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Critical Appraisal of Primary Systemic Endocrine Therapy in Receptor-Positive Postmenopausal Breast Cancer: An Update

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Key Words

Breast cancer, receptor-positive · Therapy, primary endocrine · Clinical trials · AGO guidelines · Recommendations

Summary

Even in elderly patients, greater consideration is now being given to tumor volume reduction in locally advanced breast cancer, with increased subsequent breast-conserving surgery. Neoadjuvant endocrine therapy offers the possibility of testing therapeutic efficacy in vivo, which is of great importance for optimal adjuvant treatment. Resulting therapy modifications can be expected to increase disease-free as well as overall survival. Recent results indicate that remission rates with primary chemotherapy are significantly lower in receptor-positive than in receptor-negative breast cancer and that efficacy parameters in receptor-positive tumors tend to favor primary endocrine therapy, highlighting the increased importance of this type of treatment. Aromatase inhibitors are superior to tamoxifen in terms of clinical response as well as breast conservation rate. Results from a small number of studies suggest that prolonged preoperative aromatase inhibitor therapy for up to 12 months can increase the rate of clinical and pathological complete remissions. In conclusion, primary endocrine therapy is a valid therapeutic option for postmenopausal patients with locally advanced hormone receptor-positive breast cancer and significant comorbidity, increased risk of complications with regard to anesthesia and surgery, desire for breast-conserving surgery and/or reduced suitability for chemotherapy, as well as in very old patients.

Schlüsselwörter

Mammakarzinom, rezeptorpositives · Therapie, primär endokrine · Klinische Studien · AGO-Leitlinien · Empfehlungen

Zusammenfassung

Auch bei älteren Patientinnen spielen Überlegungen zur Volumenreduktion lokal fortgeschrittener Mammakarzinome und die damit verbundene Erhöhung der Rate brusterhaltender Operationen zunehmend eine Rolle. Eine in-vivo Testung der Effektivität unter neoadjuvanter endokriner Therapie ist für eine optimale adjuvante Therapie von großer Bedeutung. Entsprechend angepasste Therapiekonzepte lassen eine Verbesserung des erkrankungsfreien- bzw. des Gesamtüberlebens erwarten. Aktuelle Ergebnisse deuten darauf hin, dass Remissionsraten bei rezeptor-positiven lokal fortgeschrittenen Mammakarzinomen im Vergleich zu denen bei rezeptor-negativen Tumoren signifikant niedriger ausfallen und die Effektivitätsparameter beim rezeptor-positiven Karzinom tendenziell für die endokrine Therapie sprechen. Dies unterstreicht die Bedeutung der endokrinen primär-systemischen Therapie. Aromatasehemmer sind Tamoxifen hinsichtlich des Tumoransprechens bzw. der Rate brusterhaltender Operationen überlegen. Einzelergebnisse deuten daraufhin, dass eine prolongierte primär-systemische Therapie mit Aromatasehemmern bis zu 12 Monaten die Rate klinischer und pathologischer Komplettremissionen erhöhen kann. Zusammenfassend ist heutzutage die primäre endokrine Therapie eine therapeutische Option bei postmenopausalen Patientinnen mit lokal fortgeschrittenem hormonrezeptorpositiven Mammakarzinom und ausgeprägter Komorbidität, hohem Narkose- und Operationsrisiko, Wunsch nach brusterhaltender Operation und/oder eingeschränkter Eignung für eine Chemotherapie sowie für Patientinnen im fortgeschrittenen Senium.

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Introduction

The standard sequence of treatment in receptor-positive breast cancer in elderly postmenopausal women consists of surgery, adjuvant endocrine or sequential chemo-endocrine therapy and radiotherapy, depending on the type of surgery (i.e. breast conservation), tumor volume and lymph node involvement. However, the choice is affected by co-morbidity and an impaired life expectancy in old age [1]. In practice, irrespective of the stage of the disease, elderly patients more often undergo mastectomies and receive less aggressive treatment because of concerns about toxicity. And, if hormone receptor-positive, they are more likely to be given exclusive endocrine therapy [2]. Breast-conserving surgery followed by radiotherapy shows similar long-term results as mastectomy [3]. Volume reduction of locally advanced cancers and the resulting rising rate of breast-conserving operations plays an increasingly important role even in elderly patients. Recent reports support the concept of primary endocrine therapy as an option for postmenopausal women with locally advanced receptor-positive breast cancer [4–7]. The results obtained to date and future treatment considerations are presented and discussed in detail below.

