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Review Article

Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer

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Abstract

Endocrine therapy is one of the mainstays of treatment for patients with hormone receptor-positive breast cancer. While this has primarily been used in the adjuvant setting, the use of neo adjuvant endocrine therapy has increased in recent years as we have developed a better understanding of breast cancer tumor biology and breast cancer subtypes. Neoadjuvant endocrine therapy is a well-tolerated treatment that can increase eligibility for breast conserving surgery in patients with hormone receptor-positive breast cancer and response to therapy allows for risk stratification of patients to guide adjuvant therapy. In addition, neoadjuvant endocrine therapy provides an outstanding platform to examine mechanisms of endocrine resistance and to optimize endocrine therapies that are currently being used to treat patients with breast cancer. Multiple ongoing clinical trials are evaluating the use of neoadjuvant endocrine therapy, alone, or in combination with other targeted agents, to better understand endocrine resistance and to identify new treatment strategies that may improve outcomes in breast cancer patients.

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INTRODUCTION

Approximately 75% of breast cancers in women are hormone receptor (HR)-positive [1] and endocrine therapy is part of standard treatment in these patients [2]. While endocrine therapy is typically used in the adjuvant setting, neo adjuvant endocrine therapy (NET) was initially used to treat elderly patients with HR-positive breast cancer, especially those patients who were not considered good surgical candidates [3,4]. However, NET is being applied more broadly in patients with HR-positive breast cancer [5-7]. This is partially due to our increased knowledge of breast cancer tumor biology and breast cancer subtypes and our understanding that many breast cancers do not respond well to chemotherapy and may be more effectively treated with endocrine therapy alone [8,9]. It has also been influenced by the need to explore mechanisms of de novo and acquired resistance to endocrine therapy, which is a critical problem which limits our ability to treat patients with advanced and recurrent disease [10-12].

Neo adjuvant endocrine therapy is significantly less toxic than neo adjuvant chemotherapy (NCT) [13-15] and has several potential benefits in the treatment of patients with HR-positive breast cancer, especially estrogen receptor (ER)-rich tumors. First, response to endocrine therapy in the neo adjuvant setting may help to select patients with tumors that are exquisitely sensitive to estrogen deprivation who may be treated with endocrine therapy alone. Second, similar to NCT, NET may improve surgical outcomes, converting patients with inoperable tumors to operative candidates and increasing breast conserving surgery (BCS) rates in patients who were only considered candidates for mastectomy. Finally, NET provides an opportunity to examine tumors that are less responsive or resistant to endocrine therapy and to identify signaling pathways that contribute to endocrine resistance and may be targeted alone or in combination with endocrine therapy.

Efficacy of neoadjuvant endocrine therapy

The initial randomized clinical trials which evaluated NET in patients with HR-positive breast cancer were primarily designed to compare the antitumor efficacy of various endocrine therapies in the neo adjuvant setting, to evaluate improvements in surgical outcomes in patients with advanced disease after administration of NET, and to develop surrogate endpoints to assess response to endocrine therapy that could be used to predict long-term outcomes and guide adjuvant treatment decisions. Several large phase II and phase III randomized clinical trials have evaluated the use of NET in patients with HR-positive breast cancer with tumors that were not considered amenable to BCS or locally advanced disease [16-19].

In the P024 trial, letrozole, a non-steroidal AI, was studied in comparison to tamoxifen [16]. This trial was a randomized, double blind, multi-center study, in which postmenopausal patients with ER and/or progesterone receptor (PR)-positive (ER/PR expression > 10%), stage II-III breast cancer, who were

inoperable or not considered candidates for BCS, were treated with either letrozole or tamoxifen for four months prior to surgery. A total of 337 patients were enrolled and the intention to treat analysis was performed for 324 patients. The study met its primary endpoint, demonstrating that objective response rates were greater with letrozole compared to tamoxifen, 55% vs. 36% (P< 0.001).Breast conserving surgery rates were also higher in patients who received letrozole compared to tamoxifen, 45% vs. 35% (P = 0.022). In the subsequent biomarker analyses, it was shown that overall response rates with letrozole were comparable in both the epidermal growth factor receptor (EGFR)/human epidermal growth factor receptor (HER)-positive and negative subsets [20], in contrast to tamoxifen, and that letrozole was more effective than tamoxifen in suppressing the Ki67 proliferative index (P = 0.0009) [21].

