Neoadjuvant endocrine treatment for breast cancer: from bedside to bench and back again?

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ABSTRACT

In recent years, considerable attention has been paid to the role of neoadjuvant chemotherapy as a pluripotent test bed for the treatment of breast cancer. Although traditionally reserved to render inoperable disease operable, neoadjuvant chemotherapy is increasingly being used to improve the chance for breast-conserving surgery, to gain information on pathologic response rates for a more rapid assessment of new chemotherapy–biologic regimens, and also to study *in vivo* tumour sensitivity or resistance to the agent being used.

Similarly, use of neoadjuvant endocrine treatment was also traditionally restricted to elderly or frail patients who were felt to be unsuitable for chemotherapy. It is therefore not surprising that, given the increasing realization of the pivotal role of endocrine therapy in patient care, there is enhanced interest in neoadjuvant endocrine therapy not only as a less-toxic alternative to chemotherapy, but also to assess tumour sensitivity or resistance to endocrine agents.

The availability of newer endocrine manipulations and increasing evidence that the benefits of chemotherapy are frequently marginal in many hormone-positive patients is making endocrine therapy increasingly important in the clinical setting. The hope is that, one day, instead of preoperative endocrine therapy being restricted to the infirm and the elderly, it will be used in the time between biopsy diagnosis and surgery to predict which patients will or will not benefit from chemotherapy in the adjuvant setting.

KEY WORDS

Medical oncology, breast cancer, neoadjuvant therapy, endocrine therapy

1. INTRODUCTION

Breast cancer is the most common malignancy in women in North America and the second after lung

cancer in terms of cancer-related deaths^{1,2}. Although overall mortality is declining, a particularly challenging situation involves patients with locally advanced breast cancer (LABC).

Clinically, LABC is divided into two distinct categories. The first encompasses women with large clinical stage IIA, IIB, and T3N1M0 tumours that are operable, but require a mastectomy rather than breast-conserving surgery to achieve ideal surgical margins. The second represents women with disease in which an initial surgical approach is unlikely to be successful in removing all existing disease—that is, stage T(any)N2M0 disease. This category also includes women who are diagnosed with inflammatory breast cancer. Patients in this second category have a poor prognosis overall because of the aggressive nature of their disease, the advanced stage of the disease at diagnosis, and the difficulty in achieving a complete surgical resection of the involved areas³.

Because of those challenges, treatment of LABC focuses on the use of neoadjuvant chemotherapy to reduce the tumour burden sufficiently to allow for successful surgery. The landmark National Surgical Adjuvant Breast and Bowel Project B-18 and B-27 trials demonstrated that administration of preoperative chemotherapy was equivalent to adjuvant chemotherapy in terms of survival endpoints and allowed for higher rates of breast-conserving surgery than are normally possible in patients with potentially operable breast cancer. The studies also demonstrated improvement in rates of relapse-free survival in patients in whom a pathologic complete response was obtained^{4,5}.

In contrast, neoadjuvant endocrine therapy originated as a therapy for elderly or frail patients presenting with hormone receptor–positive LABC. With an increased understanding of the differential responses to chemotherapy and endocrine therapy in the various subtypes of breast cancer, neoadjuvant endocrine therapy could potentially play a larger role in the treatment of LABC. The purpose of the present review is to discuss the rationale and basis for neoadjuvant

endocrine therapy, to outline the most recent neoadjuvant endocrine studies, and to discuss biomarkers that might potentially be used to identify the patients who will benefit most from this intervention.

2. ESTABLISHING THE SAFETY OF ENDOCRINE THERAPY BEFORE SURGERY

Initial studies of endocrine therapy focused on its use with tamoxifen as an alternative to surgery in patients 70 years of age and older who were poor surgical candidates and unfit for chemotherapy. The goal of those trials was to test endocrine therapy as a primary treatment option rather than as a neoadjuvant treatment. The results suggested that tamoxifen was active in that setting, achieving a clinical response rate of 48%.⁶ Yet, despite the reported responses, long-term disease control was poor, probably because no surgical intervention was undertaken.

