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Original article

Neoadjuvant endocrine therapy: Patient selection, treatment duration and surrogate endpoints

Belinda Yeo [a, b, c, *], Mitch Dowsett [b, c]

[a] Department of Medicine, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK
[b] Academic Department of Biochemistry, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK
[c] Institute of Cancer Research, Fulham Road, London SW3 6JB, UK

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ABSTRACT

Neoadjuvant endocrine treatment has become of increasing interest for downstaging primary ER+ breast cancers as it has become clear that the pathologic complete response rate of luminal tumours to chemotherapy is much lower than that of non-luminal and differs little from that to endocrine therapy. There is much more experience in postmenopausal than premenopausal women. Aromatase inhibitors are generally the agent of choice. Responses are lower in those with the low levels of ER. While duration of endocrine treatment in clinical trials has usually been standardized at around three to four months it is clear that volume reductions continue to occur beyond that time in a large proportion of cases and routine clinical practice is often to treat to maximum response. This relatively slow emergence of downstaging relates to the absence of any increase in apoptosis with endocrine therapy and dependence of responses on the antiproliferative effects of oestrogen withdrawal: apoptosis occurs but at a slightly lower rate such that cell loss is attritional. The dependence of responses on the reduced proliferation underpins the value of Ki67 as an intermediate end-point for treatment benefit with multiple studies having found that relative effects on proliferation by different drugs in neoadjuvant trials match their relative impact on recurrence. While change in Ki67 is now accepted as a validated endpoint for comparing endocrine agents in the neoadjuvant scenario, on-treatment levels of Ki67 are related to long-term prognosis more closely than pretreatment Ki67. The Preoperative Endocrine Prognostic Index (PEPI) that combines residual Ki67 score with measures of on-treatment ER and other clinicopathologic factors has also found application in clinical trials. The potential to make longitudinal assessments of both clinical and biomarker responses has encouraged the development of novel clinical trial designs for assessing the impact of agents that aim to enhance response beyond that of endocrine agents alone. Such strategies include the early measurement of residual Ki67 levels after challenge with an endocrine agent alone and evaluation of the impact of the added agent on Ki67 or other agent-specific end-points.

Introduction

Over the past decade, the therapeutic potential of neoadjuvant endocrine therapy (NET) has widened for patients with oestrogen receptor (ER) positive breast cancer. In 2015, there are three main rationales for using neoadjuvant endocrine therapy: (i) for down-staging prior to surgery; (ii) to observe the biological responses to treatment which can offer prognostic and predictive information; and (iii) to facilitate novel trial design aimed at targeting endocrine resistance.

Primary endocrine therapy was initially introduced in the pre-operative setting for patients deemed inoperable or unfit for surgery. A Cochrane review of such patients over the age of 70, comparing primary endocrine therapy versus surgery showed that whilst most patients respond to NET, the long term relapse rates were higher in those patients who did not undergo definitive surgery [1]. In the recent update, there was a progression-free survival (PFS) benefit in favour of surgery (HR 0.55, 95% confidence interval (CI) 0.39 to 0.77, $p = 0.0006$) but no overall survival (OS) advantage (HR 0.98; 95%CI 0.81 to 1.20, $p = 0.85$) [2]. As such, primary endocrine therapy without surgical intent remains recommended only for those patients deemed inoperable or unfit for surgery.

* Corresponding author. Department of Medicine, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK.
E-mail address: belinda.yeo@icr.ac.uk (B. Yeo).

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Neoadjuvant endocrine therapy vs. neoadjuvant chemotherapy

Trials comparing NET to neoadjuvant chemotherapy (NCT) show similar response rates in ER positive breast cancer. In a recent review by Charehbili et al., clinical responses for NET versus NCT ranged from 48 to 89% and 64–85% respectively [3]. In a phase II study of 239 patients comparing four cycles of neoadjuvant chemotherapy to three months of endocrine therapy, there was no difference in the objective response rates between the two groups (63.6% vs. 64.5%; $p > 0.5$) however there was more breast-conserving surgery performed for patients on endocrine therapy (33% vs. 24%; $p = 0.058$) [4]. In a smaller randomised study of luminal breast tumours, 4 cycles of NCT was compared to 6 months of NET (exemestane and goserelin for premenopausal patients) with clinical response rates of 66% and 48% respectively ($p = 0.075$) [5].