Primary Endocrine Therapy

Primary endocrine therapy was investigated almost at the same time as primary chemotherapy. However, it was mostly evaluated in elderly women in small-scale studies. First results were published as early as 1989 [8]. Compared to chemotherapy, primary endocrine therapy has the advantage that the tumor can be continuously treated and monitored from the time of diagnosis to the immediate perioperative period. As a result, the possible release of growth factors after extirpation of the tumor and hence the risk of tumor cell metastasis during surgery may be reduced [9, 10] (table 1). Approximately 20% of estrogen/progesterone receptor-positive (ER+/PR+) and 50% of ER+/PR– or ER–/PR+ breast cancers show no response to endocrine therapy [11, 12]. The in vivo efficacy testing advantage of primary endocrine therapy is therefore of crucial importance for the subsequent adjuvant therapy. Moreover, the resulting treatment modifications can be expected to improve disease-free and overall survival.

Tamoxifen

The efficacy of tamoxifen in primary systemic therapy was demonstrated in several randomized studies. A multicenter trial with 473 women over 70 years of age by Mustacchi et al. [13] showed that although primary use of tamoxifen versus surgery plus adjuvant tamoxifen resulted in an increased rate of local tumor progression ($p < 0.001$), there were fewer distant metastases ($p = 0.058$) and overall survival was identical. Similarly, Gazet et al. [14] found no difference in disease-free survival in 200 patients who were followed up for 6 years. Robertson et al. [15] saw no influence on overall survival or cause of death, despite lower locoregional control under tamoxifen. Trials on primary endocrine therapy show clinical response rates of 49–68% under tamoxifen with a mean time to response of 3–5 months and a low rate of side effects. A median reduction in tumor volume of 58% can be achieved. Comparison of primary tamoxifen followed by surgery with adjuvant tamoxifen after primary surgery showed no difference in overall survival [16].

Aromatase Inhibitors

Primary endocrine therapy using aromatase inhibitors was first investigated by Miller and Santen [17] in terms of practicability, volume reduction and rate of breast-conserving surgery. Clinical response rates of more than 40% can be achieved [7, 18, 19] (table 2).

Anastrozole

Geisler et al. [20, 21] compared direct intratumoral effects with changes in plasma estrogen under anastrozole: intratumoral as well as plasma levels of E1, E2 and E1S were reduced by up to 95%, sometimes to values below the detection limit. It needs to be remembered that breast cancers can maintain high estrone and estradiol tissue levels despite low plasma levels, and therefore plasma estrogen levels do not allow direct conclusions regarding tumor estrogen metabolism [21]. One the one hand, tissue and plasma estrogen levels tend to fall irrespective of tumor response to treatment. On the other hand, decreases in proliferation markers (i.e. Ki67, pS2) tend to be greater in responders. In addition, compared to pretherapeutic levels, the mean number of apoptopic cells falls in responders, whereas it increases in non-responders [22–24].
The IMPACT study ('Immediate Preoperative Anastrozole, Tamoxifen or Anastrozole Combined with Tamoxifen') compared primary anastrozole and/or tamoxifen therapy in a randomized double-blind design in 330 postmenopausal patients with receptor-positive, operable breast cancer ($T > 2$ cm) over a period of 3 months. No significant difference between anastrozole, tamoxifen or both in combination was found in terms of clinical response, whereas the breast conservation rate was doubled with anastrozole compared to tamoxifen alone ($p = 0.03$, RR 2.05) [25, 26]. Dowsett and Smith investigated molecular effects of the different treatment modalities and found changes in Ki67 and growth index (Ki67/apoptosis). These findings indicate that short-term changes in biomarkers can be regarded as predictive of long-term results in the primary systemic as well as adjuvant setting [22, 23].