To directly assess the role of tamoxifen in pre-surgical settings, two randomized studies compared tamoxifen with modified radical mastectomy as primary therapy in 474 patients more than 70 years of age. With a median follow-up of 80 months, Mustacchi and colleagues⁷ found no difference in breast cancer-related or overall survival between the two trial arms. In contrast, Fennessey and colleagues⁸ found inferior breast cancer-related and overall survival at a median 12.7 years of follow-up in patients receiving tamoxifen alone; however, the differences were evident only after 3 years of follow-up. Both trials found a higher rate of local progression in the absence of surgery. A meta-analysis⁹ 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 between the two treatments (hazard ratio: 0.98; $p = 0.9$); however, patients receiving surgery did experience superior progression-free survival (hazard ratio: 0.55; $p = 0.0006$).

Although variability in patient characteristics complicates the interpretation, current evidence suggests that the use of endocrine therapy before surgery is safe in women with estrogen receptor (ER)-positive disease, but is, in the long term, ineffective in achieving cure in the absence of definitive surgery. Endocrine therapy alone should therefore be considered only in patients who are poor candidates for surgery and who are expected to have a short life expectancy despite oncologic intervention.

3. NEOADJUVANT ENDOCRINE THERAPY COMPARED WITH NEOADJUVANT CHEMOTHERAPY

Although neoadjuvant chemotherapy is frequently used, the available data directly comparing neoadjuvant endocrine therapy with neoadjuvant chemotherapy are very limited. Currently, only two phase II

studies have used modern chemotherapy regimens as comparators with neoadjuvant endocrine therapy.

Semiglazov and colleagues¹⁰ conducted a randomized phase II study comparing anastrozole or exemestane for 3 months with doxorubicin plus paclitaxel every 3 weeks for 4 cycles in older postmenopausal patients with ER-positive or progesterone receptor (PR)-positive breast cancer. The study found no statistical difference between the two arms for clinical response rate (64% for endocrine therapy vs. 64% for chemotherapy), time to response (57 days vs. 51 days), or pathologic complete response (pCR: 3% vs. 6%). However, a trend toward a superior rate of breast-conserving surgery was observed in patients receiving endocrine therapy (33% vs. 24%, $p = 0.58$).

The Grupo Español de Investigación en Cáncer de Mama/2006-03 randomized phase II study¹¹ specifically recruited patients with immunohistochemically-determined luminal subtype disease [positive for ER, PR, cytokeratins 8 and 18, and negative for the human epidermal growth factor receptor 2 (HER2)]. The study compared 4 cycles of epirubicin and cyclophosphamide followed by 4 cycles of docetaxel with 6 months of exemestane (plus goserelin if the participant was premenopausal). The clinical response rate was 66% for chemotherapy [13% complete responses (CRS) and 53% partial responses reported] compared with 48% for endocrine therapy (6% CRS and 42% partial responses). Comparison of these two groups trended toward but did not reach statistical significance ($p = 0.07$). In addition, a pCR was achieved by 3 of the patients who received chemotherapy, but by none who received endocrine therapy. Mastectomy rates were similar in both arms (chemotherapy arm, 49%; hormone therapy arm, 35%; $p = 0.18$).

It is important to note that the NEOCENT (Neoadjuvant Chemotherapy versus Endocrine Therapy) trial, a multicentre randomised phase III study of neoadjuvant chemotherapy (FEC100: epirubicin, 5-fluorouracil, cyclophosphamide) compared with neoadjuvant endocrine therapy (letrozole) in postmenopausal patients with strongly ER-positive primary breast cancer who are candidates for cytoreductive systemic therapy, is testing the potential equivalency of neoadjuvant endocrine therapy and neoadjuvant chemotherapy. Now closed, NEOCENT is currently in data analysis, with results expected in the near future.

At the current time, no randomized studies have been performed that have demonstrated the equivalence of neoadjuvant endocrine therapy with adjuvant endocrine therapy. In addition, there are no randomized trials confirming that breast-conserving surgery is equivalent to mastectomy after neoadjuvant endocrine therapy. Because of the limitations in the evidence, current guidelines from the American Society of Clinical Oncology recommend that neoadjuvant endocrine therapy should be used for postmenopausal patients with ER-positive disease in whom surgery, with or without chemotherapy, would be associated

with increased risk because of advanced age or life-limiting comorbidities¹². Nevertheless, evidence suggesting a greater role for neoadjuvant endocrine therapy in the future is increasing.

