach brusterhaltender Chirurgie, welche erst durch die präoperative Applikation der Chemotherapie ermöglicht wurde.

Es wird aufgezeigt, wie die Evaluation und Zulassung neuerer Krebstherapeutika im Rahmen von präoperativen Behandlungskonzepten viel schneller als in der metastasierten oder adjuvanten Situation erfolgen kann.

Introduction

Originally patients with inflammatory or inoperable locally advanced breast cancer were treated with preoperative chemotherapy. The initial aim was down sizing and down staging of tumors in order to allow a surgical procedure such as mastectomy or even breast conserving treatment. At the time being an increasing number of patients with operable tumors is treated with pCHT [1]. In this neoadjuvant setting tumor response to treatment can be monitored. The efficacy of chemotherapeutics can be rapidly improved which might lead to improved survival. PCHT increases the rate of breast conserving surgery and thereby decreases the surgical trauma subsequently reducing morbidity, which may help improving the quality of life of patients.

Review

Aims and advantages of preoperative chemotherapy

It is a very old goal of cancer therapists to predict the tumor's response to therapy. For decades diverse in vitro approaches (tissue culture, cytotoxic assays, etc.) to test chemosensitivity and predict response have been undertaken. Up until now pCHT seems to be the only approach to test chemosensitivity in vivo and yield valid answers for breast cancer patients. The main goal of neoadjuvant chemotherapy is still the reduction of the primary tumor size. It is established that the administration of pCHT can help to avoid mastectomy and allows the treatment of a substantially higher number of patients with breast conserving surgery [2], [3], [4].

Former large randomized studies like the NSABP (National Surgical Adjuvant Breast and Bowel Project) 18 trial with 1523 patients that compared neoadjuvant with adjuvant treatment were not able to prove a survival advantage for pCHT [5], [6], [7], [8]. There was no difference between the adjuvant and neoadjuvant treatment arms either in disease-free survival (DFS) or in overall survival (OAS) [6], [8]. There have been several trials in which the neoadjuvant arm showed superior survival rates after short term follow up. However, after long term follow up this difference was no longer statistically significant [9], [10]. Nevertheless, recent studies suggest a prognostic advantage for patients treated with more advanced elaborated chemotherapy regimens [2]. Preoperative chemotherapy offers distinct advantages. One rationale is that if chemotherapy is administered prior to surgery, the reaction at the primary tumor site may be a predictive marker of micrometastatic systemic disease response [6]. As the response of the primary tumor can be measured, subgroups of patients can be identified that need more intensified treatment or eventually investigational therapy options.

The evaluation of new cancer drugs by the response of the primary tumor in vivo can be performed much more rapidly than in the past, when long follow up in the metastatic situation was needed to draw conclusions. Another advantage of pCHT is that the study groups are more homogeneous than study groups of patients with metastatic disease usually are, in which metastases in different organs and locations have to be compared with regard to response to treatment. Pathological complete response (pCR) can be used as end point for studies evaluating new agents, which might allow earlier approval of new agents by national associations approving drugs such as the US Food and Drug Administration. Classical study endpoints in the adjuvant and metastatic setting usually require years of follow up.

In the neoadjuvant setting, one can obtain tissue before therapy and compare it with residual tissue at the time...
of definitive surgery with regard to change of biologic molecular markers of response and resistance.

**In vitro data support the idea of neoadjuvant chemotherapy**

The idea that preoperative chemotherapy has a more powerful effect on survival compared with postoperative chemotherapy is based on several biological premises: Findings made by the Fisher group in various animal models showed an increased cell proliferation in residual tumor cells as well as an increase in serum growth-stimulating factors after the removal of the primary tumor [11], [12], [13], [14]. This can cause rapid growth of metastases and development of drug resistance [11], [15]. In some of these models, neoadjuvant chemotherapy reversed the effects of primary tumor removal [11], [15]. The production of angiogenesis inhibitors by the primary tumor is thought to be one mechanism for the inhibition of metastatic tumor growth [16]. PCHT might help to minimize micrometastatic tumor cell growth, which reduces the potential adverse impact of primary tumor resection.

