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RESEARCH

One-Year Neoadjuvant Endocrine Therapy in Breast Cancer

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Abstract The evaluation of the effects of 1-year endocrine therapy (NET) was aimed at. A retrospective analysis of 42 cases with 46 stage II–III invasive, hormone receptor-positive, HER2-negative breast cancers was performed. One-year NET was planned with letrozole (n=33, postmenopausal group), or with goserelin plus letrozole (n=7) or with goserelin plus tamoxifen (n=2) (premenopausal group). Surgery was performed in accordance with the initial stage and the response to therapy. With regard to the tumor remaining in the surgical specimen, risk groups were constructed: Group 1: stage 0, pathological complete regression (pCR); Group 2: stages IA-IIA; Group 3: stages ≥IIB + cases with clinical progression. Due to local progression, NET was replaced by neoadjuvant chemotherapy in three patients (four tumors). In two postmenopausal patients, letrozole was replaced by tamoxifen because of the insufficient treatment effect. In 19/42 cases, breast-conserving surgery was performed. Within Group 1, there was no cancer in four cases, while only DCIS remained in 2 (pCR: 13 %); Groups 2 and 3 comprised 25 and 15 cases, respectively. The likeliness of a good response (Groups 1 and 2 vs. Group 3) to NET was increased by 7 % for every 1 % increase of the expression of ER (OR=1.070; 95 % CI: 1.007–1.138, p=0.029). Progression-free survival differed according to treatment response (p=0.001). The post-therapy Ki67 value of ≤15 % had only a marginal effect on survival. No other associations were detected between the tumor characteristics and the therapeutic response or survival. Long-duration NET is effective and safe in cases of hormone-sensitive breast cancer.

Keywords Breast cancer · Hormone sensitivity · Letrozole · Tamoxifen · Neoadjuvant endocrine therapy · Predictive factors

Introduction

The classical goal of neoadjuvant systemic therapy (NST) given preoperatively to patients with potentially operable breast cancer is the reduction of tumor size ("down staging"), and finally the improvement of operability. The effects of NST on survival is equivalent with that of adjuvant therapy. However, neoadjuvant therapy provides chance for the observation of the therapeutic sensitivity of the tumor, and for the estimation of prognosis. While NST is traditionally a treatment modality of locally, regionally advanced cases, it is becoming more generally accepted as an alternative for the treatment of any patient who would need adjuvant systemic therapy after surgery (i.e., based on the stage or histology of the tumor), therefore NST should be considered in all these cases [1, 2].

A good response to NST may permit a decrease in the radicality of local therapy, including surgery and radiotherapy [3]. The application of NST furnishes information on the

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sensitivity of a tumor to therapy, and provides a possibility for the appropriate adaptation of the therapy [4]. A good response predicts a favorable outcome, and the prognosis may therefore be estimated more accurately. New studies on NST indicate that by the individualization of NST, its effectiveness is improved, the side-effects overall are reduced; NST serves as a good tool for the development of new treatment modalities, and has the potential to improve cost-efficiency of breast cancer care [1, 2]. NST requires good cooperation between, and the use of mutually accepted guidelines by the experts participating in the management of the disease [2].

The complete disappearance of any invasive cancer from the breast and lymph nodes, referred to as a pathological complete response (pCR), means an excellent prognosis; the FDA has proposed use of the rate of pCR as a surrogate marker that could be utilized for the accelerated approval of new drugs [5, 6]. The rate of pCR after chemotherapy in chemosensitive tumors may be as high as >40 %, while in hormone receptor-positive cases it is <10 % [6]. Especially those hormone receptor-positive cases are chemoresistant which exhibit low proliferative activity [6], and in these cases neoadjuvant endocrine therapy (NET) is an attractive treatment modality [7]. The need of personalization of systemic therapy on the basis of molecular subtypes is stressed by the St Gallen international expert consensus document 2013 [8]. In "luminal A-type tumors" representing strong endocrine responsiveness, as stated, endocrine therapy is the most critical intervention, and is often used alone in the adjuvant setting [8]. Relatively few data are available concerning the use of NET, and most are limited to the use of aromatase inhibitors in postmenopausal patients [9, 10]. NET for a period of a few months causes tumor regression in about two-thirds, and thus breast-conserving surgery (BCS) may be performed in around half of the cases. The rate of pCR in such studies is about 3 %, but this may be improved by prolonging the therapy [11–15]. Only a few studies have been performed on the population of premenopausal patients through the use of ovarian ablation with tamoxifen or an aromatase inhibitor [16, 17].

