Neoadjuvant Endocrine Therapy: Who Benefits Most?

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KEYWORDS

- Neoadjuvant endocrine therapy • Estrogen receptor–positive breast cancer
- Neoadjuvant chemotherapy • Aromatase inhibitors

KEY POINTS

- Neoadjuvant endocrine therapy (NET) can be used to downstage breast cancers in postmenopausal women with estrogen receptor–positive tumors.
- NET can be used in selected premenopausal women and is often combined with ovarian suppression.
- Complete pathologic responses are infrequent with NET; however, residual disease does not imply poor prognosis.
- NET as a single agent is less effective than in combination with trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-overexpressing tumors.
- Aromatase inhibitors are more effective than tamoxifen for downstaging with NET.

OVERVIEW

Neoadjuvant treatment of breast cancer has been established as an important strategy for understanding prognosis, biomarker evaluation, and targeted therapeutics development. Neoadjuvant treatment allows for real-time evaluation of drug efficacy by assessment of in vivo sensitivity as well as insight into the molecular alterations associated with tumor response through analysis of serial tumor biopsies. Neoadjuvant chemotherapy (NCT) has been incorporated into clinical practice for downstaging tumors for less extensive surgery and for assessing tumor response, which is associated with prognosis.[1] Similar to NCT, neoadjuvant endocrine therapy (NET) can downstage tumors and provide information on the tumor endocrine responsiveness. NET, however, has been less frequently incorporated into practice due to the slow tumor response requiring prolonged therapy as well as the less defined prognostic information that is obtained after treatment.[2] NET was initially limited to elderly

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postmenopausal women with large tumors who were poor candidates for NCT or surgery.[3–6] More recently, the ability to identify early endocrine responsiveness and the development of highly effective aromatase inhibitors (AIs) has resulted in a broader use of NET. The National Comprehensive Cancer Network guidelines suggests that appropriate candidates for NET are patients with estrogen receptor (ER)-rich tumors (Allred score of 7–8),[7] which correspond to luminal A or luminal B breast cancers.[8] Intensity of ER positivity, however, does not always parallel responsiveness to endocrine therapy.[9] Current research is directed toward identifying those patients who receive the greatest benefit from endocrine-directed therapy who could avoid cytotoxic chemotherapy. The most common class of drugs used for NET are the AIs (**Table 1**).

NEOADJUVANT ENDOCRINE THERAPY VERSUS NEOADJUVANT CHEMOTHERAPY

NET is as efficacious as NCT in downsizing tumors in patients with ER-positive disease, although the latter has more pathologic complete responses (pCRs).

Three randomized clinical trials have been conducted evaluating tumor response with NET versus NCT, all of which have shown similar response rates (**Table 2**).[10] In all 3 studies, toxicities were significantly higher with NCT versus NET. Although these studies demonstrate that downstaging is similar with both treatments, long-term outcome data are not readily available nor are defined biomarkers for patient selection for each therapy.

Semiglazov and colleagues[11] evaluated 239 postmenopausal women with ER-positive and/or progesterone receptor (PR)-positive breast cancer comparing anastrozole or exemestane for 3 months versus 4 cycles of doxorubicin plus paclitaxel every 21 days. Study endpoints included overall objective response determined by palpation, mammography, or ultrasound and the number of patients who qualified for breast-conserving surgery (BCS). The clinical objective response (determined by palpation) was similar in the endocrine group (64%) compared with chemotherapy (64%). Rates of pCR (3% vs 6%) and disease progression (9% vs 9%) did not differ significantly between the endocrine therapy or chemotherapy arms, respectively (P>.05). Rates of BCS were slightly higher in the endocrine group (33% vs 24%; P = .058). Overall, NET with AIs was better tolerated and resulted in rates similar to chemotherapy in overall objective response and BCS in postmenopausal women with ER-positive and/or PR-positive tumors.

The Grupo Español de Investigación en Cáncer de Mama (GEICAM) trial enrolled patients with operable breast cancer (T2/T3) and immunophenotypically defined luminal disease (ER-positive, PR-positive, HER2-negative, and cytokeratin 8/18-positive)[12]; 95 patients were randomized to either NCT (epirubicin plus cyclophosphamide [EC] × 4 cycles followed by docetaxel × 4 cycles) or NET (exemestane × 24 weeks, combined with goserelin in premenopausal patients). The primary endpoint was clinical response measured by MRI. The clinical response rate did not differ significantly between the arms. The clinical response was 66% for NCT (13% complete response and 53% partial response) and 48% for NET (6% complete response and 42% partial response) (P = .07). Three patients with NCT and 0 with NET achieved a pCR (P = not significant). Mastectomy rates were similar in both arms (NCT, 47%, and NET, 56%; P = .18).

The Neoadjuvant Chemotherapy Versus Endocrine Therapy (NEOCENT) trial was a multicenter trial that enrolled 44 postmenopausal women, ages less than 70, with strongly ER-positive tumors, greater than 2 cm on mammogram or ultrasound, or nodal disease greater than 2 cm.[13] Patients were randomized to NCT with 6 cycles