**Preoperative chemotherapy facilitates the study of cancer biology**

A future direction of neoadjuvant treatment could be the selection of patients based on the response to chemotherapy and biological marker profile of the primary tumor enabling the therapist to tailor chemotherapy for each patient individually. Examining tumor tissue before, during and after pCHT is possible and can be done by using modern techniques such as immunohistochemistry, fluorescence in situ hybridization, DNA microarrays, or proteomics. Wang et al. performed an interesting investigation assessing the histological features like tumor nuclear grade, mitotic activity, and biomarker expression profiles in order to predict the pathologic responsiveness of breast tumors to pCHT. The investigators concluded that the tumor nuclear grade and the proliferative activity might predict response to anthracycline-based chemotherapy [17]. Billgren et al. showed that after 3 cycles of chemotherapy a significantly decreased proliferative activity predicted a lower risk of tumor progression [18]. Symmans et al. analyzed apoptotic indices after paclitaxel therapy in a small group of patients. The apoptotic indices shortly after chemotherapy administration were predictive for tumor response [19]. Cleator et al. also found more apoptotic cells after chemotherapy but this finding was not closely related to response [20].

As in every other aspect of biomedical science novel technologies such as cDNA microarrays ("gene chips") have the potential to revolutionize the understanding of response and resistance. As cDNA microarray analysis becomes more accessible the benefits for cancer therapy are improving [21]. Sorlie et al. were the first to demonstrate that gene profiling will have implications for prognostication of patients’ outcome [22]. Van’t Veer and colleagues identified a gene expression signature indicative of a poor outcome in young women with lymph node negative breast cancer. 117 primary breast tumors were analyzed with a follow up of 5 years, and the authors were able to predict a shorter interval to the occurrence of distant metastases in a subgroup characterized by a similar gene expression pattern [23]. When traditional prognostic factors according to National Institutes of Health and St. Gallen consensus statements were compared to gene expression signature the gene based analysis proved to be superior [23]. The Dutch group did expand their analysis and examined lymph node positive and negative patients in a further study of 295 patients. They confirmed the superiority of gene profile prognostication versus conventional classification into low and high-risk groups [24]. The gene expression profile selected those patients with a high risk of relapse who would most probably benefit from further chemotherapy and could significantly reduce the number of patients who would receive unnecessary treatment. A randomized trial assessing this approach will be started soon and it might become a valuable tool for prognostication in the future.

In contrast to gene expression analysis from excised tumors after surgery, recently a cDNA microarray analysis of tumor samples gained by fine needle aspiration before treatment was performed. This might help to select a certain pCHT with respect to the individual gene signature [25].

The initiators of the neoadjuvant NSABP 27 trial were well aware of the potential of tissue analysis when they initiated a subanalysis, depicted NSABP 27R, to correlate the response to molecular gene clusters [3].

**Predictive factors for neoadjuvant chemotherapy**

Prediction means to anticipate the response of a tumor to a certain treatment analyzing its biological and clinical characteristics. In this aspect, a very recent report focused on a different aspect of gene profiling. Chang et al. used gene expression patterns for the prediction of therapeutic response to treatment. Results suggest that the development of a clinical test for docetaxel sensitivity seems feasible, this could reduce unnecessary treatment for women with docetaxel insensitive breast cancer [26].

Llombart-Cussac et al. very recently showed that gene expression profiling might be a reliable tool for pretreatment prediction of gemcitabine/paclitaxel resistance. They were able to predict resistance with an accuracy of 91% regarding both clinical and pathological response [27]. Hannemann et al. found a characteristic gene signature change in tumors that responded to pCHT. Nonresponding tumors were not characterized by a specific alteration of the gene pattern [28]. Identifying pre-treatment factors that predict chemotherapy sensitivity would potentially allow for individually tailored chemotherapy. Investigations with focus on con-
Prognostic factors

In contrast to prediction, which tries to anticipate a tumor's response to therapy, prognostication is dealing with the outcome of patients based on biological and clinical characteristics of the tumor. Adjuvant chemotherapy has been applied for decades, and therefore long-term follow-up data are available. In contrast to that, long-term experience with patients that have received chemotherapy preoperatively is rare. Lymph node metastases after neoadjuvant therapy still have a prognostic value as a predictor of the patients' outcome [36], [37]. The NSABP 18 trial showed that the presence of positive lymph nodes after pCHT is highly correlated with an inferior outcome. Therefore, axillary lymph node dissection even if original lymph node status is altered by chemotherapy application is necessary after neoadjuvant treatment in order to determine a major prognostic factor [1].

A recently published long-term analysis from the MD Anderson group on patients with cytologically proven axillary node metastases revealed that a complete eradication of metastases by pCHT lead to a very favourable prognosis. 5- and 10-year data on DFS and OS in these cases was excellent [38].

