Neoadjuvant Endocrine Therapy in Breast Cancer

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Key Words

Neo-adjuvant · Endocrine therapy · Breast cancer

Summary

Women who suffer from large or locally advanced malignant breast tumors are now commonly treated with pre-operative ('neoadjuvant') systemic therapy to improve surgical outcomes and to raise the chances for breast-conserving therapy (BCT). Until recently, chemotherapy was the treatment of choice, and primary systemic endocrine treatment was restricted to medically frail or older women with receptor-positive breast cancer. The development of modern aromatase inhibitors (AIs) and their subsequent clinical evaluation in neoadjuvant trials now provides us with an alternative to chemotherapy that is thought to be equally effective, yet considerably better tolerated. Several large prospective trials have compared tamoxifen with the non-steroidal AIs letrozole and anastrozole and the steroidal AI exemestane, with improved outcomes for all AIs in terms of tumor remission and rate of BCT. A number of predictive biomarkers now also allow us to identify those tumors that most likely respond to a certain endocrine regimen.

Schlüsselwörter

Neoadjuvant · Endokrine Therapie · Brustkrebs

Zusammenfassung

Frauen, die an einem großen oder lokal fortgeschrittenen Mammakarzinom leiden, werden heute häufig mittels präoperativer («neoadjuvanter») systemischer Therapien behandelt, um ein günstigeres kosmetisches Operationsresultat zu erzielen bzw. um ein brusterhaltendes Vorgehen zu ermöglichen. Bis vor kurzem war die Chemotherapie die Therapieoption der Wahl und eine primär endokrine Behandlungsstrategie war zumeist älteren und medizinisch kompromittierten Patientinnen mit rezeptorpositivem Mammakarzinom vorbehalten. Die Entwicklung von modernen Aromatase-Inhibitoren (AIs) und ihre Evaluierung in klinischen Studien gibt uns nun eine Alternative zum Einsatz von Chemotherapeutika, die vermutlich ebenso effektiv, jedoch deutlich nebenwirkungsärmer ist. Eine Reihe von großen, prospektiv durchgeführten klinischen Studien haben Tamoxifen mit den nichtsteroidalen AIs Letrozol und Anastrozol und mit dem steroidal AI Exemestan verglichen und ein deutlich besseres Ansprechen sowie eine signifikant höhere Rate an brusterhaltenden Operationen unter AIs gefunden. Eine Reihe von prädiktiven Biomarkern ermöglicht es uns inzwischen, auch jene Tumoren zu identifizieren, die mit großer Wahrscheinlichkeit auf eine bestimmte endokrine Therapie ansprechen.

Introduction

Neoadjuvant treatment of breast cancer offers several important advantages over postoperative therapy: It can result in considerable tumor shrinkage and thus permits breast-conserving surgery in cases that were initially considered to be in-

operable or, at best, candidates for mastectomy. It also allows the assessment of the in vivo sensitivity of malignant breast tumors to systemic treatment and gaining insight into the molecular changes that are associated with tumor response. In

cases where patients experience complete tumor remission in response to the preoperative treatment, improved long-term outcome can be expected.

While chemotherapy has been the treatment modality of choice in the past, the development of highly specific and effective aromatase inhibitors (AIs) has now also resulted in a wider use of endocrine therapy in this setting. Indeed, their favorable side effect profile and their good tolerability makes AIs an excellent alternative to initial surgery, especially in elderly and frail women with receptor-positive breast cancer.

Tamoxifen in Primary Systemic Therapy

Early observational trials of neoadjuvant endocrine therapy have evaluated the role of tamoxifen in the primary treatment of elderly postmenopausal women with locally advanced breast carcinoma (LABC) who were unsuitable for either surgery or chemotherapy. Unfortunately, in none of these trials were patients selected on the basis of estrogen receptor (ER) status. The presence of receptor-negative tumors, which are thought to derive no benefit from endocrine treatment, might thus have attenuated a more favorable outcome. Gaskell et al. [1] followed a group of 66 elderly women with primary breast cancer who were treated with tamoxifen for a minimum of 2 years. 23% of the women experienced a complete clinical response, while a partial response was seen in 34%. 23% of the women had stable disease while in 9% of patients the tumors progressed without showing any sign of response to tamoxifen. Another group investigated the effect of a tamoxifen monotherapy in 113 women aged 79 or more who presented with loco-regional breast cancer. 33% of the patients experienced a complete clinical response while a partial response was noted in 15%. A clinically meaningful benefit was observed in altogether 79% while 21% of the patients experienced disease progression. Since in both studies tamoxifen was used without consecutive surgery, the anti-estrogen has thus not formally been assessed in a 'neoadjuvant' setting. The same is also true for a number of randomized trials in which primary tamoxifen therapy was compared with surgery, and with surgery plus consecutive tamoxifen:

The St George's Hospital trial compared 100 patients treated with wide excision or total mastectomy, with 100 patients treated with tamoxifen alone. In the 6-year follow-up period, local relapse or progression occurred in 56% of the tamoxifen group and 44% of the surgery group. Mortality rates were similar in both arms [2]. Similar results have been reported from the Nottingham trial, in which patients were either treated with tamoxifen (40 mg daily) or by wedge mastectomy [3]. The European Organization of Research and Treatment of Cancer (EORTC) 10851 trial compared the use of tamoxifen alone with radical mastectomy. After a median follow-up of approximately 10 years, the authors found a significantly decreased time to progression in the tamoxifen only group (log rank

$p < 0.0001$) and significantly shorter time to local progression within the tamoxifen group (log rank $p < 0.0001$). While the overall survival in the two groups was similar, the authors concluded that tamoxifen alone leads to an unacceptably high rate of local progression or relapse and that this form of treatment should be reserved for frail patients in whom life expectancy is short.

Several further trials have compared primary tamoxifen with surgery plus consecutive tamoxifen: The Cancer Research Campaign (CRC) trial and the Group for Research on Endocrine Therapy in the Elderly (GRETA) both confirmed that surgery could not be substituted by tamoxifen monotherapy in improving local control in older women with early breast cancer, although patients were selected irrespective of ER status [4, 5]. A second Nottingham trial, in which only ER-positive tumors were included, confirmed these results [6]. None of the trials, however, found differences with respect to distant metastasis or overall mortality. While, with the exception of the GRETA trial, these trials were underpowered to investigate survival endpoints and while in all trials follow-up was too short, Fennessy et al. [7] have recently published the more than 12-year median late follow-up data of another trial comparing surgery plus tamoxifen versus tamoxifen alone in women over 70 years with operable breast cancer. 455 women were included in the trial which reported a significantly better time to treatment failure for women who underwent surgery and tamoxifen. Furthermore, both overall mortality (hazard ratio (HR) = 1.29; 95% confidence interval (CI) 1.04–1.59) and breast cancer-specific mortality (HR = 1.68; 95% CI 1.15–2.47) were both increased in the tamoxifen alone group, although the survival curves did not diverge for the first 3 years. Taken together, these data clearly support the hypothesis that surgery should not be avoided in medically fit older women with operable breast cancer who receive primary systemic treatment with tamoxifen.

Aromatase Inhibitors in the Neoadjuvant Setting

Over the last years, AIs have emerged as the gold standard for endocrine therapy in receptor-positive postmenopausal women with early and advanced breast cancer. It has therefore been suggested that AIs might also demonstrate improved efficacy in the neoadjuvant setting. The P024 trial is a prospectively randomized, international double-blind meta-center trial that compared 4 months of neoadjuvant letrozole with tamoxifen in 337 postmenopausal breast cancer patients. Tumors had to be ER and/or progesterone receptor (PR) positive and had to require mastectomy or had to be inoperable in order to be included. The primary endpoint of P024 was the percentage of patients in each treatment arm with objective response as determined by clinical palpation. Secondary endpoints included objective response rates determined by mammogram and breast ultrasound and the percentage of patients

in each arm who had become eligible for breast-conserving therapy (BCT). The trial demonstrated a significantly higher clinical response rate for letrozole when compared to tamoxifen (55 vs. 36%; $p < 0.001$) in the intention-to-treat population. An improved objective response rate for letrozole was also observed when ultrasound assessment (35 vs. 25%; $p < 0.042$) and mammographic assessment (34 vs. 16%; $p < 0.001$) were applied. Letrozole proved to be superior, irrespective of baseline tumor size (T2 vs. T3 and T4). The higher response rates assessed by clinical palpation translated into a significantly higher rate of women undergoing BCT in tumors that had initially been considered unsuitable for this procedure (45 vs. 35%; $p = 0.022$). Median time to response was 66 days in the letrozole group and 70 days in the tamoxifen group, and both treatments were well tolerated [8].

