This item is the archived peer-reviewed author-version of:

Neoadjuvant endocrine treatment in early breast cancer : an overlooked alternative?

Reference:

Van Dam Peter André, van Dam V. C. N., Altintas Sevilay, Papadimitriou, Rolfo Christian, Trinh Xuan Bich.- Neoadjuvant endocrine treatment in early breast cancer : an overlooked alternative?

European journal of surgical oncology - ISSN 0748-7983 - 42:3(2016), p. 333-342

Full text (Publishers DOI): <http://dx.doi.org/doi:10.1016/J.EJSO.2015.10.015>

To cite this reference: <http://hdl.handle.net/10067/1311670151162165141>

Abstract

During the last decade neoadjuvant endocrine therapy has moved from being reserved for elderly and frail non-chemotherapy candidates to a primary systemic modality in selected patients with hormone sensitive breast cancer. Neoadjuvant hormonal treatment in patients with hormone receptor positive Her-2 negative early breast cancer is shown to be effective and safe. It results in a higher rate of breast conserving surgery, may reduce the need for adjuvant chemotherapy, and enables a safe delay of surgery for medical or practical reasons. Clinical responses range from 13 to 100%, duration of treatment should be at least 3 months. Assessing response by imaging preferentially should include MRI of the breast particularly in lobular tumors. In studies comparing tamoxifen with aromatase inhibitors, AI proved to be superior in terms of tumor response and rates of breast conserving surgery. Neoadjuvant endocrine therapy (NET) provides a unique opportunity for studies of endocrine responsiveness and the development of new experimental drugs combined with systemic hormonal treatment. In order to assess response properly the pretreatment conditions should be defined unequivocally (eg use of hormonal replacement therapy). Change in Ki67 is accepted as a validated endpoint for comparing endocrine neoadjuvant agents. On treatment levels of Ki67 are more closely related to long-term prognosis than pretreatment Ki67.

Introduction

Surgery followed by adjuvant treatment has been the gold standard for breast cancer treatment for a long time. More recently, neoadjuvant treatment has been recognized as an important strategy in biomarker and target evaluation [1 Miller et al 2014]. Particularly preoperative chemotherapy has been widely studied and used (Fisher B JCO 1998). It is generally considered to be a more active and better documented neoadjuvant regimen compared to NET, although it is clearly more toxic (Ellis et al JCO 2001). Endocrine therapy has been far less popular due to the slow response rate of most hormone sensitive tumors, requiring long duration of therapy and risking the benefit of early surgical intervention (Krainick-strobel UE, BMC Cancer 2008). Assessing tumor response to the treatment to explore the prediction of long-term relapse free survival is also less obvious. (Kaufmann M, Ann Surg Oncol 2012). Therefore NET has been tested initially in postmenopausal women who were not fit for chemotherapy or surgery due to medical co-morbidities or in patients who aimed to change the extent of surgery from mastectomy to a breast conserving operation. The development of highly effective aromatase inhibitors has resulted in a wider use of endocrine therapy in this setting (Sinder CF 2008, Breast care).

Safety of neoadjuvant endocrine treatment in hormone sensitive breast cancer

In the eighties the potential benefit of endocrine monotherapy was initially suggested in early studies of tamoxifen used as primary treatment in elderly women with breast cancer who were too frail to undergo other forms of treatment (Chia et al 2010, Preece et al 1982; Horobin et al 1991, Bergman et al 1995). Response rates were in the range of 30% or higher, and long lasting responses were observed in some patients (Preece et al 1982, Bergman et al 1995). Randomized trials of tamoxifen only versus surgery followed by adjuvant tamoxifen showed that surgery is important to optimize the local control of the disease but has no impact on the overall survival (Willsher et al 1997, Mustacchi 2003, Hin 2006, Chakrabarti 1990). A meta-analysis comparing primary

surgery with primary endocrine therapy using tamoxifen in women more than 70 years of age was unable to find a significant difference in overall survival (HR 0.98; $p=0.9$) although patients receiving surgery did experience superior progression-free survival (HR 0.55; $p = 0.0006$) (Hind D et al, Cochrane 2006). Current evidence therefor suggests that the use of NET is safe in women with hormone receptor positive disease, but in the long term is ineffective to achieve a permanent local control in the absence of definitive surgery (Saleh et al 2014). These findings led to the design of subsequent neoadjuvant studies using aromatase inhibitors in younger postmenopausal women with bulky hormone receptor positive disease in an attempt to improve surgical outcome (Chia et al 2010).