The NSABP 18 trial also showed a correlation between pathologic response to primary therapy and overall survival as did Chollet et al., who presented data with 15 years of follow up [39]. Overall survival and DFS rates were significantly higher in patients who had a pCR compared to the group in which response was not complete. In most studies undertaken so far, clinical response as well as pathological response to pCHT has turned out to be a reliable prognostic factor [40], [41], [42], [43], [44]. Only a few studies found little evidence that clinical and pathological response to pCHT predicted survival [10], [45]. Gajdos et al. performed a retrospective analysis in locally advanced breast cancer and found that the pathological response was not related to DFS and OS [46]. The prognostic value of a pCR does not seem to be compromised by residual ductal in situ carcinomata (DCIS), which occur in 3% of cases [47]. A pathological complete remission as defined by the NSABP is the absence of invasive tumor tissue, without respect to nodal status and DCIS components. Buchholz et al. showed that in patients with a poor response to neoadjuvant chemotherapy, conventional treatments can achieve reasonable outcomes in the subgroups of lymph node-negative disease or estrogen receptor (ER)-positive disease [48]. In the groups of women with ER-negative disease, positive lymph nodes and for those with progressive disease during pCHT, however, more active/intensified systemic and local therapy regimens have to be applied. Based on those findings inductive chemotherapy might allow to select patients who obtained sufficient treatment and those who need different or additional treatment.

In a setting where traditional prognostic factors are changed due to treatment, surrogate markers for prognostication have to be evaluated. Candidates are oncogenes or tumor suppressor genes, such as p53 that have been shown to be of prognostic significance [49]. In a meta-analysis of immunohistochemically evaluated p53 expression of more than 9000 breast cancer patients, the prognostic and predictive value of p53 overexpression appeared weak [50]. This could be explained by the fact that the correlation between p53 protein accumulation measured by immunohistochemistry, and p53 mutation detected by sequencing is less than 75% in breast carcinoma [51], [52]. Using sequencing, a strong prognostic and predictive value of p53 mutations has been reported in more than 25 studies involving over 6000 patients [53]. The metaanalysis of these studies revealed that mutations in the p53 gene are an independent prognostic factor for adverse DFS and OS in breast cancer patients [54].

Proliferative activity has been evaluated before and after pCHT by many study groups. Although the data are still conflicting most studies found that clinical response is associated with a reduced proliferation of breast cancer cells after pCHT [20], [55], [56]. A high Ki67 labeling index before pCHT is associated with response because chemotherapy does mostly have an impact on dividing cells [57].
Generally, the correlation with DFS and OS of clinical tumor response and marker expression remained weak [57].

Bcl-2 was also thought to be a potential marker. Many studies evaluated bcl-2 as a marker but it did not turn out to be a significant marker for prognostication of outcome or a good predictor of response [55], [57], [58]. New more reliable indices for response to treatment and also for prognostication have to be investigated.

**Does pCHT affect hormone receptor expression?**

Results of investigations regarding the influence of pCHT on hormone receptor status remain non-conclusive [59], [56], [60]. Taucher et al. (2003) investigated the steroid receptor expression in breast cancer patients before and after pCHT [61]. Although there is broad clinical evidence that adjuvant chemotherapy is more effective in hormone receptor negative patients, Taucher et al. described a modulation towards receptor negative cell population induced by pCHT [61], [62]. The fact that receptor content cannot logically be measured in a tumor after a pCR adds to the problem and makes it even more difficult to finally determine the true impact of pCHT on steroid receptor expression.

**Sentinel biopsy and neoadjuvant chemotherapy**

In spite of the increasing use of pCHT and sentinel node biopsy, there is limited information on the feasibility and accuracy of sentinel node biopsy (SNB) following neoadjuvant chemotherapy. The number of studies concerned with SNB in the neoadjuvant setting is small and the small size of these trials probably accounts for the variability of the estimates [63], [64], [65], [66]. But most probably the desirable future trials evaluating SNB after pCHT will not be performed with the same efforts as the comparison of conventional axillary lymph node dissection and SNB. Xing et al. tried to review this issue and found that 10 out of 11 studies showed favourable results, with the ability to identify a sentinel lymph node in 84% to 98% of cases, and reported false negative rates ranging from 0% to 20%. The accuracy of sentinel lymph node biopsy following preoperative chemotherapy for breast cancer ranges from 88% to 100%. Although knowledge is based on single institution and small trials the published literature supports the use of sentinel lymph node biopsy for assessment of the axilla in patients with clinically node-negative disease following preoperative chemotherapy [67]. The biggest study concerned with this issue is the NSABP B 27 trial which lead to encouraging results comparable to the situation before systemic therapy and is consistent with a recent meta-analysis [68], [69].