Table 1. Advantages and disadvantages of primary endocrine therapy

Advantages	Disadvantages
Earliest possible systemic therapy (even in patients with impaired general health).	Delay of local treatment for non-responders, subsequent therapy unclear in the adjuvant situation.
Low toxicity, thus use is almost unrestricted by age and comorbidity.	Increased risk of thromboembolic side effects and endometrial cancer (tamoxifen). Long-term side effects of aromatase inhibitors unknown (i.e. impairment of cognitive functions etc.).
Inhibition of intra- and postoperative tumor cell dissemination.	Induction of resistance mechanisms.
Treatment may use intact tumor structures (i.e. receptors, blood vessels).	Receptor-negative tumor areas remain unaffected.
Therapeutic activity can be visualized in vivo, adjuvant therapy may be planned accordingly.	Initially (4–8 weeks), structural tumor changes without measurable volume reduction.
In vivo evaluation of treatment effects: rapid investigation of relevant predictive and prognostic factors, down-staging of tumor and affected lymph nodes.	Tumor burden remains in situ with the possibility of tumor cell dissemination/metastasis.
Increased rate of breast-conserving surgery.	More difficult to plan surgery, increased rate of secondary interventions including secondary mastectomy, necessity of radiotherapy.
Unlimited duration (data so far available for up to 12 months).	Continuous treatment monitoring required.
The patient can see therapy effect immediately.	Results concerning disease-free and overall survival still unclear.

Table 2. Median tumor volume reduction (as measured by ultrasound) achieved by primary endocrine therapy – summary of the Edinburgh results (modified from [17])

Substance	Patients, n	PR (n)	SD (n)	PD (n)	Mean volume reduction, %	BCS after 3 months, %
Tamoxifen	65	30	34	1	48.0	58.5
Letrozole	24	21	2	1	81.0	100.0
Anastrozole	23	18	5	0	75.5	91.3

PR = Partial remission, SD = stable disease, PD = progressive disease, BCS = breast-conserving surgery.

Exemestane

In a small study (n = 13), exemestane was used for 3 months in postmenopausal, estrogen receptor-rich breast cancer. Treatment reduced cellular proliferation and PgR expression [27]. 11 out of 12 patients showed a marked reduction in aromatase activity in the tumor and the surrounding breast tissue, which correlated well with the volume reduction (median 85.5%) achieved by the primary systemic therapy. In a further study (n = 79) on postmenopausal receptor-positive breast cancer, clinical response (88.6%) to exemestane was higher than to tamoxifen (57.2%) [27]. The same advantage for the exemestane group was seen regarding the rate of breast-conserving surgery (38.7 vs. 10.8%) with a low rate of side effects [9, 24]. Combination of exemestane and the cyclooxygenase-2-inhibitor celecoxib led to a minimal improvement in clinical response. Prolonging the phase of neoadjuvant therapy to 4–5 months led to a higher breast conservation rate (45.2%) [28]. Recent results of another phase II study [29] support the previous findings: 55 patients with ER+ breast cancer and an average age of 77 (67–88) years were treated with exemestane for 6 months. 25 women showed a clinical response, tumor size remained unchanged in 24 patients, and only 1 patient showed primary progression. The average time to operation was 7 months, breast-conserving surgery was possible in 21 patients, 17 underwent mastectomy and 12 were not operated on at all. A complete pathological response in the breast and axilla was obtained in 3 and a partial response in 14 cases. Only grade I–II toxicities occurred. The relationship between response and change in tumor biological factors during 16 weeks of exemestane therapy was investigated (n = 41) where no correlation between pretherapeutic and perioperative levels of ER alpha, PgR, Ki67, HER2, ER beta, aromatase, COX-2 and clinical response was found [30, 31].