Optimal duration of neoadjuvant endocrine treatment

As the response to endocrine treatment is slow, duration of neoadjuvant treatment in most clinical trials has usually been standardized at around 3 to 6 months (Yeo B Breast 2015). Volume reductions continue to occur beyond that time in a large proportion of cases and in routine clinical practice one could consider to treat preoperatively until maximum response. This relatively slow emergence of downstaging relates to the absence of any increase of apoptosis with endocrine therapy and dependence of responses on the antiproliferative effects of estrogen withdrawal (Dunbier et al Clin Cancer Res 2013; Yeo Breast 2015). Increased angiogenesis detected in responders to neoadjuvant AI treatment may represent a stromal response to dying and /or dead cells as part of tumor-stroma interaction following estrogen depletion (Chan MS, Expert Opin Ther targets 2012). The optimal duration of NET is therefor not unequivocally defined. Fontein et al (Eur J Cancer 2014) found an overall response rate of 58.7% at 3 months and 68.3% at final palpation (> 3 months) in 102 patients treated with neoadjuvant exemestane for 6 months. Llombart-Cussa A (Clin Transl Oncol 2012) conducted a prospective phase II trial with letrozole 2.5 mg daily to maximum response as primary systemic therapy in 70 postmenopausal (> 65 y old) with ER/PgR+ operable breast cancer. A total of 43 out of 65 (76.8%) evaluable patients achieved an objective response, 29 (51.8%) being partial and 14 (25%) complete. The median time to objective response was 3.9 months (CI 3.3-4.5) and the median time to maximum response was 4.2 months (CI 4.0-4.5), although 20 (37.1%) patients achieved maximal response within 6-12 months. In a prospective randomized trial comparing 4 to 6 months preoperative exemestane 25 mg daily (Hojo et al Breast 2013) found responses were equal. Similar observations were made by Krainovich-Syrobelt et al (BMC cancer 2008) treating patients with 4-8 months neoadjuvant letrozole. Ruzs et al (Pathol Oncol Res 2015) performed a retrospective analysis of 46 patients with stage I-III invasive hormone receptor positive breast cancer who received 1 year neoadjuvant endocrine therapy. Due to local progression NET was replaced by neoadjuvant chemotherapy in 3 patients. pCR was seen in 13% of the premenopausal patients. They concluded long-duration NET is effective and safe. Four to six months AI as NET seems an optimum duration, but with modest persistent benefits thereafter.

Assessing response to NET by clinical examination and /or imaging

In most studies a combination of physical examination and various imaging modalities are used to assess response rate to NET. As some hormone sensitive tumors such as lobular carcinomas, do not have well circumscribed borders response measurements may vary depending on the imaging technique used and do not always correlate with clinical findings. In addition responses can be slow which implicates that it may take

many months to confirm the definitive response status of a patient. In our experience a combination of physical examinations, ultrasound scanning, mammography and MRI scanning functions fairly well. Clinical assessment and imaging should be performed at predefined fixed time point to detect patients progressing under NET as soon as possible. Takeda et al (2012 Eur J Radiol) showed that contrast enhanced MRI allows fairly accurate measurements after NET. Ueda et al performed a small interesting study in 12 patients with estrogen receptor positive breast cancer on the role of PET-CT in the evaluation of response to 12 weeks neoadjuvant letrozole 2.5 mg daily. Sequential FDG PET/CT scans were performed at baseline, at 4 weeks (PET2) and prior to surgery (PET3). The average decrease in SUV(max) at PET2 compared with the baseline PET was 61% in the metabolic responders (N=6) compared to 14% (N=6), and at PET3 64% vs 17 % respectively compared to baseline (p=0.0004 and p 0.06). The metabolic responders showed a marked decrease in KI67 LI at 2 weeks after the initiation of treatment (62.9%, p = 0.04) and at surgery (91.7%, p= 0.03). Cell cycle response monitored by KI67 correlates with metabolic response monitored by tumor SUV(max) and therefor it seems feasible to use FDG PET/CT to predict cell-cycle response after 4 weeks of NET. Due to the high cost of FDG PET/CT this modality is currently not used in the vast majority of NET study protocols and in clinical practice.

Biomarkers and genomic tests for predicting response to neoadjuvant endocrine therapy

Ellis et al (2001) found evidence suggesting a correlation between the degree of ER expression and the treatment response. Although the absolute numbers were small, they observed a tamoxifen associated tumor response only in tumors with high ER expression (ie an Allred score of 6 and more), while letrozole also showed responses at lower expression levels (3 and more). They therefor (Ellis et al JCO 2001) conducted a prospective trial in postmenopausal patients with ER+ and/or PR+ primary breast cancer patients ineligible for BCS who were randomly assigned to 4 months of neoadjuvant letrozole 2.5 mg daily or tamoxifen 20mg. Sixty % versus 41% of patients responded to the treatment (p=0.004), and BCS was feasible in 48% versus 36% (p=0.036) of patients respectively. Differences in response rates were most marked for tumors that were positive for ErbB-1 and/or ErbB-2 and ER (88% vs 21 %, p = 0.0004). Although the HER1 and HER2 status may not be the only cause for the superiority of letrozole over tamoxifen, these data suggest that overcoming resistance pathways associated with the ErB-1 and ErbB-2 expression are a significant component of the improvement in outcomes associated with endocrine treatment.