It is possible that pCHT affects the lymphatic drainage pattern thus the sentinel node identification could become more difficult. This question is of utmost importance, because sentinel node biopsy if feasible and accurate following pCHT could spare a lot of patients from axillary lymph node dissection. As 30%-40% of patients with lymph node metastases including in the sentinel node become tumor-free after the administration of neoadjuvant chemotherapy [8], [70], [71].

**Agents and new combinations for neoadjuvant chemotherapy**

We do not exactly know to what degree the improved pCR rate brought about by the addition of docetaxel will translate into an improvement in OS. But we know for sure that systemic chemotherapy fails to induce a pCR in at least 70% of treated patients.

Most drug regimens for pCHT use standard drug regimens, which have shown their high efficacy in the adjuvant and metastatic disease setting. The benefit of adjuvant therapy has been proven by multiple randomized trials and confirmed by the Oxford Overviews in two metaanalyses [72], [73]. Since the early study of 1974 from Bonadonna, who proved the benefits of adjuvant chemotherapy, therapy protocols were changed, and new drugs were introduced [74]. The addition of taxanes (docetaxel or paclitaxel) to anthracycline and cyclophosphamide containing neoadjuvant regimens in the NSABP 27 trial with 2411 women with operable breast cancer and other recent studies suggested a benefit [2], [3], [75]. Pathologic complete response rates as well as clinical response rates increased from 26% up to 34% and from 40% up to 65%, respectively, not considering the most recent smaller trials that need confirmation.

Newer combinations have to take different toxicity profiles into account. Gemcitabine, a pyrimidine analogue, has shown activity in a variety of solid tumors with a good toxicity profile. Further, gemcitabine is not cross-resistant to anthracyclines and taxanes [76], [77]. Several phase I/II/III studies are currently assessing gemcitabine combined with anthracyclines, taxanes, and/or vinorelbine. This is another suitable candidate for a combined chemotherapy regimen both in the neoadjuvant situation and metastatic disease. Preliminary findings demonstrated increased pCR rates and good tolerability of these regimens in patients with breast cancer [77], [78], [79]. For instance Schneeweis et al. 2003 reported a pCR rate of 28% in a smaller trial combining epirubicin, docetaxel and gemcitabine [80]. The success of trastuzumab in the metastatic setting and its good toxicity profile make this drug a candidate for neoadjuvant and adjuvant approaches. At the time being, trastuzumab is being evaluated in several preoperative studies in combination with conventional chemotherapy. First toxicity trials were encouraging and warranted a subsequent trial named NOAH, which is performed by the Milan group [81].

Unprecedented pCR rates of 65.2% respectively 47% were recently achieved in smaller trials which included the use of trastuzumab in the neoadjuvant setting [82], [83]. Interestingly even patients with positive hormone receptor status achieved a pCR of 61.5% and hormone
receptor negative patients a rate of 70%, with a combined pCR rate of 67% in a small trial performed by the MD Anderson group. Clearly these small trials need confirmation in bigger studies but these are undoubtedly inspiring figures.

As taxanes seem to let to higher pathological response rates they will be included in newer combinations [70]. Based on data gained from more advanced cases, in which capcitabine lead to the improvement of the overall survival, it is a possible candidate for future regimens [84]. Fluropyrimidines had been dropped from adjuvant regimens in the early 1990, which was not primarily based on supporting data: As we saw the return of fluoropyrimidines in the adjuvant setting, they will very probably be part of future preoperative regimens.

**Can the use of alternate schemes with non-cross resistant chemotherapeutics improve response?**

One of the questions the GEPARTRIO-trial might answer is whether the administration of a non-cross resistant regimen (vinorelbine, capcitabine) after patients did not respond to initially given 2 cycles of TAC (docetaxel, doxorubicin, cyclophosphamide) is more beneficial for patients than the continuation of the TAC regimen [85]. The addition of docetaxel to the neoadjuvant chemotherapy almost doubled the percentage of patients undergoing a pCR. The addition of this non cross-resistant drug seems reasonable although the addition did not increase the rate of breast preservation, which was identical in both groups [70].

Thomas et al. were able to demonstrate that the use of alternate non-cross-resistant adjuvant chemotherapy might be beneficial for the outcome [86]. In this smaller trial, patients with poor response to initially administered three cycles of a doxorubicin-based regimen were randomized to further 5 cycles of VACP (vincristine, doxorubicin, cyclophosphamide and prednisone) or to an alternate non-cross resistant VbMF regimen (vinblastine, methotrexate with calcium leucovorin rescue and fluorouracil). Differences did not reach statistical significance but patients receiving VbMF had a trend towards higher relapse-free and overall survival [86].