The Immediate Preoperative Anastrozole, Tamoxifen or Combined with Tamoxifen (IMPACT) [17] and the Preoperative "Arimidex" compared to Tamoxifen (PROACT) [18]. Trials both compared the efficacy of anastrozole, another non-steroidal AI, to tamoxifen in postmenopausal women with HR-positive breast cancer. In contrast to letrozole, which demonstrated superior response rates to tamoxifen in the P024 trial, anastrozole failed to demonstrate statistically higher response rates than tamoxifen in both trials. The IMPACT trial enrolled 330 postmenopausal women with ER-positive (ER expression > 1%) operable or locally advanced, potentially operable breast cancer [17], Patients were randomly assigned to receive either anastrozole (A), tamoxifen (T), or the combination (C) for 3 months prior to surgery. There was no statistically significant difference in response rates between the 3 arms measured by both clinical exam (A 37%, T 36%, and C 39%) and ultrasound (A 24%, T 20%, and C 28%).However, there was a trend toward improvement in surgical outcomes in patients who received anastrozole alone. Of the 124 patients who were initially considered only candidates for mastectomy, BCS was performed in 44% who received anastrozole compared to 31% who received tamoxifen (P = 0.23). In addition, similar to letrozole in the P024 trial, response rates were higher in patients with HER-2 positive breast cancer with anastrozole compared to tamoxifen (58% vs. 22%; P = 0.18), although this was not statistically significant due to the small patient numbers. The PROACT trial included 451 postmenopausal women with ER and/or PR-positive breast cancer with large, operable or potentially operable tumors who were randomly assigned to receive anastrozole or tamoxifen for 12 weeks prior to surgery [18]. Concurrent chemotherapy was allowed in the trial; however, 314 patients were treated with endocrine therapy alone. The objective response rates were similar in both the anastrozole and tamoxifen arms measured by clinical exam (50% vs. 46.2%) and ultrasound (39.5% vs. 35.4%). However, in patients who received endocrine therapy alone, there was a statistically significant improvement in BCS rates in patients who received anastrozole compared to tamoxifen (43% vs. 30.8%; P = 0.04).

Building on the results from these trials, the American College of Surgeons Oncology Group (ACOSOG) designed the phase II Z1031 trial, to compare the efficacy of the aromatase inhibitors letrozole, anastrozole, and exemestane in the neoadjuvant setting in postmenopausal women with clinical stage II-III, ER-positive breast cancer [19]. Slightly higher clinical response rates were observed in patients who received letrozole and anastrozole compared to exemestane (74.8% vs. 69.1% vs. 62.9%, respectively), however, the biological activity of all three agents appeared to be equivalent based on changes in the Ki67 proliferative index. In addition, surgical outcomes were improved in all 3 groups with 51% of patients who were considered mastectomy-only candidates at the start of treatment undergoing BCS and 83% of patients who were marginal candidates for breast conservation undergoing BCS. Furthermore, the overall BCS rate of 68% in this trial is similar to that observed in trials using NCT [22,23].

The results of a recently reported clinical trial also demonstrate the feasibility of NET in premenopausal women [24]. The Study of Tamoxifen or Arimidex, combined with Goserelin acetate, to compare Efficacy and safety, STAGE trial, was a phase III trial that randomized 197 premenopausal women with ER-positive (ER expression ≥ 10%), HER-2 negative operable, stage II breast cancer to receive either anastrozole + goserelinortamoxifen + goserelin for 24 weeks prior to surgery. Clinical response rates were significantly greater in the anastrozole group compared to the tamoxifen group, 70.4% and 50.5%, respectively (P = 0.004). The reduction in the Ki67 index was also greater in patients who received anastrozole (P < 0.0001).Importantly, the treatment was well-tolerated in both groups, with the majority of patients reporting mild or moderate treatment-related side effects.