As pathologic complete responses after NET are rare they have not been used to as a predictor of longterm survival. Immunohistochemical assessment of Ki-67 in core biopsies of the tumor taken before, during and at the end of NET may represent a clinically useful and valid surrogate of outcome in patients with ER-positive breast cancer. Comparing neoadjuvant anastrozole, tamoxifen or anastrozole combined with tamoxifen prospectively in 330 patients, Dowsett et al (Dowsett M Clin Cancer Res 2005, Dowsett M J Natl Cancer instut 2007) showed that 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) but was similar between tamoxifen and the combination. This result closely paralleled the later observed relative recurrence-free survival with the same types of treatment after a median follow-up of 10 years in the ATAC trial in 9366 patients (Cuzick J, Lancet Oncol 2010). Looking at clinical response

rate in a similar study Smith et al (2005 JCO) could not find a correlation between clinical response after NET and long-term outcome, suggesting that changes in Ki-67 are a better prognostic marker. These authors studied the expression of Ki67 in tumor biopsy samples taken before and after 2 weeks of presurgical treatment with anastrozole or tamoxifen or the combination of these drugs in 158 patients with hormone receptor positive primary breast cancer. In multivariate analysis a higher Ki67 expression at two weeks was associated with a lower recurrence-free survival ($p < 0.001$ and $p 0.04$) whereas higher Ki67 values at baseline were not (Dowsett et al 2007 J Natl Cancer Inst). Similar observations were reported by Bedard PL et al (2011 Endocr Relat Cancer). The POETIC trial including more than 4000 postmenopausal ER+ patients randomly assigned to receive 2 weeks of presurgical treatment with AI or not is the largest study currently assessing the clinical utility of on treatment Ki67 as a predictor of long term outcome (Klintman M J Natl Cancer institt mono 2015- Paradoxical Ki67 increase after NET have been observed in several studies. In the Z1031 study some patients were seen having a low Ki67 and Luminal A assignment at baseline, which had a rise in Ki67 and Luminal B assignment, suggesting the increase was not simply the result of erroneously low baseline Ki67 values. Tumor heterogeneity and treatment resistant cell populations which can become more dominant can explain some of the observations. However, an important factor which cannot be ruled out is that in many neoadjuvant study protocols the clinical circumstances at the moment of the baseline biopsy are not well defined. The use of hormonal replacement therapy or other hormonal medication and the required wash out time, or the interval between a pretreatment castration and the start of NET is not always precisely defined, but these factors can affect Ki67 values significantly (Conner P Breast cancer res Treat 2003)

The Preoperative Endocrine Prognostic Index (PEPI) that combines residual Ki67 score with measures of on-treatment ER and other clinicopathologic factors also found application in clinical trials (Yeo B Breast 2015). Recently it has been demonstrated that a four-marker immunohistochemical panel (ER, PR, Her-2 and Ki67) may have the ability to guide adjuvant therapy and predict long term outcomes for hormone receptor positive breast cancer (Cheang MC et al, J Natl Cancer institt 2009). Ying M (Chin J Cancer res 2013) et al showed that neither pre-treatment ER expression nor the combined index of pretreatment ER and PR were able to predict cell cycle response to neoadjuvant endocrine treatment with anastrozole for 16 weeks, but that the combined index of pretreatment ER, PR, Her-2 and Ki67 expression levels could predict this response. A small study by Madeira et al (BMC cancer 2013) suggests the effects of NET appear to be dependent on the ratio of ERalpha/ERbeta expression.

Recently Ueno et al showed that the 21-gene recurrence score (RS) was predictive for the response to neoadjuvant exemestane in postmenopausal women with ER/PR+ breast cancer (Ueno T Int J Clin Oncol 2014).. The clinical response rate was significantly higher in patients with a low RS (19/32, 59%) compared to patients with a high RS (3/15, 20%, $p = 0.015$). RS values in pretreatment samples were highly correlated to RS in post treatment samples. Arthur et al showed that the changes in gene expression in response to neoadjuvant letrozole are highly similar between responding invasive lobular and invasive ductal carcinomas; genes involved in proliferation were down regulated and those involved with immune function and extracellular matrix remodeling were up regulated. Molecular differences between histologic subtypes were maintained upon treatment (Arthur LM Cancer Res 2014). Dunbier et al (Clin Cancer res 2013)

showed that a high baseline expression of an inflammatory molecular signature is associated with a poor antiproliferative response to neoadjuvant AI treatment, and this signature should be assessed as a novel biomarker. Chan et al Int J Biol Markers 2012) observed a significant increase in the ratio of CD8+ to T regulatory cells in responders to neoadjuvant AI treatment. In the ACOSOG Z1031 it was demonstrated that PAM50 analysis identified A-unresponsive nonluminal subtypes (HER2 enriched and basal like) in 3.3% of patients with ER-rich breast cancer (Ellis 2011). Clinical response and surgical outcomes were similar in luminal A versus luminal B tumors; however a PEPI of 0 (best prognostic group) was highest in the luminal A subset (27.1% vs 10.7%; $p = 0.004$). In the absence of a PAM50 result a baseline Ki67 level of 10% or less was significant in univariable analysis for predicting PEPI-0 status and could also be used to identify patients at baseline suitable for neoadjuvant endocrine therapy. Several studies are ongoing trying to identify the hallmarks of AI drug resistance by epigenetic profiling and next generation sequencing (Jansen MPM Cancer res 2013)