It seems most promising to combine non-cross resistant chemotherapeutical drugs for the neoadjuvant treatment. This was recently confirmed by the Aberdeen trial. Although not strongly statistically powered, the initial results of this trial suggest that switching from an anthracycline-based regimen to a taxane-based regimen improves both the pCR rates and the 3-year survival rate [2], [4] (Figure 1).

Patients that had responded to 4 cycles of anthracyline chemotherapy were randomized to 4 additional cycles of anthracyline or docetaxel. Patients who turned out to be anthracyline resistant received 4 additional cycles of docetaxel chemotherapy. The possibility of in vivo assessment enabled the authors to make an interesting discovery. In anthracyline resistant patients, switching to a non cross-resistant drug like docetaxel did not improve the response. Combining anthracyclines and taxanes in anthracyline sensitive patients lead to an unprecedented high rate of pCR [87].

Taking recently reported clinical trials together both responders and non-responders to an anthracycline-based regimen potentially derive additional benefit from crossover to an alternate non-cross-resistant therapy [88]. It will be important to see if the improved pCR rates are associated with improved OS, especially in patients who achieve a complete response with taxanes. The follow up of most studies is not long enough to state whether the better clinical and pathological response really leads to a better DFS and OS. First preliminary results of the Aberdeen trial after a median follow-up of 3 years suggested an increase for patients receiving docetaxel after responding to the anthracycline-containing regimen. As it was a comparably small study, the survival results should be interpreted with caution [4].

Despite these promising regimens at the time being a combined treatment of an anthracyline/cyclophosphamide/taxane regimen is the recommended neoadjuvant
Sequential, dose-dense and conventional mode of chemotherapy administered

Trials in the adjuvant and neoadjuvant setting tested different modes of chemotherapy. Sequential therapy (one drug at a time rather than concurrently), dose-dense therapy and conventionally administered drugs have been compared. Citron et al. recently presented data from a big adjuvant trial where 1973 patients were analyzed. Sequential and conventional administration lead to rather similar results. Only the two weekly dose intense scheme of chemotherapy with granulocyte colony stimulating factor (G-CSF) support was superior in terms of outcome and toxicity. In contrast, Jakisch et al. performed a neoadjuvant trial and compared dose intense adriamycin/docetaxel to sequential adriamycin/cyclophosphamide with sequential docetaxel (AC>T) administration [91]. An interim analysis suggested far superior pCR rates for the sequential application mode, and therefore, further recruitment was halted. Pathologic complete response rates achieved with AC>T lead to comparable results in two independent trials [NSABP 27 (18.7%), GeparDuo-study (16.1%)] [3], [91]. In the study conducted by Untch et al. sequential application of two weekly dose intense epirubicin and paclitaxel yielded a better pCR (18%) than epirubicin/paclitaxel (10%) given concurrently [92]. Actively recruiting trials (e.g. trials of the German Association of Gynecological Oncology (AGO) PREPARE and TECHNO) integrate modern concepts of treatment like dose dense, dose intensified, sequential therapy and as well as tumor targeting with trastuzumab in pCHT, and will further clarify in what way to administer pCHT best.