Letrozole

An initial phase I/II study in 24 postmenopausal women with receptor-positive locally advanced breast cancer, who were

Table 3. Prolongation of primary endocrine therapy (modified from [42])

Duration of therapy, months	Patients, n	Median reduction[a], % (range)	Complete clinical response, patients, n (%)
0–3	42	52 (37–62)	at 3 months: 4 (9.5)
3–6	42	57 (26–100)	at 6 months: 12 (29)
6–12	22	66 (22–100)	at 12 months: 8 (36)

[a]95% CI.

preoperatively treated with letrozole for 3 months, showed a clinical response rate of 92%. Based on this pilot study, efficacy of primary endocrine letrozole versus tamoxifen therapy for 4 months in 344 patients was then compared in a randomized multicenter phase III double-blind study [4]. Clinical response showed a significant advantage ($p < 0.001$) for letrozole (55%) over tamoxifen (36%). The rate of breast-conserving surgery was significantly higher in letrozole-treated patients (45 vs. 35%, $p = 0.022$). Achievement of a clinical objective remission (complete/partial) was independent of the initial tumor size ($p = 0.22$), lymph node status ($p = 0.46$) or age ($p = 0.95$). Primary progression of the disease occurred under letrozole in 13 (12%) and under tamoxifen in 21 (17%) patients. Complete clinical remissions (cCR) were more frequent under letrozole (10%) than under tamoxifen (4%). The rate of pathological complete remissions (pCR) was equally low in both arms (2 vs. 3 patients) [4]. Similar results were obtained by Sokol et al. [31] after 3 months of primary letrozole therapy (n = 22, stage IIIB) with a total response rate of 67%, a complete remission rate of 8%, and a breast conservation rate of 50%. In another study of 3 months of letrozole (n = 50), Jackson et al. [32] demonstrated an anti-proliferative (Ki67) and anti-estrogenic effect without any observed change in estrogen receptor expression in serial biopsies taken before and after 10–14 days of therapy as well as at the time of surgery. Changes in Ki67 expression were independent of response to therapy. However, tumors that showed virtually no response had higher initial Ki67 expression [33]. In contrast to tamoxifen, letrozole was able to change the histopathological grading by reducing the parameters nuclear polymorphism and nuclear grade [34, 35].

Aspect of Her2 neu Overexpression

Overexpression of Her2 neu confers on the affected cancer cell aggressive behavioral traits, including enhanced growth and proliferation, increased invasive and metastatic capability and stimulation of angiogenesis [36]. Preclinical and clinical data indicate that expression of Her2 is involved in endocrine resistance. Patients with Her2 overexpression had lower ER levels and were modestly less responsive to tamoxifen [37]. Results of adjuvant trials outline the importance of hormone receptor expression and Her2 status for response to therapy with aromatase inhibitors. Tumor response to tamoxifen directly correlates with the degree of hormone receptor positivity but stands in reverse relation to Her2 overexpression, as shown in neoadjuvant clinical trials. However, letrozole has proven efficacy in tumors with only moderate expression of steroid/hormone receptors and Her2 overexpression. This favors therapy with an aromatase inhibitor in Her2-overexpressing breast cancer also in the neoadjuvant setting.

Prolongation of Duration of Primary Endocrine Therapy

After evaluation of the results of the tamoxifen versus letrozole study, it was decided to modify inclusion criteria for a phase II study with longer duration of neoadjuvant letrozole [17]. Under monthly check-ups, it was possible to prolong primary therapy with letrozole up to 8 months. The aim was to examine whether this prolonged duration could result in a better overall response, with greater tumor reduction and increased cCR and pCR rates. First evaluation (n = 33) after a treatment period of 1.9–8.6 months (median 5.1 months) showed a 90% response with a mean tumor size reduction of 68% after longer administration compared with 57% response after a 4-month administration period. pCR was achieved in 6% and partial remission in 64% of patients with a 67% breast conservation rate [40]. Treatment was very well tolerated, hot flushes occurred in 43.8% and fatigue in 15.6%. No patient discontinued prematurely due to side effects [41]. Renshaw et al. [42] investigated prolonged primary letrozole therapy in 142 women with locally advanced breast cancer, with the aim of obtaining further reduction in tumor volume (table 3). The optimal duration of primary endocrine therapy depends on the desired volume reduction. Prolonged primary systemic endocrine therapy is associated with better response, greater reduction in tumor volume and an increased rate of breast-conserving surgery. The safety of primary letrozole therapy has been investigated up to a period of 12 months.