Two large international trials have compared the efficacy of 3 months of neoadjuvant endocrine treatment with anastrozole or tamoxifen in receptor-positive women with early breast cancer. The primary endpoints in both trials were comparable with objective clinical response measured by calliper in one and objective clinical response measured by ultrasound in the other trial. Both trials also included a response evaluation with the respectively complementary assessment method and a surgical evaluation in terms of whether BCT was feasible subsequent to neoadjuvant therapy as secondary endpoints. The two trials, which were both conducted as double-blind, double-dummy randomized international multicenter trials, differed, however, in the fact that PROACT (PreOperative Arimidex Compared with Tamoxifen) allowed concurrent chemotherapy and was not restricted to operable breast cancer, whereas IMPACT (IMmediate Preoperative Arimidex, Tamoxifen or Combined with Tamoxifen) did not. In the 202 postmenopausal women who received anastrozole in the PROACT trial, no significant improvement in the objective response rate could be observed when compared to the 201 patients who received tamoxifen, irrespective of whether ultrasound or clinical assessment was used. There was, however, a higher response rate in the anastrozole group within the group of patients in whom initially mastectomy had been recommended. This translated into an increased rate of BCT (43 vs. 30%; $p = 0.04$). Both treatments were well tolerated.

In addition to an anastrozole and a tamoxifen monotherapy arm, the IMPACT trial also included a third arm in which both treatments were offered in combination. The authors found no significant difference in the objective response rate in any of the three arms, regardless of whether calliper measurement or ultrasound was used. In analogy to the PROACT trial, however, women receiving neoadjuvant anastrozole had a higher chance of undergoing BCT than women receiving tamoxifen (46 vs. 22%; $p = 0.03$). A combined analysis of the two studies including a total number of 535 patients found a significant improvement in overall response rate (ORR) in women receiving anastrozole in the subgroup of patients who had presented with tumors that had initially been considered to re-

quire mastectomy (47 vs. 35%, $p = 0.026$ for calliper measurement; 36 vs. 26%, $p = 0.021$ for ultrasound measurement). As seen in the individual analyses, more tumors became candidates for BCT in women receiving anastrozole than in women receiving tamoxifen in the total combined patient population (47 vs. 35%; $p = 0.021$).

Several clinical trials have also investigated the efficacy of the steroidal AI exemestane in the neoadjuvant setting. With the exception of a study by Semiglazov et al. [9], however, they are all somewhat hampered by small study numbers and the fact that most of them are not published as full papers. The trial reported by Semiglazov et al. [9] compared 3 months of preoperative exemestane with tamoxifen in 151 women with early breast cancer. Clinical ORR was the primary endpoint whereas mammographic and ultrasonographic ORR as well as the rate of patients undergoing BCT were secondary endpoints. Clinical ORR on palpation was 76% in the AI group as compared to 40% in the tamoxifen group ($p = 0.05$), while no significant differences were seen between the two study arms when the tumors were evaluated by mammography or ultrasound (64 vs. 37%, $p = 0.082$ and 61 vs. 37%, $p = 0.092$, respectively). Exemestane did, however, result in a significantly higher rate of BCT than tamoxifen (37 vs. 20%; $p = 0.05$) [9]. Several one-armed studies have also shown the efficacy of exemestane in the neoadjuvant setting: In an early Scottish trial conducted in 12 patients, 10 patients had a $< 50\%$ reduction in tumor size after 12 weeks of preoperative exemestane therapy [10]. With a fairly similar protocol and 4–5 months of preoperative exemestane, Tubiana-Hulin et al. [11] measured the preoperative tumor response by ultrasound and reported a partial response in 65% and a complete response in 6% of cases. Another single-arm trial conducted by the Austrian Breast and Colorectal Cancer Study Group (ABCSCG) in 80 women with early breast cancer reported response rates of 38 and 41% with sonographic and mammographic longitudinal measurements, respectively, after 4 months of preoperative exemestane [12]. Furthermore, a smaller trial conducted by Takei et al. [13] demonstrated a clinical response in 27 (66%) of 41 evaluable patients and a pathological response in 13 (43%) of the 30 patients who underwent surgery after 4 months of therapy, thereby underscoring the efficacy of the only steroidal inhibitor that is currently available.

So far, the safety and efficacy of AIs in the neoadjuvant setting has mainly been established through a direct comparison with tamoxifen, and an indirect comparison is prohibitive due to the different methods used for tumor size evaluation and to significantly different tumor characteristics in the respective trials. Nevertheless, by the American College of Surgeons Oncology Group (ACOSOG) Z1031, a randomized phase III trial is now under way which compares 4 months of neoadjuvant letrozole, exemestane, or anastrozole in postmenopausal receptor-positive women with stage II–III breast cancer. The study's primary endpoint is to identify the most promising AI, which is then to be compared with neoadju-

vant chemotherapy in a consecutive phase III trial in the same patient population.