It has been observed that it is difficult to achieve a pCR in ER-positive tumours with chemotherapy; for example, the GEPAR DUO trial, a randomized phase III study conducted in the neoadjuvant setting, was able to achieve a pCR in only 6.2% of patients with ER-positive disease; the rate in patients with ER-negative disease was 22.8%¹³. Because the largest disease-free survival benefit of neoadjuvant chemotherapy is observed only in patients who achieve a pCR, a low pCR rate in ER-positive disease makes it questionable whether the toxicities of chemotherapy are justified in that population, especially when the overall prognosis with these tumours is good regardless of whether a pCR is achieved¹⁴.

4. AROMATASE INHIBITORS COMPARED WITH TAMOXIFEN IN THE NEOADJUVANT SETTING

The use of third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) in the adjuvant setting has become a recognized standard of care based on studies demonstrating superiority of those agents over tamoxifen¹⁵. Four randomized studies have addressed the question, and all four indicated the superiority of aromatase inhibitor therapy.

The P024 trial was a randomized, double-blind, multicentre study that randomized 324 postmenopausal women with ER- or PR-positive (or both) breast cancer to letrozole 2.5 mg daily or tamoxifen 20 mg daily for 4 months¹⁶. In the intention-to-treat analysis, a statistically significant improvement in the overall objective response rate (by clinical palpation) was observed in the letrozole group compared with the tamoxifen group (55% vs. 36%, $p < 0.001$). In addition, letrozole was superior to tamoxifen in terms of ultrasonography response (35% vs. 25%, $p < 0.042$), mammographic response (34% vs. 16%, $p < 0.001$), and rate of breast-conserving surgery (45% vs. 35%, $p < 0.022$). Notably, only a few pCRs were seen in the breast in either group (2 with letrozole, 3 with tamoxifen).

The IMPACT trial, a phase III randomized, double-blind, multicentre trial, randomized 330 postmenopausal women with ER-positive operable or LABC to anastrozole, tamoxifen, or a combination of tamoxifen and anastrozole for 12 weeks before breast surgery¹⁷. Objective response rates for those agents were 37%, 36%, and 39% respectively based on calliper measurement, and 24%, 20%, and 28% based on ultrasonography. Those differences were not statistically significant. A trend toward an improved rate of breast-conserving surgery was observed for patients receiving anastrozole (44% vs. 31%), but again, the difference was not statistically significant ($p = 0.23$).

The PROACT trial was a multicentre, double-blind study in 451 postmenopausal women with ER-positive invasive cancer randomized to 3 months of preoperative anastrozole or tamoxifen¹⁸. The study permitted concurrent chemotherapy at the investigator's discretion, with such treatment being given to 29% of the patients treated with anastrozole and 32% of those treated with tamoxifen. The study showed no significant difference in response between the groups receiving tamoxifen and anastrozole. If patients who received concurrent neoadjuvant chemotherapy are excluded from the evaluation, the objective response rates for anastrozole and tamoxifen were, respectively, 48.6% and 35.8% as measured by callipers ($p = 0.04$) and 36.6% and 24.2% as measured by ultrasonography ($p = 0.03$). Improvement in actual surgery occurred in 43% of anastrozole-treated patients and 31% of tamoxifen-treated patients ($p = 0.04$). Although PROACT was conceptually different from P024 and IMPACT because it permitted concurrent chemotherapy, it is supportive of the conclusion that aromatase inhibitor therapy is superior to tamoxifen in the neoadjuvant setting.

The STAGE trial, a phase III randomized, double-blind, multicentre study, allocated 197 premenopausal women with ER-positive, HER2-negative breast cancer to anastrozole 1 mg daily or tamoxifen 20 mg daily for 6 months¹⁹. In that study, anastrozole was superior to tamoxifen in terms of calliper response (70.4% vs. 50.5%, $p = 0.004$), ultrasonography response (58.2% vs. 42.4%, $p = 0.027$), and magnetic resonance imaging or computed tomography response (64.3% vs. 37.4%, $p = 0.032$).

5. ISSUE OF OPTIMAL DURATION OF NEOADJUVANT ENDOCRINE THERAPY

One critical question of clinical practice raised by the neoadjuvant endocrine therapy trials is this: What is the optimal duration of treatment to achieve a high proportion of responders and a maximal clinical response?