Combined Primary Chemoendocrine Therapy

The aim of combined chemoendocrine therapy is to achieve additive or synergistic effects with both treatment modalities. This would enable a reduction in the doses of the cytotoxic

Table 4. Results of the comparative study of primary endocrine therapy versus primary chemotherapy [49, 50]

	ORR clinical, %	ORR MG, %	pCR, %	BCS, %	Local recurrence rate [49], %	Local recurrence rate [50], %	3-year DFS (%), %
Primary chemotherapy	66.6	66.6	7.4	23.9	3.2	4.2	80.2
Primary endocrine therapy	53.3	46.6					79.3
Anastrozole			3.3	33.3	3.3	5.4	
Exemestane			6.8	34.0	3.4	2.6	

ORR = Overall response rate, MG = mammography, pCR = complete pathological remission, BCR = breast-conserving surgery, DFS = disease-free survival.

agents with a more balanced side effect ratio and continuous perioperative tumor control. In Germany, this concept was applied in the GEPARDO study (German Preoperative Adriamycin Docetaxel) with combination doxorubicin + docetaxel chemotherapy (4 cycles) applied as a dose-dense versus a conventional regimen +/– tamoxifen. Yet, no significant advantage in terms of pathological complete remissions could be demonstrated between chemo- and chemoendocrine treatment [43].

Clinically negative lymph nodes and a negative estrogen receptor status was predictive for a higher pCR rate [44, 45]. Based on the demonstration of synergistic antitumor effects of epirubicin combined with exemestane in a hormone-dependent breast cancer model [46], clinical trials have been carried out comparing various primary systemic chemoendocrine combinations with exemestane and different cytotoxic agents (epirubicin, docetaxel, paclitaxel) with respect to optimal dose and toxicity [46, 47]. The protocol arm epirubicin and exemestane showed promising results with clinical responses in 11/15 cases (partial/complete) and 1 pCR, while causing only moderate side effects. However, the docetaxel/exemestane combination showed substantial unexpected non-hematological side effects, such as diabetic metabolic changes [48].

Direct Comparison of Primary Endocrine versus Primary Cytotoxic Therapy

A study on postmenopausal ER+ and/or PR+ breast cancer (T2N1–2, T3N0-N1, T4N0) compared primary chemotherapy (n = 62) consisting of 4 cycles of doxorubicin 60 mg/m^2 + paclitaxel 200 mg/m^2 every 3 weeks with 2 different primary endocrine therapies, i.e. exemestane (n = 29) or anastrozole (n = 30), for 3 months (table 4). Clinical overall response was more marked under primary chemotherapy (p = 0.05), but there was no difference in pCR, and the percentage of breast-conserving operations was higher after primary endocrine therapy. The authors therefore concluded that primary endocrine therapy was a preferable treatment modality in elderly or comorbid women [49, 50].

Limits of Primary Endocrine Therapy

The proportion of primary progressive breast cancers under primary endocrine therapy (12–15%) is markedly higher than that under primary systemic chemotherapy (3–5%). The influence of primary progression on disease-free or overall survival and the optimal therapeutic options following primary progression are still unclear. Up to now, the primary systemic therapy is discontinued upon tumor progression and the patient then undergoes surgery. In the absence of long-term data, no definitive statements can be made about disease-free survival or rate of local relapse in primary progression.

Remaining Questions

Many clinically relevant questions regarding primary endocrine therapy have still not been adequately answered by the study results available to date.

Most Effective Substance or Combination

There are no data directly comparing all endocrine therapy options. Data for exemestane exist only from phase II studies. Anastrozole and letrozole show the same proportion of breast-conserving surgery after 3–4 months of the neoadjuvant treatment phase, but the rate for letrozole increases (67%) after prolongation up to 12 months, without compromising the efficacy by toxicity [42].

Duration of Treatment

The optimal duration of primary systemic endocrine therapy has not yet been established. However, there is evidence that in the case of continuous response prolongation of the primary systemic treatment phase can lead to longer remissions or even pCR. To date, primary endocrine therapy has been studied: i) until local tumor progression, ii) for 4 months (tamoxifen vs. letrozole), iii) for 3 months (tamoxifen vs. anastrozole vs. combination; exemestane), iv) for 4–6 months (exemestane), v) for up to 8 months with confirmed remission or until complete clinical/imaging remission (letrozole), vi) for up to 12 months (letrozole).