Fulvestrant in the Neoadjuvant Setting

Fulvestrant, also known as ICI 182,780, is an ER antagonist which, in contrast to tamoxifen, has no agonist activity and which works both by down-regulating and degrading the ER [14]. In contrast to AIs, fulvestrant is administered by monthly injections. At the approved dose of 250 mg/month fulvestrant is at least as effective as anastrozole in the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer progressing or recurring on anti-estrogen therapy, and is also an active first-line treatment. Although 250 mg/month fulvestrant is clearly effective, it takes 3–6 months to achieve steady-state plasma levels. This would obviously compromise its efficacy and limit its use in the neoadjuvant setting [15]. The use of a loading-dose (LD) regimen (250 mg/month plus 500 mg on day 0 and 250 mg on day 14 of month 1) has been suggested in order to achieve faster responses and to prevent early relapse. In addition, a high-dose (HD) fulvestrant regimen (i.e. 500 mg/month) has been demonstrated to lead to a more pronounced ER down-regulation than the current 250 mg/month dose *in vitro* [16].

In the Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors (NEWEST) trial, an open-label phase II study, 211 postmenopausal women with receptor-positive LABC were randomized to receive either fulvestrant at the approved dose of 250 mg/month or a HD regimen of 500 mg/month for 16 weeks. Efficacy was assessed using levels of Ki-67, a marker of tumor cell growth which has been directly related to long-term prognosis when levels are measured at diagnosis. While no significant differences were observed in terms of clinical response, fulvestrant 500 mg significantly reduced Ki-67 levels by more than 78.8% and fulvestrant 250 mg reduced it by 47.3% ($p < 0.0001$) after 4 weeks of treatment. There were also significant differences in the expression of downgraded ERs between the two doses in favor of the 500-mg dose ($p < 0.0003$). Both doses were well tolerated, suggesting that a HD regimen might be a safe and effective option in primary systemic therapy of LABC [17].

Biological Predictors of Response

While in the early trials with tamoxifen patients were not selected for treatment based on their receptor status, it is now well known that only ER- and/or PR-positive tumors are likely to respond to any kind of endocrine treatment [18]. In an elegant re-analysis of the P024 data, Ellis et al. [19] found evidence for a direct correlation between the degree of ER expression and treatment response: By using the semi-quantitative Allred scoring system, they observed a tamoxifen-

associated tumor response only in tumors that exhibited high ER expression (i.e. an Allred score of 6 and more), while letrozole already yielded tumor responses at scores of 3 and more [19]. Although the absolute numbers are small, it is possible that the somewhat superior efficacy of AIs over tamoxifen in the adjuvant setting might at least in part be due to increased AI efficacy in tumors expressing low and intermediate levels of ER.

Other important factors that predict outcome in neoadjuvant endocrine treatment include HER1 and HER2. In the P024 trial population, the same group found evidence for a lower response to tamoxifen in tumors that overexpress HER1 and/or HER2, with a response rate of only 14% as compared with 41% for HER1- and HER2-negative tumors ($p = 0.01$). Letrozole was, however, effective in both HER1- and/or HER2-positive and -negative tumors (response rate of 58 vs. 54%). The AI was particularly effective in HER1- and/or HER2-positive tumors that also expressed the ER, with a response rate of 88% in the letrozole group compared to 21% in the tamoxifen group (odds ratio (OR) for response: 28; $p = 0.0004$). These data suggest that, while the HER1 and HER2 status might not be the only cause for the superiority of letrozole over tamoxifen, overcoming resistance pathways associated with ErbB-1 and ErbB-2 expression is a significant component of the improvement in outcomes associated with letrozole treatment observed in this clinical trial.

There is now growing data suggesting a role for early changes in the proliferative marker Ki-67 in predicting response to neoadjuvant endocrine therapy. One of the aims of the IMPACT trial was to test the hypotheses that changes in Ki-67 after 2 weeks and/or 12 weeks would predict clinical tumor response to anastrozole and tamoxifen and could be translated into long-term outcome differences between treatments in adjuvant therapy. Indeed, suppression of the proliferation marker Ki-67 after 2 and 12 weeks was significantly greater with anastrozole than with tamoxifen ($p = 0.004$ and $p < 0.001$, respectively) but was similar between tamoxifen and the combination ($p = 0.600$ and $p = 0.912$, respectively). This result closely parallels that seen for the relative recurrence-free survival with the treatments after a median follow-up of 31 months in the Arimidex Tamoxifen Alone or in Combination (ATAC) trial in 9366 patients. The data obtained in IMPACT thus indicate that short-term changes in proliferation in the neoadjuvant setting may be able to predict outcome during adjuvant use of the same treatments [20].