In the present retrospective single-center study, we analyzed the effects of NET administered for a period of 1 year in cases with apparently endocrine-responsive breast cancer. We investigated the early outcome and survival, and possible predictors of the prognosis.

Patients and Methods

Patients were eligible for NET if they had histologically confirmed invasive breast cancer in stages II or III (UICC/AJCC TNM classification system vs. 7.0) and if imaging examinations, including chest X-ray, abdominal ultrasonography and bone scan, ruled out distant metastases. The initial local/regional tumor status and that after NET were evaluated through physical examination, mammography, ultrasonography and breast MRI in some cases. The initial tumor size was determined from the size of the mammographic abnormality, or, if there was no abnormality, via the MRI image. Prior to the start of NET, three tissue cylinders for histopathological examinations were taken from each patient with a 16 G core needle. In three of four patients with bilateral breast cancer, only fine needle aspiration proved the existence of cancer in the less advanced tumor. In potential candidates for BCS, a clip (O-Twist-Marker, BIP Biomed. Instrumente & Produkte GmbH, Germany) was inserted into the tumor for visualization purposes before the NET.

Treatment with letrozole (n=33, postmenopausal group), or with goserelin plus letrozole (n=7) or with goserelin plus tamoxifen (n=2) (premenopausal group) was planned for 1 year. The therapeutic response was monitored by palpation every 3 months, or with imaging if necessary. In the event of progression, NET was replaced by neoadjuvant chemotherapy; if the therapeutic effect was judged to be insufficient, letrozole was replaced by tamoxifen. After 1 year of NET, surgery was designed individually with regard to the post-therapy imaging results and the initial tumor stage. The imaging response based on mammography was evaluated in accordance with the WHO criteria [18]. Sole sentinel lymph node biopsy at the time of surgery was aimed at in cases of clinical lymph node negativity. If the sentinel lymph was found to be metastatic, complementary axillary block dissection was performed. pCR was taken as the absence of any invasive cancer in the breast or the axilla; the presence of an in situ tumor component was permitted [6]. On the basis of the volume of the tumor remaining in the surgical specimen, the following risk groups were constructed:

Group 1: no invasive tumor (stage 0)
Group 2: small-volume residual tumor (stages IA–IIA)
Group 3: large-volume residual tumor (stages ≥IIB) + cases with clinical progression.

Following surgery, postoperative radiotherapy and adjuvant systemic therapy were applied in accordance with the institutional guidelines.

Durations of progression-free survival (PFS) and overall survival (OS) times were calculated from day 1 of NET to the date of any tumor progression (local/regional progression, local relapse after surgery, or distant metastasis) and the date of death for any reason, respectively. Analyses were carried out from the aspects of the associations of the tumor response and the PFS with (a) the initial tumor predictive markers, such as the ER, PgR and HER2 status, and the Ki67 and TOP2A protein expressions, (b) the remaining tumor volume/risk group, and (c) the differences in the tumor characteristics after the NET.