Neoadjuvant endocrine therapy has also been compared to NCT in several randomized trials [13,14,25]. In a phase II trial, 239 postmenopausal women with stage II-III, ER and/or PR-positive breast cancer were randomized to either endocrine therapy with anastrozole or exemestane or chemotherapy with doxorubicin and paclitaxel every 3 weeks for 4 cycles [13]. The results showed similar clinical response rates (64% vs. 64%), pCR rates, (3% vs. 6%), and disease progression rates (9% vs. 9%) when comparing NET to NCT. Breast conserving surgery rates were slightly higher in patients who received NET compared to NCT (33% versus 24%; P = .058).In a smaller study that randomized 95 pre- and postmenopausal women with operable, luminal breast cancer to NET with exemestane (+ goserelin in premenopausal women) or NCT with epirubicin and cyclophosphamide (4 cycles) followed by docetaxel (4 cycles), clinical response rates were 48% in patients who received NET and 66% in patients who received NCT [14]. In patients with low Ki67 (≤ 10%) the response rates were similar between the NET and NCT groups, 58% vs. 63%, respectively (P = 0.74), while patients with higher Ki67 (>10%) responded better to NCT (NET 42% vs. NCT 67%; P = 0.075).In addition, there was no significant difference in BCS rates when comparing treatment groups (NET 56% vs. NCT 47%; P = 0.2369).In both trials, toxicity was significantly greater in patients receiving NCT compared to NET [13,14].

Collectively these trials demonstrate that NET is effective in down staging HR-positive tumors and increasing patient eligibility for BCS. The treatment is well-tolerated, has significantly lower toxicity than NCT, and with appropriate patient selection results in BCS rates that are similar to NCT.

Assessing response to and patient selection for neoadjuvant endocrine therapy

While NC trials primarily use pathologic complete response (pCR) as a measure of efficacy and to provide prognostic information, the majority of patients with HR-positive breast cancer will not achieve a pCR whether NET [13,16-19] or NCT [13,23,26] is utilized. In addition, while tumor characteristics at diagnosis have generally been used to guide treatment decisions, tumor characteristics after treatment may be more prognostic. Therefore, alternative methods to assess response predict long-term outcomes and guide treatment recommendations have been developed for NET.

Expression of Ki67 in tumors is a marker of cellular proliferation, and a change in Ki67after short-term exposure to an investigational agent in the neoadjuvant setting is frequently utilized to evaluate the efficacy of treatment [27]. Using tumor biopsies from the IMPACT trial, Dowsett et al., demonstrated that a reduction in Ki67 expression levels was observed in tumors after 2 weeks of treatment and was largely maintained after 12 weeks of treatment in the majority of patients [28]. It was shown that Ki67 levels after initiation of treatment were more strongly associated with recurrence-free survival (RFS) (log-rank P = .008) than baseline Ki67 levels (log-rank P = .07) [29]. In addition, although the clinical response rates were similar in the IMPACT trial between anastrozole and tamoxifen, the reduction in Ki67 expression was significantly greater in those patients who received anastrozole [30]. This significant biomarker difference predicted the results from the Arimidex, Tamoxifen, Alone or in Combination (ATAC)adjuvant endocrine trial, which demonstrated improvements in disease-free survival and time to recurrence in those patients who received anastrozole [31,32]. The prognostic significance of post treatment Ki67 levels on RFS was also demonstrated for patients treated in the P024 trial [33]. Therefore, a change in the Ki67 proliferative index after short-term endocrine therapy provides prognostic information on long-term outcome and may help to select patients with highly endocrine responsive tumors who may be safely treated with endocrine therapy alone.