Neoadjuvant Endocrine Therapy versus Chemotherapy

A number of studies have suggested that preoperative chemotherapy may be less effective in postmenopausal women with ER- and/or PR-positive tumors. In a retrospective analysis, Colleoni et al. [21] evaluated the outcome of 399 patients with large or LABC (cT2–T4, N0–2, M0) who had been treated

with preoperative chemotherapy. They found that the absence of ER and/or PR was associated with significantly higher rates of pathological complete remission ($p < 0.0001$). Not unexpectedly, however, they also observed a significantly better 4-year disease-free survival in ER-positive tumors (74%) when compared to ER-negative tumors (41%; HR 3.22; 95% CI 2.28–4.54; $p < 0.0001$) [21]. The hypothesis is further strengthened by results from the NSABP-B27 trial in which patients treated with 4 cycles of preoperative doxorubicin/cyclo-phosphamide with or without 4 subsequent cycles of docetaxel showed higher pathologic response rates if they were ER negative (16.7 vs. 8.3% in ER positive, respectively; $p < 0.001$) [22].

In the European Cooperative Trial in Operable breast cancer (ECTO), neoadjuvant doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil (CMF) induced clinical complete plus partial remission in 78%. When tumor characteristics were further evaluated for their ability to predict response, the only factor significantly associated with pathologic complete response in a multivariate analysis was a negative ER status (OR for ER negative 5.77; 95% CI 3.49–9.52; $p < 0.0001$) [23].

Given these results, it is therefore somewhat surprising that few studies have compared primary systemic endocrine therapy with chemotherapy in receptor-positive breast cancer patients. And only data from one prospectively randomized, controlled trial comparing the efficacy of neoadjuvant chemotherapy with AI treatment in postmenopausal women with receptor-positive tumors are currently available: In their study, Semiglazov et al. [24] randomly assigned 121 patients with T2–T4, ER- and/or PR-positive breast cancer initially ineligible for breast-conserving surgery to receive either anastrozole 1 mg/day or exemestane 25 mg/day for 3 months, or four cycles of a chemotherapy regimen containing doxorubicin 60 mg/m² and paclitaxel 200 mg/m² prior to surgical tumor resection. Study endpoints included ORR as assessed by palpation, mammography and ultrasound, and the rate of BCT. The authors found a clinical objective response in 64% of patients in both the endocrine therapy and chemotherapy treatment

groups. Similarly, rates of pathological complete response (3 vs. 6%) and rates of disease progression (9 vs. 9%) did not differ significantly between the endocrine therapy and the chemotherapy group, respectively. Interestingly, there was a non-significant trend towards higher rates of breast-conserving surgery in the endocrine group (33 vs. 24%; $p = 0.058$). The fact that the median time to clinical response was comparable in both the AI and the chemotherapy group (51 vs. 57 days; $p > 0.05$) suggests that a treatment period of 3 months was not biased in favor of either of the regimens.

The most frequent toxicities from chemotherapy were alopecia (79%), grade 3/4 neutropenia (33%), and grade 2 neuropathy (30%). Endocrine treatment was generally well tolerated, with hot flushes, fatigue, vaginal bleeding and arthralgia being the most common adverse events. No deaths occurred during the preoperative treatment in either of the groups [24]. Although this trial was designed as an open-label trial and has reported a relatively short median follow-up of less than 3 years, it has nevertheless demonstrated that preoperative endocrine therapy with AIs is well tolerated and offers the same rate of overall objective response and BCT in postmenopausal patients with receptor-positive breast cancer.

Conclusion

Neoadjuvant endocrine therapy is effective in down-staging tumors and is particularly useful in tumors initially deemed inoperable or too large for BCT. Third-generation AIs such as letrozole, anastrozole and exemestane have all shown superior clinical responses and higher rates when compared to tamoxifen. They seem to be particularly effective in tumors with low or intermediate ER expression and in tumors that overexpress HER1 and/or HER2. In comparison to chemotherapy, primary systemic endocrine therapy offers similar objective response rates, yet is considerably better tolerated. AIs have therefore emerged as the gold standard in the primary systemic treatment of receptor-positive, postmenopausal breast cancer.

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