Histopathology, Immunohistochemistry

Tissues were fixed in buffered formalin and embedded in paraffin. Four to five-micrometer-thick whole-tissue sections were used for the immunohistochemistry. The ER, PgR, HER2, Ki67 and TOP2A immunohistochemical results were extracted from the original reports. Immunohistochemistry studies (Dako Autostainer) were performed using the following antibodies: ER (SP1, Lab Vision, Thermo Scientific, Waltham, MA, USA), PgR (PgR636, Dako, Glostrup, Denmark), HER2 (SP3, Histopathology, Pécs, Hungary), Ki67 (MIB-1, Dako, Glostrup, Denmark), and TOP2A (Ki-s1, Lab Vision, Fremont, CA, USA). Expression was determined by using Dako EnVision FLEX/HRP, DAB+ Chromogen (Dako, Glostrup, Denmark). The ER, PgR and HER2 stainings were interpreted in accordance with the European guidelines for quality assurance in breast cancer screening and diagnosis (fourth edition) [19, 20]. In the case of Ki67, the recommendations of the international working group were followed [21]. A similar method was used for the determination of the TOP2A status. The nuclei of 50 tumor cells were counted under the microscope, and the proportion of stained cells was recorded. In both cases, a cut-off value of 15 % was applied to separate negative (≤15 %) and positive samples (>15 %).

Statistical Analysis

The associations between the multiple versus the continuous variables were analyzed by the one-way ANOVA test. In order to examine the changes in the tumor features after NET, the paired sample *t*-test and the McNemar test were used for the continuous and categorical variables, respectively. Binary univariate logistic regression models were applied to examine the potential predictive role of the expression of ER. PFS and OS were estimated with the Kaplan-Meier method. The effects of the pathology results on PFS were analyzed with the Cox regression model. The IBM SPSS version 20.0 for Windows (IBM Corp., Armonk, NY, USA) was utilized for statistical analysis.

Results

Therapeutic Effects

Between 04/2005 and 01/2014, 42 patients were eligible for the present analysis. The mean age (±SD) was 62.3± 12.1 years (postmenopausal patients: 67.0±8.3, premenopausal patients: 44.9±6.4 years). The histologic type was invasive ductal carcinoma (n=35, 81.4 %), invasive lobular carcinoma (n=7, 16.3 %) or mucinous carcinoma (n=1, 2.3 %). The patient- and tumor-related features are shown in Fig. 1. The treatment consisted of letrozole (n=33, postmenopausal group), or goserelin plus letrozole (n=7) or goserelin plus tamoxifen (n=2) (premenopausal group). In three patients (n=4 tumors, 8.7 %), the hormone therapy was changed to chemotherapy because of local progression. These patients were included in the survival analyses, but the pathological results on their surgical specimens were not used. In two postmenopausal cases, letrozole was replaced by tamoxifen because of the insufficient treatment effect after 6 or 9 months. After an overall 12 months of NET, these patients exhibited partial regression on clinical examination, but no relevant regression at pathological evaluation; mastectomy was performed in both cases. The imaging responses to NET were as follows: complete regression: n=7; partial regression: n= 30; no change: n=5. The following surgical interventions were carried out: excision: n=19, mastectomy: n=23, sentinel lymph node biopsy (SNB): n=20, axillary block dissection± SNB: n=22. pCR was observed in 14.3 % of the operated cases, and in 13 % of all cases: in four cases, no cancer was present in the breast and the lymph nodes; in two cases, only DCIS remained. In fact, although there was no cancer in the breast, lymph node metastases still remained in two cases. In risk groups 2 and 3, there were 25 and 15 tumors, respectively. In 1 node-negative case in group 2, only isolated tumor cells were found in the breast. The treatment results are presented in Table 1 and Fig. 1.

Five of 39 patients received adjuvant chemotherapy after the surgery due to the lack of a significant therapeutic effect, and in one case because of the change in the phenotype to triple negativity. Altogether 37 patients continued the same endocrine therapy as that before the surgery. Most tumors in the premenopausal group were of stage II and grade 2, and the expression of ER and PgR was similarly high, while that of Ki67 and TOP2A was less than in postmenopausal patients (data not shown); 2/10 tumors showed pCR.