Risk of local relapse

High tumor regression rates of approximately 70% made pCHT the standard therapy option for patients with locally advanced or inoperable breast cancer. One of the cardinal questions is whether there are more local recurrences in patients having successfully been downstaged with pCHT and subsequently treated with breast conserving surgery? In a large trial on patients with operable breast cancer with a median follow up of 8 years, no statistically significant difference was found in local recurrence-free survival between patients with pCHT and patients treated with adjuvant chemotherapy [93]. Long term investigations in patients with locally advanced breast tumors revealed that women with a good clinical response whose breast was conserved, showed the lowest local recurrence rates [94]. Likewise, these patients had a better long-term outcome with a 5-year survival of 96% [94], [95]. Women with locally advanced disease for whom mastectomy was necessary have a weaker response to chemotherapy and therefore have a less favorable prognosis. They are at higher risk of local relapse and development of new contralateral cancer [94], [96]. On the other hand, Gajdos et al. did not find any correlation between response and DFS or OS [46]. However, the risk for intramammary recurrence in patients with breast conservation made possible by pCHT was reported to be increased in several studies [8], [10]. A recurrence rate of up to 14.5% dependent on the clinical tumor size before pCHT has been reported [8]. This is thought to be caused by multifocal tumor shrinkage leading to multifocal residual disease and the difficulty to adequately assess the surgical margins. In studies comparing adjuvant with neoadjuvant treatment, local recurrence rates were not increased in preoperatively treated patients [8]. It is still a contradictory issue whether pCHT followed by breast conserving surgery where usually a mastectomy would have been performed is lead to a higher rate of local recurrence [8], [10], [97]. It seems that the risk of locoregional tumor recurrence after pCHT is largely dependent on conventional risk factors such as tumor stage before chemotherapy and histological parameters [98], [99]. Immunohistological risk factors seem to play a minor role. Chen et al. analyzed risk factors for local-regional recurrence and ipsilateral breast tumor recurrence in patients treated with pCHT. Risk factors for these recurrences were advanced nodal involvement at diagnosis, residual tumor larger than 2 cm, multifocal residual disease, and lymphovascular space invasion [100]. Nevertheless, it has been stressed that in the case of adjuvant as well as in the case of neoadjuvant chemotherapy adjuvant radiotherapy is crucial to prevent intramammary recurrence. Whether locoregional recurrence has any impact on OS in patients treated with pCHT cannot be answered at the present time. Although it is not very likely that the outcome of these patients differs from that of patients treated with postoperative chemotherapy. This question will be answered by future studies. With regard to the increased pCR rates, the importance of surgery for the prevention recurrence has to be stressed. One study compared complete responders to pCHT who were only treated with radiotherapy, with partial responders who were treated with surgery and radiotherapy. The investigation showed that the patient group treated with surgery were a lot less likely to have local recurrence [101]. A very recent retrospective conducted study by Shen et al. (2004) investigated patients with 14 locally advanced breast cancer treated with 4 cycles of neoadjuvant chemotherapy, who underwent breast conservation therapy. The actuarial ipsilateral breast cancer recurrence rate was rather low with 6%. The authors concluded that a selected group of patients who experience tumor shrinkage and resolution of skin changes with neoadjuvant chemotherapy are suitable candidates for breast conservation therapy [102]. There is a general agreement that, despite the problem of multifocal residual disease surgery is performed with...
resistant clones may proliferate and disseminate [107].

Radiotherapy

In most studies dealing with neoadjuvant chemotherapy, conventional postoperative radiotherapy was applied in cases when mastectomy was omitted and breast-conserving surgery performed. Bucholz et al. performed a study to evaluate in which cases radiotherapy was beneficial [99]. In all cases more advanced than stage III radiotherapy is clearly indicated. In patients with stage II, disease recurrences were too infrequent to clearly prove the benefit of radiotherapy, another interesting investigation to illustrate the potential of radiotherapy. Gerlach et al. demonstrated very high remission rates when pCHT was combined with preoperative radiotherapy. Pathological complete remission rates were increased from 3% to 42% but the significance for DFS and OS still needs to be proven [103]. Radiotherapy after pCHT should be administered according to the same recommendations as for the adjuvant situation. Chest wall radiation after mastectomy should be required based on initial tumor size. An increasing number of patients experience a pCR, in these cases, whole breast irradiation is required after breast-conserving surgery [104]. At present the need for radiotherapy of the axilla after pCHT cannot be based on definitive data, but there are data that radiotherapy is not a substitute for surgery [105].

Possible disadvantages of preoperative chemotherapy

Traditional prognostic factors are altered due to neoadjuvant treatment - the stage is modified. Prognostic factors have to be reevaluated and other surrogate markers like pCR have to be considered for patient management and treatment decisions. There is a delay in treatment for cases with progressive disease. Early surgical removal of chemotherapy insensitive disease might prevent a systemic spreading of cells giving rise to micrometastases. There may also be cases that are overtreated by extensive pCHT regimens especially in node negative cases because pCHT is usually administered before histological analysis of axillary lymph nodes. However, considering the current recommendations for adjuvant therapy, where therapists are inclined to treat more intensively, overtreatment might only encounter a smaller subset of patients [104]. Another concern is that the likelihood of residual intraductal components that may be left in situ during breast-conserving surgery might be higher in preoperatively treated patients [106].

Solid tumor cells are not a uniform population. A tumor consists of chemotherapy-sensitive and chemotherapy-resistant cell populations. There is a risk that during neoadjuvant therapy, when primary surgery is delayed, resistant clones may proliferate and disseminate [107]. However, the rate of progressive disease on neoadjuvant systemic therapy is <5% [108]. In this respect, data from neoadjuvant trials in lung cancer patients have to be mentioned. Delay of primary radiotherapy was detrimental for survival in those patients [109]. In breast cancer delay of radiotherapy is not detrimental. Therefore this is more of a theoretical concern, one fundamental and important result of completed neoadjuvant trials was that the outcome of patients treated preoperatively is not worse, when compared to patients treated in the adjuvant setting with immediate radiotherapy after surgery [5], [6].