Comparison of neoadjuvant tamoxifen to aromatase inhibitors in postmenopausal women

Ellis et al (JCO 2001) conducted a prospective trial in postmenopausal patients with ER+ and/or PR+ primary breast cancer patients eligible for BCS who were randomly assigned to 4 months of neoadjuvant letrozole 2.5 mg daily or tamoxifen 20mg. Sixty % versus 41% of patients responded to the treatment ($p=0.004$), and BCS was 48% versus 36% ($p=0.036$) respectively. Differences in response rates are most marked for tumors that were positive for ErbB-1 and/or ErbB-2 and ER (88% vs 21 %, $p = 0.0004$). Similar results were observed in terms of surgery downstaging when anastrozole was compared to tamoxifen in the 38% of patients who were not considered eligible for BCS at study entry (Dowsett et al Clin Cancer res 2005).

In the P024 trial 324 postmenopausal women with hormone receptor positive breast cancer were randomized to be treated with either letrozole 2.5 mg daily or tamoxifen 20 mg daily for 4 months. In the intention to treat analysis, a statistically significant improvement in the objective response rate by clinical palpation, ultrasonography and mammographic response was observed in the letrozole group compared to the tamoxifen group (respectively 55% vs 36%, $p < 0.001$; 33 vs 25%, $p < 0.042$; 34% vs 16%, $p < 0.001$), and there was a higher rate of breast conserving surgery (45% vs 35%, $p 0.022$). Pathologic complete responses were rare (2 with letrozole and 3 with tamoxifen) (Ellis MJ et al Br Canc Res Treat 2007).

The Immediate Preoperative Anastrozole, Tamoxifen or Combined with Tamoxifen (IMPACT) trial was designed to test the hypothesis that the clinical and/or biological effects NET might predict long-term outcome of patients in the ATAC adjuvant trial, which required long term follow-up. (Smith JE JCO 2005) Postmenopausal women with ER positive, non-metastatic operable or locally advanced invasive breast cancer were randomly assigned to have neoadjuvant tamoxifen 20 mg (N=108), anastrozole 1 mg (N=113) or a similar combination of tamoxifen and anastrozole daily (N=109) for 3 months. There were no differences in objective response rates. Forty four % of patients received BCS after anastrozole compared to 22% after tamoxifen ($p = 0.23$; this difference became significant for patients who were deemed feasible for BCS by their surgeon (46% vs 22% respectively, $p = 0.03$).

In the PROACT trial, comparing preoperative anastrozole 1 mg (N=228) to tamoxifen 20 mg (N=223) daily for 12 weeks with or without chemotherapy objective responses were seen by ultrasound measurements in respectively 50% and 46% of patients (Catalotti L Cancer 2006). In the hormonal therapy-only patients (N:314) feasible surgery at baseline improved after 3 months in 43% of patients receiving anastrozole and 30.8% receiving tamoxifen ($p = 0.04$).

A metaanalysis of the above trials showed that that preoperative AI was more effective than preoperative tamoxifen. Pooled results of clinical efficacy showed a clinical objective response rate (RR 1.29; $p = 0.002$), ultrasound objective response rate (RR 1.29; $p = 0.002$) and BCS rate (1.36; $p < 0.001$). Hot flashes, nausea and fatigue were not different between both groups, but headache was more frequent in the AI group ($p = 0.011$) (Seo JH Cancer Chemother Pharmacol 2009)

Semiglazov et al (2005) reported a small trial comparing 3 months of preoperative exemestane with tamoxifen in 151 women with breast cancer in an abstract, but this study has never been published as a full paper. Clinical ORR on palpation was 76% in the exemestane group 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%, $p = 0.092$). The use of exemestane resulted in a significantly higher rate BCT than tamoxifen (37% vs 20%, $p = 0.05$)