Sequence of Postoperative Therapy

Adjuvant endocrine therapy is generally used as a continuation of primary endocrine therapy administered in randomized studies. The decision to then treat with aromatase inhibitors is supported by large trials of up-front adjuvant (ATAC, BIG1–98) [51, 52], early sequential (IES, ARNO/ABCSG) [53, 54] or prolonged (MA 17) [55] adjuvant therapy.

Patient Age

The optimal age for using primary endocrine therapy in postmenopausal patients has not yet been established. It is likely that the overall benefit may be greatest in elderly women due to their general health and the increased rate of hormone receptor-positive tumors.

Discussion

Postmenopausal and elderly patients with hormone receptor-positive breast cancer constitute the largest subgroup among breast cancer patients. In line with primary chemotherapy, primary endocrine therapy leads to tumor downstaging and thus demonstrated in vivo efficacy and increased breast conservation rates. So far, results of the first (phase II studies with tamoxifen) and second (phase III trials with aromatase inhibitors: Fem 024, IMPACT) generation trials of primary systemic endocrine therapy have had very little effect on routine clinical practice. This may be due to the rather low rate of complete remissions – an endpoint considered important, at least for primary systemic chemotherapy – and the comparatively high rates of primary tumor progression.

Recent data suggest that remission rates of primary chemotherapy in locally advanced receptor-positive breast cancer are significantly lower than those in receptor-negative tumors [44, 45, 56]. In addition, direct comparison with primary systemic chemotherapy seems to hint at a beneficial effect of primary endocrine therapy regarding efficacy parameters. These results render primary endocrine therapy an increasingly attractive therapy option particularly in elderly women with receptor-positive breast cancer. Recent results demonstrate equivalence regarding overall survival for primary endocrine therapy (tamoxifen) followed by surgery in progressive disease compared to standard therapy with surgery and subsequent adjuvant endocrine therapy [57]. The limited data comparing primary endocrine therapy for a specified period immediately followed by surgery with primary chemotherapy shows no difference in disease-free survival [58].

A higher rate of breast-conserving surgery may lead to more follow-up operations and local recurrences. However, the clinical relevance of this is uncertain in view of the older age of patients receiving primary endocrine therapy, subsequent radiotherapy and adjuvant chemotherapy in case of positive nodal status. It needs to be stated that there are still no reliable data on the long-term course of the disease, overall survival and cost-effectiveness of primary endocrine therapy. The only substantiated aspect is the increased rate of breast-conserving surgery.

pCRs which in primary chemotherapy are regarded prognostically significant because they are associated with improved disease-free and overall survival [59], have so far only been achieved in up to 5% of cases after primary endocrine therapy. Patient compliance with the comparatively well tolerated primary endocrine therapy is very high. Aromatase inhibitors are superior to tamoxifen in terms of tumor response [4, 25, 26]. Results from a number of studies suggest that the rate of cCR and pCR can be increased by prolonged primary aromatase inhibitor therapy.

Recommendations for Clinical Practice

Currently available data have led the AGO Breast Expert Panel of the German Cancer Society (DKG) and the German Society of Obstetrics and Gynecology (DGGG) to assign a recommendation grade '+' to primary endocrine therapy in their annually updated evidence-based breast cancer guidelines (*www.ago-online.org*) [60]. This means that this therapy may be of limited benefit to patients and may be performed in the routine setting when indicated. So far, a general recommendation of this therapy option outside of clinical studies cannot be issued. However, since receptor-positive breast cancer tends to show limited response to primary chemotherapy, the option of primary endocrine therapy should be discussed with the respective patients.

Primary endocrine therapy is a valid therapy option for postmenopausal women with locally advanced hormone receptor-positive breast cancer, marked comorbidity, increased anesthesiological and surgical risk, the desire for breast-conserving surgery, restricted suitability for primary systemic chemotherapy and advanced age [61, 62]. Duration of treatment should be based on the volume reduction achieved and may be continued until local progression without limiting the period of overall survival. In comparison with tamoxifen, aromatase inhibitors are more effective and should be the first choice, particularly in tumors showing HER2 overexpression [39].

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