Neoadjuvant endocrine therapy trials such as P024 (4 months)¹⁶, IMPACT (3 months)¹⁷, and PROACT (3 months)¹⁸ generally—and relatively arbitrarily—set the duration of neoadjuvant endocrine therapy to 3–4 months, although some trials occasionally used long durations, such as the 4–8 months in the German Neoadjuvant Letrozole trial²⁰ and the 6 months in the STAGE trial¹⁹, thus leaving open the question of the optimal duration of such therapy.

The question of duration has recently been valuably clarified^{21–23}. Dixon and colleagues²¹ found that continuing letrozole beyond the traditional 3–4 months provided additional clinical reduction in tumour size and, consequently, enlarged candidacy for breast-conserving surgery. Similarly, the small ($n = 70$) Spanish multicentre, open-label, phase II trial from Llombart-Cussac and colleagues²² explored maximal response to letrozole in 70 postmenopausal

breast cancer patients (age > 65 years). The trial found a median time to objective response of 3.9 months and a median time to maximum response of 4.2 months, but we note that more than one third of all patients (37.1%) achieved a maximal response only later, within 6–12 months. Because in that trial no responders were recorded after 8 months, and few between 6 and 8 months, it seems a reasonable compromise to allow no less than a 4-month duration, and up to 6 months if viable, so that the largest proportion of patients can achieve a maximal response to neoadjuvant endocrine therapy. That approach was confirmed in neoadjuvant trials of exemestane^{24,25}, in which the objective response rate continued to improve after 4 months of treatment²⁴ and 24-week aromatase inhibition provided a significant reduction in Ki-67 index²⁵.

It is clear, then, that in many trials and in clinical practice, endocrine therapy might too often be given for a suboptimal duration (our observation among colleagues is that a 3-month duration is in fact more common than a 4-month duration in clinical practice). With respect to endocrine agents other than tamoxifen and aromatase inhibitors, fulvestrant at first blush appears to have a somewhat shorter median time to response of 3.1 months^{26,27}, but that time frame fails to include a large segment of potential responders, as was made abundantly clear in the phase III CONFIRM randomized controlled trial²⁸. In that trial, the time-to-response analysis found that, within the first 3 months, a mere 18.4% of patients in the 250-mg dose arm and 9.1% in the 500-mg arm achieved a documented objective response, but at 6 months, the objective response rates rose to 58% (250-mg arm) and 55% (500-mg arm). Those findings collectively suggest that clinical practice should shift to a longer duration of neoadjuvant endocrine therapy—out to at least 4 months, but preferably 6 months—to achieve a higher incidence of maximal response. Indeed, the lack of such a shift helps to account for the relative infrequency of pCR in traditional neoadjuvant endocrine trials, given that use of neoadjuvant endocrine therapies for 4 months rarely results in pCR²⁹.

6. COMPARISON OF AROMATASE INHIBITORS IN THE NEOADJUVANT SETTING

The large randomized phase II ACOSOG-Z1031 trial compared exemestane, letrozole, and anastrozole head-to-head in the neoadjuvant setting. That trial was closed in 2009 after recruiting 377 postmenopausal patients with clinical stage II or III breast cancer. Participants were randomized to receive one of the three aromatase inhibitors for 16 weeks before surgery, with the identified primary endpoints being overall response, clinical CR and pCR, and rates of breast-conserving surgery. The trial reported a 16-week clinical response rate of 62% for exemestane; 74% for letrozole, and 69% for anastrozole.

No differences were observed in surgical outcomes or suppression of Ki-67 (a proliferative marker used to identify the effect of endocrine therapy on the tumour) between the three arms³⁰.

7. NEOADJUVANT ENDOCRINE THERAPY IN PATIENTS WITH HER2-POSITIVE DISEASE

As a negative predictive factor for endocrine responsiveness, HER2 status has also been widely investigated. Early work in this area came from the P024 study, which tested for ER, PR, HER1, and HER2 status by immunohistochemistry. That study initially demonstrated that HER2-positive patients were statistically more responsive to letrozole than to tamoxifen³¹. However, after further review with fluorescence *in situ* hybridization to evaluate HER2 status, a difference was no longer observed. That finding may have technical and statistical causes: Only 9.2% of 305 patients were HER2-positive by fluorescence *in situ* hybridization, and that group had mostly received letrozole therapy³². An evaluation of the IMPACT trial demonstrated that, in HER2-positive patients, a reduction in Ki-67 staining 2 weeks after initiation of endocrine therapy was predictive for benefit; patients in whom no significant reduction in Ki-67 was found experienced worse disease-free survival³³. Other large adjuvant trials have also shown that HER2 positivity is a negative predictive factor for endocrine benefit and is also associated with the poorest prognosis, even with neoadjuvant chemotherapy^{34,35}.