Other studies with neoadjuvant aromatase inhibitors in postmenopausal women

At least 6 relatively small studies ($n = 11$ to 38) have evaluated neoadjuvant therapy with exemestane.[33–38](#) Dixon et al evaluated the effect of neoadjuvant exemestane in 13 postmenopausal women with ER-positive, operable, and locally advanced breast cancer.[33](#) Exemestane was given for up to 3 months. Median tumor volume evaluated by clinical examination, mammography, and ultrasound was reduced by 86%, 84%, and 83%, respectively. After treatment, 10 patients had breast-conserving surgery with clear margins, and 2 underwent mastectomy. In a phase 2 study reported by Tubiana-Hulin et al, 38 postmenopausal women with ER-positive operable breast cancer received 4 to 5 months of neoadjuvant exemestane.[38](#) Tumor response was evaluated by using National Cancer Institute Response Evaluation Criteria in Solid Tumors.[39](#) Six percent of patients had a clinically complete response, 65% had a partial response, 24% had stable disease, and 45% had breast-conserving surgery. In DB et al (Eur J Cancer 2014) performed a phase II trial in 102 patients with stage T2-T4ac hormone receptor positive breast cancer which were treated by six months preoperative exemestane. Overall response rate by palpation was 64.5% by clinical palpation, 70.3% by MRI, 41.6% by ultrasound and 48.2% by mammography respectively. Feasibility for BCS improved from 61.8% to 70.6% ($p = 0.012$). Taken together, these studies suggest that neoadjuvant exemestane is effective against hormone receptor-positive breast cancer. Dixon JM et al (Breast Cancer res Treat 2011) assessed the effectiveness of > 3 months neoadjuvant letrozole in postmenopausal women with ER-rich invasive lobular cancer. The mean reduction in tumor volume at 3 months as 66% measured clinically, 61% measured by ultrasound and 54% measured by mammography. The rate of successful breast conservation was 81% (25/31). Similar results were seen in a phase IIb/III clinical trial of preoperative letrozole 2.5 mg daily in 33 postmenopausal women with unilateral

locally advanced breast cancer. Letrozole enabled BCS in about 75% of the patients ((Kraus-Strobel BMC Cancer 2008). Debdel et al (Am J Surg 2014) performed a retrospective analysis of 204 patients receiving neoadjuvant endocrine therapy with T2 (> + 30 mm) or T3 tumors in their unit. NET was administered for 7.3 months (median) and BCS was achievable in 53% of patients. Disease progression during treatment was 6.9% and actuarial risk of local relapse was 3% at 5 years and 15% at 10 years. Five and 10y metastasis relapse free survival was 78 and 63% respectively. Grade 3, negative progesterone receptors, and absence or slow response to neoadjuvant therapy were associated prognostic factors. In the NEOS trial health related quality of life was assessed in 497 postmenopausal patients with T1c-T2N0M0 ER/PR+HER having NET and showed that NET with letrozole had no impact on global HRQoL, but did influence endocrine related symptoms such as hot flush..

Comparison different neoadjuvant aromatase inhibitors in postmenopausal woman

The question which AI is superior was addressed by the open-label ACOSOG Z1031 trial, which compared 16 weeks of exemestane 25 mg, letrozole 2.5 mg and anastrozole 1 mg daily as neoadjuvant therapy for patients with strongly ER+ stage II or III breast cancer. In the 374 women included in the intent to treat analysis the clinical response rate was 60% (95%CI: 51-69%) with exemestane, 72% (95%CI: 62-78%) with letrozole and 68% (95%CI: 58-75%) with anastrozole. Progression was infrequent in each arm, at an incidence of 5% to 7%. (Ellis MJ JCO 2011). Ki67 and PEPI data demonstrated that the three agents tested are biologically equivalent and therefore likely to have similar adjuvant activities.

Neoadjuvant fulvestrant in postmenopausal women

Fulvestrant is a complete estrogen receptor antagonist. It is a pure anti-oestrogen which does not exert any partial agonist effects and in addition accelerates the proteasomal degradation of the estrogen receptor (Cheung KL Expert Opin Invest Drugs 2002). NEWEST (Neoadjuvant Endocrine therapy for Women with Estrogen Sensitive Tumors) compared the biological and clinical activity of 16 weeks fulvestrant 500 mg (N=109) versus 250 mg (N=102) in the neoadjuvant breast cancer setting in an open label randomized multicenter phase II trial in patients with postmenopausal ER+ locally advanced breast cancer. At week 4 fulvestrant 500 mg resulted in a greater reduction of Ki67 labeling index and ER expression respectively (-78.8 vs -47.4%, $p < 0.0001$ and -25% vs -13.5 %, $p = 0.0002$). PR suppression was not significantly different. At week 16 tumor response rates were 22.9% versus 20.6% with considerable decline in all markers, suggesting greater biological activity of fulvestrant 500 mg. (Kuter I, Breast Cancer Res Treat 2012). These neoadjuvant data were confirmed by the CONFIRM trial prospectively comparing the two dosages of fulvestrant in 736 patients with advanced or recurrent estrogen receptor breast cancer. The PFS analysis showed that the 500 mg regimen was associated with a significantly longer PFS compared to the 250 mg regimen (6.5 months vs 5.5 months, CI 0.68-0.94, $p = 0.006$) (Di Leo A et al, JCO 2010). A longer then preplanned follow-up analysis showed a median OS of 26.4 m vs 22.3 m, CI 0.69-0.96, $p = 0.016$) (Di Leo et al 2013)