Association Between Tumor Response and Tumor Characteristics

The changes in ER, PgR or HER2 expression after NET were analyzed in 32 tumors since the cases that progressed (n=4) or in which there was no remaining invasive tumor in the breast (n=8) could not be included (Fig. 1). The HER2 status did not display significant changes, however in a single case, although the core biopsy indicated HER2 negativity, in the surgical specimen, HER2 immunohistochemistry showed HER 2+, and FISH revealed HER2 gene amplification. The expression of ER (p=0.002), PgR (p=0.001), Ki67 (p=0.012) and TOP2A (p=0.029) decreased significantly in the surgical specimens as compared with the core biopsies taken before treatment (Fig. 1). A higher initial ER expression was related to a better response to NET (Table 1). The likeliness of a good response (Groups 1 and 2 vs. Group 3) to NET was increased by 7 % for

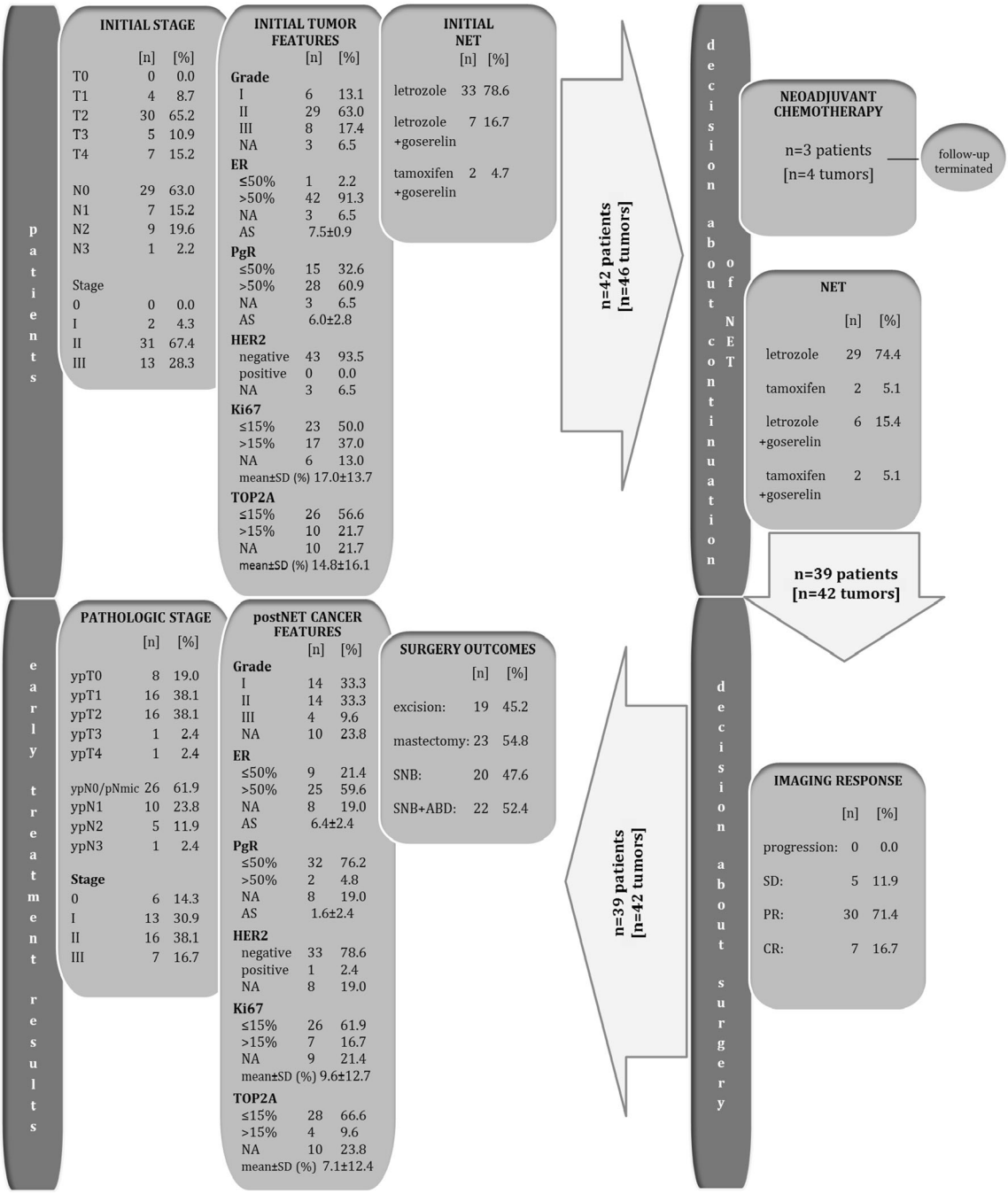

Fig. 1 Overview of the neoadjuvant endocrine therapy of patients in the analysis. *ABD* axillary block dissection, *AS* Allred score (mean±SD), *CR* complete regression, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *NA* not available, *NET* neoadjuvant endocrine therapy, *PgR* progesterone receptor, *PR* partial regression, *SD* stable disease, ±*SD* standard deviation, *SNB* sentinel node biopsy, *TOP2A* topoisomerase II-alpha

every 1 % increase of the expression of ER (OR=1.070; 95 % CI: 1.007–1.138, p=0.029). No significant associations were detected between the initial expression or the reduction of PgR, Ki67 or TOP2A and the therapeutic response or the PFS. A positive (>15 %) expression of Ki67 in the surgical specimen predicted a risk of progression of HR=5.432 (95 % CI: 1,202–24,553, p=0.028).