The Preoperative Endocrine Prognostic Index (PEPI score) was developed from the analysis of tumors from patients treated in the P024 trial [33]. Post treatment biomarkers including ER status and Ki67 proliferative index and post treatment pathologic variables including tumor size, histologic grade, nodal status, and treatment response were examined to determine the impact of these factors on RFS and breast cancer-specific survival (BCSS). On multivariate analysis, post treatment ER status, Ki67 proliferative index, tumor size, and nodal status were associated with RFS and BCSS. These 4 factors were utilized to develop a prognostic model that risk stratifies patients into 3 groups based on PEPI score (low risk = 0, intermediate risk = 1-3, high risk = ≥4).Those patients with a PEPI score of 0 have a very low risk of recurrence and may be considered for adjuvant endocrine therapy alone, while those patients with a high PEPI score ≥ 4 should be considered for more aggressive adjuvant therapy. This prognostic model was validated on 203 patient samples from the IMPACT trial, and demonstrated a statistically significant separation in RFS curves for patients based on PEPI scores. In addition, using this prognostic model in the ACOSOG Z1031 trial, there was no significant difference in the proportion of patients in each treatment arm who achieved a PEPI score of 0, demonstrating similar efficacy of the treatment regimens [19]. Since some endocrine therapies such as fulvestrant down regulate ER expression, and this may not necessarily reflect a poor prognosis after NET, a modified PEPI score has also been developed that does not include ER Allred score [34].

In terms of optimizing patient selection for NET, the P024 and IMPACT trials both demonstrated higher response rates in patients with higher ER expression [17,20]. Based on this information, the ACOSOG Z1031 trial only included patients with ER-rich tumors with Allred scores ≥ 6 [19]. These inclusion criteria likely accounts for the higher overall response rates that were observed in the Z1031 trial (62.9% - 74.8%) [19], compared to letrozole (55%) and tamoxifen (36%) in the P024 trial [16] and anastrozole (37%) and tamoxifen (36%) in the IMPACT trial [17]. In the ACOSOG Z1031 trial, multiple biomarkers were assessed including baseline and post treatment Ki67 levels, the PEPI score and pretreatment PAM50 intrinsic tumor subtypes to determine how pre and post treatment biomarkers could be integrated to provide prognostic information and to better select patients for NET [19]. Changes in the Ki67 proliferative index after treatment and the percentage of patients with a PEPI score of 0 after treatment were similar for each of the treatment arms. The PAM50 tumor subtype analysis was able to identify unresponsive tumor subtypes in 3.3% of patients. The baseline and post treatment Ki67 levels were significantly higher in luminal B tumors than in luminal a tumors. In addition, although clinical response rates and surgical outcomes were similar in patients with PAM50 luminal A and luminal B subtypes, a greater percentage of patients with luminal A subtype had a PEPI score of 0 following treatment (27.1% vs. 10.7%, P = .004). On univariate analysis, both a baseline Ki67 level of ≤ 10% and luminal A tumor subtype were associated with a PEPI score of 0.However, on multivariate analysis, luminal A tumor subtype was the dominant predictor of a PEPI score of 0.Therefore, pretreatment molecular analysis of tumors to identify more favorable subtypes may be one way to select patients for NET. In the absence of PAM50 tumor subtype analysis, high ER expression and a baseline Ki67 of ≤ 10% maybe an alternative means to select suitable candidates. Other genomic tests that are predictive of hormone sensitivity such as the 21-gene recurrence score (RS) may also be helpful for patient selection [35]. Two small studies that examined the association between the 21-gene RS and response rates to NET demonstrated that clinical response rates were higher in patients with low RS compared to those with high RS [36,37]. One of the studies also demonstrated similar response rates to NET when comparing patients with low and intermediate risk RS [37]. Additional studies are attempting to develop gene signatures that may better predict response using pretreatment and on treatment tumor analysis [38].