Contraindications for preoperative chemotherapy

Patients with operable disease and multiple tumors, whose tumor responds very slowly to systemic therapy or patients with tumors whose response is very difficult to evaluate should not be treated with neoadjuvant therapy. Patients with multiple tumors require mastectomy regardless of response to treatment. Some authors also claim that invasive mucinous tumors and invasive lobular carcinomas should at least not be treated with endocrine neoadjuvant therapy due to the exceptionally slow response of those tumors to therapy. Keeping this in mind pCHT should be indicated with caution. Mathieu et al. also came to the conclusion that pCHT for invasive lobular breast cancer should be questioned, according to an observed low rate of response with consequent ineligibility for breast-conserving surgery [110]. Patients with hormone receptor positive tumors should also be rather cautiously treated with neoadjuvant therapy. Subgroup analysis of several studies revealed that in such patients only a pCR rates of 3%-10% were achieved. Consequently hormone receptor negativity turned out to be an independent predictive factor for the accomplishment of a pCR [111], [112].

Future directions of modern technologies for the neoadjuvant treatment

As there is an enormous prognostic difference between responders and non-responders to neoadjuvant chemotherapy, investigators seek to discriminate between the two groups with modern imaging techniques. Data for fluorodeoxyglucose positron emission tomography (PET) is still very preliminary, but it might have a predictive value for the pathological response of tumors in the future [113], [114]. At the time being we can not answer the question what to do with patients that do not respond to pCHT. Clearly these patients have an adverse prognosis and first attempts to improve this situation aimed to increase response by preoperative chemoradiosensitizing strategies [115]. In order to overcome the problem of low response to neoadjuvant treatment of hormone receptor positive patients endocrine and cytostatic agents were combined.
In the small GENARI trial exemestane was combined with lower doses of epirubicin, and interim results suggest good therapeutic efficacy and excellent tolerability [116]. Besides the new approaches in the field of gene expression profiling Pusztai and coworkers attempted to measure the proteomic response in patients treated with pCHT. They monitored plasma protein changes attributable to neoadjuvantly administered paclitaxel and FAC therapy. They found a protein response in breast cancer patients that was absent in the healthy control group. This as yet unidentified protein could be a candidate marker of micrometastatic disease after surgery [117].

Goals for future clinical trials

If you deal with preoperative chemotherapy you have to ask for the goals and objectives of ongoing and future trials. Naturally the improvement of pCR rates has to be a major goal as it is the surrogate marker for survival. However it is not the only task that should be focused on. Because major prognostic factors are altered due to pCHT other markers are needed in order to decide on the necessary intensity of therapy. Prognostic factors also have to be improved in order to overcome the problem of overtreatment of nodal negative patients. Therefore markers should be capable to identify patients that need less intensified treatment. Furthermore predictive statements need to be improved to achieve that every tumor is treated with the most efficient approach. Therefore real progress can only be accomplished if investigators take the identification of both prognostic and predictive markers into account when designing new trials for pCHT. It is not desirable in the setting of an investigational trial only to combine the most efficient drugs for breast cancer to achieve an impressing histologic response, because this might not enlarge our future therapeutic options nor does it allow to individualize therapy. Trials that take the response to a treatment into account and then randomize to alternative options as exemplified for example in the Aberdeen trial seem more reasonable, and have the potential to significantly improve our knowledge and treatment efficacy. Alternative options include not only different drugs and drug combinations but also sequential, dose intensified as well as oral application modes. Future trials should also include the assevation of tumor tissue and serum samples in order to analyze markers of prognostication and prediction with respect to the patient’s history, treatment and outcome.