Survival

After a median follow-up time of 45.2 (17.2–111.6) months, six patients developed distant metastases, and one patient a new cancer in the opposite breast. Three patients died, two because of metastatic breast cancer, and one for a reason other than breast cancer. The

Table 1 Age and initial tumor features according to pathological tumor response

	Group 1: pCR (n=6)	Group 2: major response (n=25)	Group 3: lack of major response/ progression (n=15)	p
Age (years, mean±SD)	61.4±14.3	65.8±10.0	56.7±13.1	0.080
ER (mean±SD)				
Percentage of stained tumor cells	84.0±8.9	88.3±9.4	75.7±19.9	0.034
Allred score	7.4±0.9	7.8±0.6	7.2±1.1	0.112
PgR (mean±SD)				
Percentage of stained tumor cells	48.0±34.2	68.7±29.3	52.3±40.7	0.252
Allred score	4.8±2.9	6.9±2.0	5.1±5.1	0.106
Ki67				
Percentage of stained tumor cells (mean±SD)	23.0±23.1	17.7±11.4	13.3±13.5	0.399
≤15 %, n (%)	3 (50.0)	11 (44.0)	9 (60.0)	0.302
>15 %, n (%)	2 (33.3)	12 (48.0)	3 (20.0)	
TOP2A				
Percentage of stained tumor cells (mean±SD)	13.0±6.7	15.6±16.4	14.1±19.7	0.939
≤15 %, n (%)	3 (50.0)	15 (60.0)	8 (53.3)	0.712
>15 %, n (%)	2 (33.3)	6 (24.0)	2 (13.3)	

estimated mean PFS time was 74.2 (95 % CI: 60.4–88.0) months, and the estimated mean OS time was 92.8 (95 % CI: 80.0–105.7) months. The tumor volume remaining after NET predicted PFS levels of 85.3, 70.6 and 41.4 months in risk groups 1, 2 and 3, respectively (p=0.001) (Fig. 2). The HR of PFS in groups 1 and 2 was 0.131 (95 % CI: 0.016–1.056, p=0.056) and 0.101 (95 % CI: 0.022–0.468, p=0.003), respectively, as compared with group 3. No association was detected between the PFS and tumor characteristics. OS was not analyzed in relation with these parameters because of the limited number of events.