Neoadjuvant endocrine treatment in premenopausal women

Recent data from the adjuvant randomized TEXT and SOFT trials show that the aromatase inhibitor exemestane plus ovarian suppression significantly reduces

recurrences as compared to tamoxifen plus ovarian suppression, particularly in patients younger than 35 years (ref). Few data are available on NET in premenopausal women. Barbie TU et al (Ann Surg Oncol 2015) reported single institution retrospective data on 17 premenopausal patients who were treated with a combination of a gonadotrophic releasing hormone agonist with either an aromatase inhibitor (N=14) or tamoxifen (N=3) for 4-6 months. Eleven had a clinical response based on RECIST criteria (64.7%) and six underwent BCS. Response rate was similar compared to that of a cohort of postmenopausal control patients treated in their unit (58%, 85/145). The STAGE trial was a phase III randomized double blind multicenter study allocating 197 premenopausal women with ER+, Her-2- breast cancer to neoadjuvant treatment with goserelin 3.6 mg/month with anastrozole 1 mg daily or tamoxifen 20 mg daily for 6 months. Response rates were very high: anastrozole was superior to tamoxifen in terms of caliper response (70.4% vs 50.5%, $p = 0.004$), ultrasonography response (58.2 vs 42.4%, $p = 0.027$), and magnetic resonance imaging of computed tomography response (63.3 vs 37.4%, $p = 0.032$). These studies suggest that NET treatment is highly effective in well selected premenopausal patients. This field of research is clearly open for further trials.

Neoadjuvant endocrine therapy compared to neoadjuvant chemotherapy in postmenopausal women

Few studies have compared primary systemic endocrine therapy with chemotherapy in receptor positive breast cancer patients. In an attempt to reduce the need of preoperative chemotherapy in postmenopausal patients with hormone sensitive non-metastatic breast cancer Semiglazov et al conducted a phase 2 randomized trial comparing primary endocrine therapy to chemotherapy (Semiglazov VF, Cancer 2007). Patients were randomly assigned to have 3 months preoperative treatment with either exemestane 25 mg (N = 60) or anastrozole 1 mg daily (N=61) or 4 cycles of neoadjuvant chemotherapy (doxorubicin 60 mg/m² with paclitaxel 200 mg/m² every 3 weeks) (N = 118). Rates of pathological complete response (3% vs 6%) and disease progression (9% vs 9%) did not differ significantly in the endocrine therapy or chemotherapy group, BCS rates were higher in the endocrine group (33% vs 24%; $p = 0.058$). Toxicity was higher in the patients treated with preoperative chemotherapy (alopecia 79%, grade 3/4 neutropenia 33%, grade 2 or more neuropathy 30%). The GEICAM cooperative group reported a small randomized phase II study of chemotherapy vs exemestane in pre- and postmenopausal women with hormone sensitive, her-2 negative luminal breast cancer (Alba et al 2012). They were randomly treated with either to chemotherapy (four cycles of epirubicin plus cyclophosphamide every 3 weeks followed by 4 cycles of docetaxel every 3 weeks) or exemestane 25 mg daily (with goserelin if premenopausal). The response rate was higher for chemotherapy in the premenopausal patients (18 of 24 in the chemotherapy arm vs 12 of 27 in the endocrine therapy arm, $p = 0.027$), but comparable in postmenopausal women and those with a low baseline Ki67. The authors concluded that luminal patients with a low proliferation index (Ki67 < 10%) could potentially avoid chemotherapy. Recently the NeoCENT (Neoadjuvant Chemotherapy versus ENdocrine Therapy) trial closed randomization. In this prospective multicenter randomised phase III study neoadjuvant chemotherapy (6x 3 weekly cycles of FEC100: epirubicin, 5-fluorouracil, cyclophosphamide) was compared to letrozole 2.5 mg daily for 18-23 weeks in postmenopausal patients with strongly ER positive breast cancer (Palmieri et al, Br Cancer Res Treat 2014). Although the primary endpoint of the study were recruitment

feasibility and tissue collection, secondary endpoints included clinical, radiological and pathologic response rates, quality of life and translational endpoints. Of the 44 patients randomized (out of 63 eligible patients) 12 chemotherapy showed radiological response compared with 13 letrozole patients. Compared with baseline, mean Ki-67 levels fell in both groups at day 2-4 and at surgery (fold change 0.24, 95% I: 0.12-0.51, and 0.24, 95%CI 0.15-0.37 respectively). Recruitment and tissue collection data were met, but a larger trial was deemed unfeasible by the authors due to slow accrual. Wright et al (Am J Clin Oncol) reported equivalent outcomes in a retrospective study assessing 140 postmenopausal patients with ER+HER2- breast cancer who were treated with neoadjuvant endocrine versus neoadjuvant cytotoxic therapy. Although larger and more mature studies reporting long-term outcomes are necessary, these studies suggest that particularly in strong hormone receptor positive tumors with a low Ki67% endocrine therapy is at least as effective as cytotoxic treatment.