Targeting endocrine resistance

In addition to improving surgical outcomes in women with stage II-III, ER-positive breast cancer and providing prognostic information, NET provides the opportunity to examine mechanisms of endocrine resistance, to optimize and

compare endocrine therapies that are currently available, and to investigate new targeted therapies that may be utilized alone or in combination with endocrine therapy to delay or prevent endocrine resistance or to treat endocrine resistant tumors. Preclinical studies have demonstrated multiple mechanisms that contribute to endocrine resistance including increased growth factor receptor expression (EGFR, HER-2, insulin-like growth factor-1 (IGF-1R)), activation of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathways, ligand-independent ER α activation, and crosstalk between ER signaling and other signaling pathways [10-12]. Targeting these receptors and downstream signaling pathways alone or in combination with endocrine therapy has been investigated in preclinical studies [39-43] and in clinical trials [44-51], primarily for patients with advanced or metastatic breast cancer. The preclinical studies have been very effective in predicting clinical outcomes. While combination therapy in general appears to be superior to single agent therapy, it depends on which therapies are being combined and whether they are utilized in endocrine therapy naïve patients, patients with acquired endocrine resistance, or patients with de novo endocrine resistance. Therefore, appropriate patient selection for these clinical trials is key. Translating these studies to the neoadjuvant setting allows for on treatment assessment of both biomarkers and tumor tissue and may be a more effective means of identifying critical signaling pathways involved in endocrine resistance, guiding treatment for patients with endocrine resistant tumors, and evaluating the impact of new targeted therapies.

Several randomized phase II trials have investigated the use of NET in conjunction with targeted agents, combining letrozole +/- everolimus [52], letrozole +/- lapatinib [53], anastrozole +/- gefitinib [54], and gefitinib +/- anastrozole [55]. Baselga et al. randomized 270 postmenopausal women with operable, ER-positive breast cancer to treatment with letrozole +/- everolimus in order to target crosstalk between the PI3K/Akt/mTOR and ER pathways [52]. Clinical response rates and suppression of Ki67 expression were greater in patients who received combination therapy compared to letrozole alone (68.1% vs. 59.1%, P = .062; ln (Ki67) < 1: 57% vs. 30%).These findings are in contrast to the trials using mTOR inhibitors in combination with endocrine therapy in patients with advanced or metastatic disease in which improvements in outcomes were only observed with the addition of an mTOR inhibitor in patients with acquired endocrine resistance [46-48]. There was also significantly more toxicity in patients who received ever olimus and letrozole compare to letrozole alone, 22.6% vs. 3.8%.

The use of tyrosine kinase inhibitors to target signaling through EGFR and HER-2 in combination with endocrine therapy has not been as successful. In a phase II trial evaluating the addition of lapatinib, a small molecule inhibitor of both EGFR and HER-2, to letrozole, 92 postmenopausal women, with HR-positive, HER-2 negative, stage II-IIIA breast cancer were randomized to letrozole +/- lapatinib for 6 months prior to surgery [53]. Clinical response rates were similar between the lapatinib and placebo arms, 70% vs. 63%, and there was no significant difference in changes in Ki67 between the two arms. As in previous neoadjuvant studies, there was a significant conversion rate from mastectomy only to BCS in both the lapatinib and placebo arms, 46% and 58.9%, respectively. In a second trial combining gefitinib, a small molecule inhibitor of EGFR, and anastrozole, postmenopausal patients with HR-positive breast cancer received treatment on one of 3 arms, anastrozole + gefitinib, anastrozole -> anastrozole + gefitinib, and anastrozole alone, with changes in Ki67 levels being the primary endpoint [54]. There were no significant differences in the mean change in Ki67 measurements between the anastrozole + gefitinib and anastrozole alone arms for all time points that were measured. There was also a non-significant trend toward better objective response rates in the anastrozole alone arm compared to the combination, 61% vs. 48% (P = .08).In another study that compared gefitinib +/- anastrozole in postmenopausal patients with ER-positive, EGFR-positive breast cancer, although a greater reduction in Ki67 was observed with the combination therapy, there was no anastrozole alone arm [55]. Therefore, while gefitinib may have some activity in breast cancer, it may not add to the efficacy of endocrine therapy alone. In addition, based on preclinical studies, these tyrosine kinase inhibitors may only be effective once acquired endocrine resistance has developed,[43] highlighting the importance of patient selection for these clinical trials.