Discussion

This retrospective analysis demonstrated that 1 year of NET with letrozole was effective in patients with apparently hormone-sensitive breast cancer. In 13 % of the cases, pCR was achieved, two-thirds showed a significant regression and <10 % presented a progression. A good response was related to high expression of the ER: the likelihood of tumor regression was increased by 7 % for every 1 % increase of ER expression, however, probably due to the limited number of cases, no similar association could be verified for pCR alone. PFS was related to the regression brought about by the NET, and the results for premenopausal and postmenopausal patients did not differ significantly.

One of the advantages of the neoadjuvant approach is that the benefits of the systemic therapy and thus the prognosis may be assessed in vivo. The achievement of pCR is a predictor of an excellent outcome after neoadjuvant chemotherapy. This also seems true for the subgroup of hormone-sensitive breast cancers [6], though the prognosis may be favorable in this cancer type even in the absence of pCR. The significance of pCR after NET is more puzzling, since pCR is a rare event after NET of conventional duration [7, 9, 14, 15]. To predict the outcome, different approaches have been implemented. Ellis et al. made use of the long follow-up data of the P024 neoadjuvant endocrine trial to develop a prognostic index ("preoperative endocrine prognostic index, PEPI") incorporating the posttherapy tumor size, the nodal status, the grade, ER, Ki67 and the response to therapy [22]. The PEPI was validated in the independent IMPACT trial [23]. DeCensi et al. observed that Ki67 was a good predictor of the prognosis after short-term NET, with a 5.5-times higher risk of death in cases with a posttreatment Ki67≥20 % [24]. In good agreement with these findings, we found that the remaining cancer burden and posttreatment Ki67 were the only significant predictors of PFS.

The identification of tumor features that allow prediction of the response to NET for patient selection is essential. We treated patients with breast cancers that were probably hormone-sensitive: only the selection of HER2-negative cancers with an ER or/and PgR expression >50 % was permitted. Indeed, the most significant predictor of the response was the initial expression of ER, in agreement with the data of Ellis et al. [22, 25] and Toi et al. [12]. Although the high grade of the cancer or the high expression of Ki67 in it may be indicators of hormone resistance, these markers do not exclude a

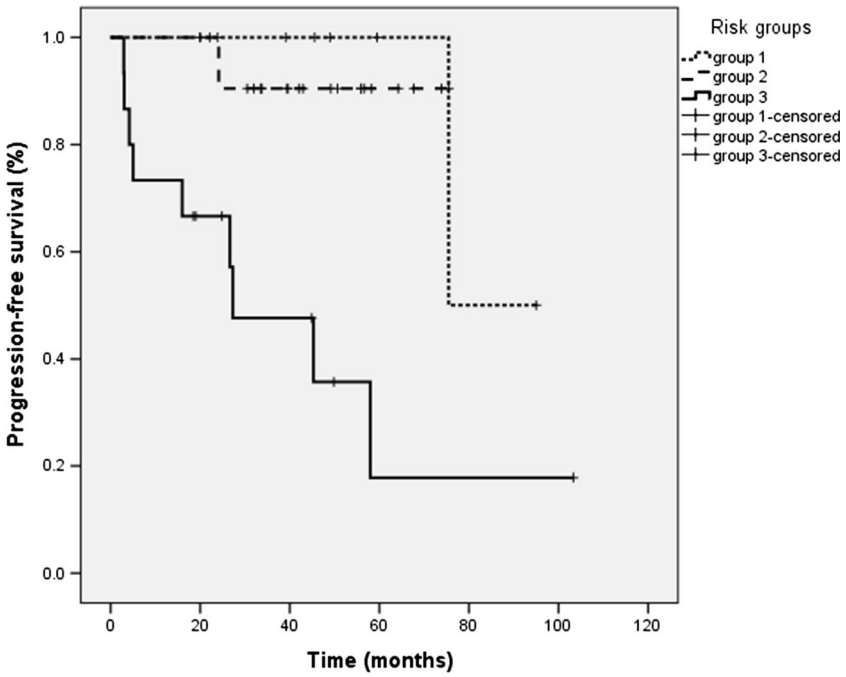

Fig. 2 Progression-free survival (PFS) in the three risk groups after the completion of 1-year neoadjuvant endocrine therapy as estimated by the Kaplan-Meier method (n=42 patients, p=0.001)