Current trials and recent findings of ongoing studies

[118]
GEPARDO: The study investigated whether the addition of docetaxel (Doc) leads to increased pCR rates. Preoperative chemotherapy was combined with Tamoxifen in a subset of patients.
GEPARDUO: AC and sequentially Doc proved to be superior to dose-dense A/Doc. After the second analysis of preliminary results an independent data monitoring committee recommended to end the trial.
ECTO: Two adjuvant chemotherapy arms versus one neoadjuvant treatment arm. A longer duration of administration of different chemotherapeutics was leading to better results. Results from the ECTO study and the CALGB 9344 trial suggested that only ER-negative patients benefit from the addition of taxanes [119].
GEPARTRIO: One aspect was testing chemosensitivity in vivo. After 2 cycles of TAC patients were stratified with respect to response to treatment. Responders obtain altogether 6 cycles of TAC and the others are randomized to continue with TAC or to get vinorelbine/capecitabine chemotherapy [120].
NOAH: This is a trial to evaluate trastuzumab in a neoadjuvant approach. Immunotherapy is combined with conventional chemotherapy.
TECHNO: Trastuzumab is administered pre- and postoperatively.
GENARI: Exemestane is increasing the efficacy of epirubicin and other chemotherapeutics [121], [122]. This study evaluates two different concentrations of epirubicin in combination with exemestane [123]. Current trials are summarized in Table 1.

Conclusions

Various trials showed that neoadjuvant treatment of breast cancer is a safe and effective way of treatment. Neoadjuvant therapy is still in the developing stages to treat operable and more advanced breast cancer. We have learned from the chemotherapy trials that neoadjuvant treatment is a tool to discover resistance pathways and therefore might help to overcome them. Recent results prove the potential of neoadjuvant therapy trials for the investigation of new cytostatic agents. Clinical outcome and response to treatment are available after a short period of time and biopsy material is available for scientific evaluation. Evaluation of predictive factors and correlation of therapy response to the genetic profile of the tumor with modern technologies will allow improved selection of patients with increasingly tailored therapy. In contrast, the adjuvant therapy setting does not offer the possibility to meticulously analyze response due to the lack of a measurable primary tumor response. There is little doubt that this mode of therapy will continue to teach us new lessons about the biology and therapy of breast cancer. The reviewed studies used combinations of anthracyclines, taxanes, platinum salts as well as or other two or three drug combination chemotherapies. Randomized trials are ongoing to determine the optimal dose, sequence, and composition of preoperative chemotherapy regimens. With regard to daily clinical use outside of clinical trials, four cycles of an anthracycline-containing regimen sequenced with four cycles of a taxane given before surgery appear to produce optimal reduction in tumor volume [124].
### Table 1: A few examples of current neoadjuvant trials

| Name of trial | Inclusion criteria | Regimen, drugs, no. of cycles, sequence | Postoperative therapy |
|---------------|-------------------|----------------------------------------|-----------------------|
| GEPAR-DO     | T≥3cm, N0-2, M0   | ADoc x 4 v. ADoc x 4 + Tam             | RT + Tam 5 years      |
| GEPAR-DUO    | operable breast cancer T2, N0-2, M0 | ADoc x 4 v. AC x 4 + Doc x 4 | Tam for ER+/PR+      |
| ECTO         | T>2cm              | OP A x 4 + CMF x 4 + Tam 5y. v. OP A Pao x 4 + CMF x 4 + Tam 5y. v. A Pao x 4 + CMF x 4 + Tam 5y. OP | RT + Tam 5 years. |
| GEPAR-TRIO   | T2-3 operable, T4a-d | DocAC x 2 all patients then staging cCR/cPR: DocAC x 4/DocAC x 6 OP cNC (Her2-FISH-Stratification) DocAC x 4/Vinorelbine/Capecitabine x 4 OP |                       |
| GeDoc        | T≥2,5cm, Nx, M0   | EpiDocGem (Gem d1 and d8) x 6 OP       | Tam/Gn-RH            |
| NOAH         | Her 2+/Her 2− pCHT +/- T | ADoc x 3 + Doc x 4 + CMF x 3 + H OP v. ADoc x 3 + Doc x 4 + CMF x 3 OP Control arm HER neg. Patients: ADoc x 3 + Doc x 4 + CMF x 3 OP |                       |
| TECHNO       | T1-3, Her 2+      | EC x 4 > Pacli x 4 + H OP              | RT + T every 3 weeks |
| GENARI 1     | See GENARI 3      | Exemestane x 16 weeks OP               |                       |
| GENARI 3     | Postmenopausal, ER and/or PR +, T>2cm, T2/3/4a-c, pN0-2, M0 | Epi (20mg) weekly x 12 + Exemestane OP v. Epi (30mg) weekly x 12 + Exemestane OP |                       |

Tam = tamoxifen, A = adriamycin/doxorubicin, Doc = docetaxel, C = cyclophosphamide; Epi = epirubicin, Gem = gemcitabine, Pacli = paclitaxel, T = trastuzumab; OP = surgery, v. = versus, cNC = clinically no change, cCR = clinically complete remission, cPR = clinically partial response

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