Combining neoadjuvant endocrine treatment with neoadjuvant chemotherapy

Patients with large ER positive tumors candidate to preoperative chemotherapy may also benefit from concurrent endocrine intervention. This issue has been scarcely investigated due to concerns arising from unfavorable results which have emerged from an adjuvant trial of concurrent tamoxifen and chemotherapy (Torrisi R, Breast Cancer res Treat 2011). Torrisi et al (2011) retrospectively investigated the activity of letrozole plus GnRH agonist concurrently with preoperative chemotherapy in premenopausal women with locally advanced ER positive breast cancer compared to an unmatched control group of similar patients having preoperative chemotherapy only, followed by tamoxifen and GnRH-agonist after surgery. The pCR rate was 5.0 % vs 1.1% and a statistically greater suppression of Ki67 was observed in patients receiving chemoendocrine therapy as compared to controls (p =0.003). Surprisingly 5y DFS was 78% vs 41 % in favor of the chemoendocrine therapy (HR 0.46, p= 0.0047) . The combination of exemestane with chemotherapy as neoadjuvant treatment was evaluated prospectively in 2 phase 1 studies. Wolf et al treated 14 patients with locally advanced breast cancer with exemestane and increasing doses of epirubicin. Ten of 14 patients were evaluable: 2 patients had a complete response, 4 had a partial response, 3 had stable disease, and 1 had progressive disease. Six patients received breast-conserving surgery. Lichtenegger et al carried out a phase 1 study in 11 patients with locally advanced breast cancer with exemestane and increasing doses of docetaxel. These investigators reported that 78% of patients had a partial response and 22% of patients had stable disease. The above data are certainly provocative and therefore more prospective randomized studies are warranted to establish the role of addition of endocrine therapy to chemotherapy as a standard preoperative approach.

Which adjuvant treatment after neoadjuvant endocrine therapy ?

Hardly any data are available on the optimal adjuvant treatment after endocrine therapy. Pragmatically one could say that complete responders could be further treated postoperatively with endocrine therapy and that patients progressing under NET are likely to need adjuvant cytotoxic treatment. However decision making in the remaining group of patients is difficult. In a retrospective analysis of 144 ER/PR+ patients in operable with BCS Grassadonia et al (Ann Surg Oncol 2014) who had NET (with anastrozole, letrozole or exemestane) administration of adjuvant chemotherapy was significantly correlated the disease free survival in univariate analysis (p = 0.007), but did

not come up in the multivariate analysis looking at overall survival. In the NEOS trial, a multicenter phase 3 randomized controlled trial in postmenopausal women with ER/PR+ breast cancer, the need for additional chemotherapy in patients who responded well to neoadjuvant letrozole for 24-28 weeks preoperatively will be assessed. Data on disease free survival, which is a primary endpoint of the study, are currently not yet available (Taira N V Breast Cancer Res Treat 2014)