good effect of hormone therapy. A change in Ki67 seems to be an early indicator of a response, and may be used with this aim as soon as after 2 weeks of endocrine therapy [26]. Indeed the study by Allevi et al. indicated that a decrease in Ki67 expression is manifested in the early phase of the treatment, and the expression does not decline further on the prolonged administration of letrozole for 4, 8 or 12 months, despite the seemingly time-dependent tumor regression [14]. A more sophisticated method for the prediction of hormone sensitivity could be gene expression profiling. Mello-Grand et al. reported and validated a gene expression signature that predicted the response after NET with anastrozole or letrozole [27]. Through testing of the 21-gene expression profile in the neoadjuvant exemestane JFMC34-0601 study, a low or intermediate versus a high recurrence score distinguished responders and those without a therapeutic effect [28].

The optimum duration of NET has not yet been established. In a few studies, the length of NET with aromatase inhibitors was analyzed in relation to the downstaging of the tumor and the rate of BCS. Dixon et al. administered letrozole for 3–24 months; the continuation of letrozole beyond 3 months increased the number of women who initially required mastectomy but subsequently became eligible for BCS [13]. In a similar study with NET for a duration of 4–8 months, the longer the letrozole therapy, the higher the rate of BCS achieved [29]. Carpenter et al. set out to identify the treatment duration needed to obtain the highest rate of BCS; a median time of 7.5 months (95 % CI 6.3–8.5 months) was sufficient to achieve tumor regression that allowed BCS [30]. Likewise, in the study by Hojo et al., the rates of clinical response and BCS were higher after 6 months than after 4 months of exemestane therapy [15]. Thus, it has been well demonstrated that, in respondents, the tumor regression is continuous during NET. The rate of pCR clearly increases as the NET period is extended. When NET is administered for 3–4 months (independently of the drug used), pCR is a rare event [7]. In the study by Hojo et al., only a single case with pCR was found among 25 postmenopausal patients treated with exemestane for 6 months [15]. Allevi et al. systematically treated three cohorts of 40 patients each with letrozole NET for 4, 8 and 12 months, respectively [14]. In parallel with the clinical response, the rates of pCR in the 3 groups were 2.5, 5.0 and 17.5 % (p<0.04). In our study of 46 cases, the rate of pCR after 1 year of letrozole therapy was 13 %; our data extend the limited experience acquired with NET concerning pCR.

A few published data are also available on NET in premenopausal patients. In the GEICAM/2006-03 study, the premenopausal patients were randomized to neoadjuvant chemotherapy versus exemestane therapy combined with goserelin [31]. While the treatment results were equivalent in the postmenopausal group, significantly more responses were observed in the chemotherapy arm than in the NET arm among the premenopausal patients (probably due to the lack of patient selection). Most of the previously reported NET studies were performed with aromatase inhibitors, but conflicting data recently appeared relating to their adjuvant use in premenopausal patients [32, 33]. We found letrozole to be equally effective in the premenopausal and postmenopausal groups. Debled et al. reported an analysis of routine NET in a large cancer center, but the proportion of their premenopausal patients was only 6 %; the use of NET in hormone-sensitive cases was

stressed [34]. In our practice, NET is selected for premenopausal patients provided that a high expression of ER and PgR is detected, and the grade and the proliferation markers are low. We believe that endocrine therapy is the most effective treatment mode in truly hormone-dependent cancers, and NET is a possibility whereby this may be checked while the tumor is in place; through the observation of the response, NET may be regarded as a safety measure for the design of adjuvant therapy.

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