8. BIOMARKERS AND GENOMIC EVALUATIONS FOR PREDICTING RESPONSE TO, AND LONG-TERM OUTCOMES WITH, NEOADJUVANT ENDOCRINE THERAPY

Unlike neoadjuvant chemotherapy, neoadjuvant endocrine therapy has a low pCR rate. Nevertheless, survival outcomes in treated patients are relatively good, suggesting that pCR is not a suitable marker of benefit for patients receiving this type of therapy. As a result, a great deal of research is attempting to identify the subgroup of patients with ER-positive disease who are highly sensitive to endocrine therapy and unlikely to benefit from the addition of chemotherapy.

The creation of the preoperative endocrine prognostic index represents one such effort. This index was generated based on data obtained from 228 tumour samples in the P024 trial; it was subsequently validated using a dataset from the IMPACT trial. Multivariate analysis identified tumour size (T1/2 vs. T3/4) and node status (positive vs. negative) by pathology examination, the natural logarithm of the Ki-67 value, and the ER status of the tumour as independent prognostic variables for benefit from neoadjuvant endocrine therapy. Patients who score 0 on the index are those who will most likely derive

benefit from neoadjuvant endocrine therapy³⁶. Ellis and colleagues³⁷ presented biomarker data from the Z0131 trial recently. They demonstrated that 30.3% of luminal A patients and 12% of luminal B patients enrolled in that trial scored 0 on the index; that subgroup represents candidates who are potentially ideal for endocrine therapy as their sole neoadjuvant and adjuvant systemic treatment.

Genomic investigations are also playing a role in the identification of tumour gene signatures that correspond to endocrine therapy benefit. Microarray evaluations resulted in identification of the major subtypes of breast cancer, known as luminal A, luminal B, HER2-positive, claudin-low, and basal. Each of the subtypes is associated with a different prognosis and different responses to endocrine therapy, chemotherapy, and targeted therapies, with patients having the luminal A subtypes being the best candidates for endocrine therapy alone³⁸.

A more refined genomic signature can be found in the Oncotype DX assay. This validated 21-gene signature test is the most commonly used genomic test in North America. It looks at 5 reference genes and 16 target genes that include ER and progesterone receptor expression and at other genes involved in proliferation and invasion³⁹. The TAILORX study is a multicentric randomized clinical trial evaluating the Oncotype DX assay as a clinical tool to identify candidates with ER-positive disease who will benefit from the addition of chemotherapy in the adjuvant setting⁴⁰. The results from TAILORX might be able to be extrapolated to the neoadjuvant setting, hopefully identifying patients who will benefit most from neoadjuvant endocrine therapy. Another genome-based tool, MammaPrint, a 70-gene profile array, is currently being investigated for its clinical validity. Two studies are underway: the MINT study in the neoadjuvant setting (search for NCT01501487 at <http://clinicaltrials.gov/>) and, in Europe, the MINDACT study in the adjuvant setting⁴¹.

In terms of future directions, the ongoing POETIC trial⁴² is evaluating the use of 2 weeks of preoperative endocrine treatment to predict response from adjuvant endocrine therapy. That trial is aiming to accrue approximately 4000 postmenopausal ER-positive breast cancer patients and will also be investigating a number of biomarkers for response. Hopefully, it will be making further contributions in this area.

9. CONCLUSIONS

In recent years, neoadjuvant endocrine therapy has moved from being reserved for elderly and frail non-chemotherapy candidates to potentially being considered a primary therapeutic modality in selected patients, given the increasing evidence that adjuvant chemotherapy has just a limited role for patients with ER- or PR-positive, HER2-negative disease. With further advances in biomarkers—in particular,

results emerging from the POETIC trial—the role of neoadjuvant endocrine therapy should become much clearer in the near future.

10. CONFLICT OF INTEREST DISCLOSURES

MC has received honoraria for talks (AstraZeneca) and attendance at advisory boards (AstraZeneca, Novartis). The remaining authors have no financial conflicts of interest to disclose.

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