Combining neoadjuvant endocrine treatment with targeted drugs

Cross-talks between HR and the intracellular signaling triggered by tyrosine kinase receptors (such as HER2, EGFR, PDGFR) have been demonstrated in preclinical studies to play a role in de novo or acquired resistance to endocrine therapy (Shin I Clin Cancer Res 2006, Arpino G Clin Cancer Res 2004). More downstream pathways, such as the phosphoinositide-3-kinase (PI3K)/Akt signaling pathway, can be involved in endocrine resistance and are potentially interesting to target (Miller TW JCO 2011). As NET allows longitudinal assessments of both clinical and biomarker responses, this has encouraged the development of novel clinical designs for assessing the impact of agents that aim to enhance response beyond that of endocrine agents alone. Such strategies include the early measurement of residual Ki67 levels after challenge with an endocrine agent alone and the evaluation of the impact of the added agent on Ki67, or other agent specific biological and clinical endpoints (Yeo B Breast 2015). These trials can not only be used to identify the mechanisms of action of novel agents but also to predict optimal subsequent adjuvant therapy for individual patients (Levasseur N, Minerva Chir 2015). Baselga et al (JCO 2009) used this approach in a phase II randomized study comparing neoadjuvant everolimus (an mTOR inhibitor) plus letrozole 2.5 mg daily versus letrozole alone 4 months preoperatively in 270 patients with ER+ breast cancer. Response rate at clinical palpation and reduction of Ki67 at 14 days was higher in the first group (respectively 68.1% vs 59.1%; $p = 0.062$ and 57% vs 30%, $p < 0.01$). The results of this study and the BOLERO 2 trial, showing a significant prolongation of the progression free survival of patients treated with a similar experimental drug combination in metastatic ER/PR+ breast cancer, led to the rapid FDA approval of the use of everolimus combined with exemestane in breast cancer patients (Hortobagyi G NEJM 2011, Qiao L Int J Clin Exp Med 2014). Two trials combined an AI daily with celecoxib (a cyclooxygenase inhibitor) 400 mg daily versus AI alone and could not demonstrate meaningful differences (Chow LW J Steroid Biochem Mol Biol 2008; Lustberg MB, Clin Breast cancer 2011). A single arm study in 25 patients assessing the activity of letrozole and bevacizumab, a monoclonal antibody inhibiting VEGF, showed an objective clinical response in 68% of patients with 4 complete responses (16%). Masserweh S et al (Breast cancer Res Treat 2011) performed a small phase II study randomizing 15 patients with previously untreated hormone receptor positive breast cancer to receive neoadjuvant anastrozole 1 mg daily with monthly fulvestrant 250 mg, or anastrozole 1 mg combined with fulvestrant 250 mg monthly and gefitinib 250 mg daily for 3 weeks. After a second biopsy all patients received the second treatment arm for 4 months. At 3 weeks Ki67 was significantly reduced in the second arm ($p = 0.01$) with a parallel reduction in expression of Cyclin D1 ($p = 0.02$). Of the 12 patients finishing the treatment, there were 2 CR (17%), 3 PR (25%), 5 SD (41%) and 2 (17%) PD. Two other neoadjuvant studies assessing the activity anastrozole with or without gefitinib 250 mg daily provided similar results ((Smith IE JCO 2007; Polychronis A Lancet Oncol 2005). Chow et al (Cancer Lett

2008) studied the combination of Imatinib, a potent inhibitor of PDGFR, with letrozole preoperatively in 13 women . Recent neoadjuvant studies have shown that the combination therapy targeting HER2 (dual HER2 blockade with or without endocrine therapy) has activity in a substantial percentage of patients, eradicating HER-positive tumours without chemotherapy and with a favourable toxicity profile (Pernas Simon S Ther Adv Med Oncol 2014). Neoadjuvant represents an enormous step forward in the treatment of HER-2 positive breast cancer, but this is beyond the scope of this review. Currently several neoadjuvant studies are ongoing combining an AI with other potent drugs, such as PI3K inhibitors and CDK4/6 inhibitors, in an attempt to improve effectivity of endocrine treatment of breast cancer.

Conclusion

At present the assessment of new systemic treatment in early breast cancer requires the conduct of very large randomized adjuvant clinical trials involving thousands of patients, with follow-up extending several years before results emerge. The implications in terms of time and cost are enormous (Dowsett et al Clin Cancer res 2005). Using reliable intermediate endpoints after neoadjuvant treatment allows for more rapid evaluation of drug efficacy, the assessment of in vivo sensitivity of malignant breast tumors to endocrine treatment and gaining insight into the molecular changes that are associated with tumor response. The main advantage of neoadjuvant endocrine therapy is that the breast tumor, which is still present in the patients breast during therapy, can be followed clinically and by radiologic measurements immediately reflecting the effect of treatment. Second, tumor biopsies may be taken before, during and at the end of treatment allowing intra patient comparisons. These tumor biopsies may also be used for the evaluation of different drug treatments (Geisler J et al J Steroid Biochem Mol Biol 2012). Efforts of molecular profiling of the post-neoadjuvant residual disease hold the potential to lead to personalized therapy for breast cancer patients with early stage high risk disease (Zardavas D Annu Rev Med 2015). Adjuvant endocrine therapy trials should only be conducted once adequately powered neoadjuvant studies have indicated superior KI67 suppression in patients receiving experimental endocrine treatment (Goncalves R Nat rev Clin Oncol 2012)

Alba E, Calvo L, Albanell J, De la Haba J, Chacon J, Arcusa Lanza A, Sanchez Rovira P, Plazaola A, Lopez Garcia-Asenjo J, Luch A on behalf of GEICAM . Chemotherapy versus hormone therapy as neoadjuvant treatment in luminal breast cancer: a multicenter, randomized phase II study (GEICAM/2006-03. J Clin Oncol 2010;28(7S): abstract 500.

Semiglazov VF, Semiglazov VV, Ivanov VG et al. Neoadjuvant endocrine therapy: exemestane vs tamoxifen in postmenopausal ER+ breast cancer patients. Proc Am Soc Clin Oncol 2005;23(16S) abstr 530.

Predictors of early recurrence of ER positive breast cancer among women receiving endocrine therapy include larger tumor stage and positive nodal status, lower levels of hormone receptor expression, higher grade and proliferative markers, Her-2 overexpression and high recurrence score on multigene assays (Burstein HJ, JCO 2012).