The ALTERNATE trial is an example of an ongoing phase III, randomized NET trial which is comparing existing endocrine therapies to evaluate differences in endocrine resistance and to examine signaling pathways which contribute to endocrine resistance [34]. In addition, biomarker analysis using Ki67 measurements and the modified PEPI score will be utilized to guide treatment recommendations. This biomarker driven treatment strategy was examined in a cohort of patients from the ACOSOG Z1031 trial (Z1031B) [56]. Patients with a Ki67 proliferative index of > 10% after 2 to 4 weeks of NET could be triaged to NCT, with the hypothesis that these endocrine resistant tumors would be more responsive to chemotherapy. Of the 36 women who were switched to NCT, pCR was only observed in 2 patients (5.5%).Although the results did not support the hypothesis, Z1031B demonstrated the feasibility of this approach.

The ALTERNATE trial was opened for accrual through the Alliance for Clinical Trials in Oncology in December 2013. Postmenopausal women with ER-positive, HER2-negative invasive breast cancer, T2-4 N0-3 M0, are randomly assigned to received 6 months of NET with fulvestrant alone, fulvestrant and anastrozole, or anastrozole alone, followed by recommendations for adjuvant endocrine therapy. Resistance to endocrine therapy is defined as a Ki67 proliferative index at 4 or 12 weeks of > 10%, radiographic evidence of progression, or a PEPI score of > 0 after completion of neoadjuvant therapy. The primary objective of the study is to determine whether endocrine resistance rates are lower in the fulvestrant arms of the study. Secondary endpoints include comparison of surgical outcomes, clinical and radiographic response rates, and the degree of Ki67 suppression. In addition, tumor tissue and serum will be collected to investigate signaling pathways involved in endocrine resistance. There are many additional ongoing NET trials using endocrine therapy alone or combined therapies including PI3K inhibitors, cyclin-dependent kinase (Cdk) inhibitors, mTOR inhibitors, HER-2 targeting and vaccines (Table 1).

Table 1: Neoadjuvant trials combining endocrine therapy and targeted agents.

Treatment Strategy	Agents	Clinical Trials.gov ID
HER-2 targeting	Letrozole/Tamoxifen + Lapatinib&Trastuzumab	NCT01973660
	Letrozole + Trastuzumab	NCT02214004
	Letrozole + Trastuzumab & Pertuzumab	NCT02411344
Cdk 4/6 inhibitor	AI/AI+Goserelin/ Tamoxifen +/- Palbociclib	NCT02592083
	Letrozole +/- Palbociclib	NCT02296801
	Anastrozole (+/-Goserelin) +/- PD0332991	NCT01723774
PI3K inhibitor	Letrozole +/- BYL719 or Buparlisib	NCT01923168
	Letrozole +/- GDC-0032	NCT02273973
mTor inhibitor	AI + Everolimus	NCT02236572

CONCLUSION

Neoadjuvant endocrine therapy is a well-tolerated and effective treatment in women with HR-positive breast cancer. This treatment approach increases patient eligibility for BCS and response to therapy provides important prognostic information that may be used to guide adjuvant therapy. Patients with ER-rich tumors with low proliferative rates appear to be most suited for this treatment, demonstrating higher response rates and more frequently achieving a PEPI score of 0 after treatment. One of the major benefits of NET is that on treatment assessment of biomarkers and tumor tissue may be performed. This allows for the identification of endocrine responsive tumors, mechanisms of endocrine resistance, and new targets for treatment. These findings can then be utilized to test new treatment strategies to overcome endocrine resistance or to develop individualized treatment approaches for patients. Although several clinical trials have investigated combining endocrine therapy and targeted agents in the neoadjuvant setting, the results of these studies have been quite variable. Understanding how endocrine therapy and targeted agents interact and which patients are best suited for each treatment approach will be key to the success of ongoing and future clinical trials.

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