It is possible that indirect comparisons of pathological complete response (pCR) rates between NET and NCT may be biased since many patients may not be suitable for both treatments. Valid comparisons of the effectiveness of each approach in the same patients can only be made in randomised clinical trials comparing NCT to NET. For example, in one randomised feasibility study of postmenopausal patients with ER-rich primary breast cancer, six cycles of anthracycline chemotherapy was compared to 18–23 weeks of letrozole [6]. Given its slow accrual, a randomised phase 3 study was deemed unfeasible. There were no pCRs seen in all 44 patients recruited. In a phase II pilot study of neoadjuvant chemotherapy in postmenopausal patients who have 'AI-resistant' breast cancer (defined as having a Ki67 values >10% after 2–4 weeks of AI) the pCR rate was low (2/36 patients; 5.6%) [7].

Pathological complete responses are less often seen in luminal tumours, regardless of the type of neoadjuvant systemic therapy administered [8]. In a meta-analysis of seven German neoadjuvant trials including 3332 women, von Minckwitz et al. reported a pCR rate of 13% in hormone receptor positive and 36% in hormone receptor negative patients treated with neoadjuvant chemotherapy [9]. In the multivariable analysis, two additional cycles of chemotherapy was associated with improved pCR for hormone receptor positive patients only (positive test for interaction between treatment effect and HR status; $p = 0.039$).

Surgical downstaging

Neoadjuvant endocrine therapy has the ability to downstage breast tumours prior to surgery. This may mean converting an otherwise inoperable patient into an operable one, enabling breast conserving surgery (BCS) rather than mastectomy or reducing the need for re-excision surgery for positive margins. Downstaging rates vary depending on whether patients who are considered inoperable at baseline are included [10]. Approximately 45–50% of patients who would require upfront mastectomy will be converted to BCS after NET [10–12].

Patient selection

Historically, NET has been selected in postmenopausal woman with large ER positive tumours who may be frail or with significant commodities making upfront surgery less desirable. This patient population is often older (with a mean age of 70 years) than in other early breast cancer trials, which may account for sometimes limited long-term follow up. More recently, because of its ability to identify early endocrine resistance, upon which new clinical trials are being built to investigate novel agents, the use of NET has diversified to a more general ER positive breast cancer population, and beyond only frail patients "in whom surgery with or without chemotherapy would be associated with an increased risk because of advanced age or relevant and life-limiting comorbidities" [13].

Premenopausal patients have been largely excluded from most of the neoadjuvant endocrine trials, predominantly due to the bias that younger woman with large cancers will require chemotherapy and hence it being the preferred neoadjuvant regime. The largest premenopausal study of NET (STAGE) randomised 204 woman with ER positive operable breast cancer to 24 weeks of goserelin plus either anastrozole or tamoxifen [14]. The primary endpoint of best overall tumour response was analysed for non-inferiority. In the anastrozole arm, 70.4% of patients had a complete or partial response versus only 50.5% with tamoxifen, this difference being statistically significant (19·9%, 95%CI 6·5–33·3; $p = 0·004$).

Type of endocrine therapy

Tamoxifen dominated the early studies of administering primary endocrine therapy for patients with ER positive breast cancer. However the majority of subsequent neoadjuvant studies have compared tamoxifen with an aromatase inhibitor, or differences between the aromatase inhibitors.

Table 1 shows four main neoadjuvant endocrine trials, three of which compared the aromatase inhibitors to tamoxifen. The P024 study randomised 337 postmenopausal women with ER positive breast cancer that were all unsuitable for upfront BCS (14% were considered inoperable) to four months of either letrozole or tamoxifen and showed the former had a significantly better response rate (ORR 55% vs. 36%, $p < 0.001$) [11].

The IMPACT trial, comparing 12 weeks of anastrozole, tamoxifen or its combination, showed no significant different in the primary outcome measure of objective response between the three arms (37%, 36%, and 39% respectively) [12]. However, there were significantly more breast conserving surgeries in the anastrozole arm (46% vs. 22%, $p = 0.03$) [12]. In the PROACT study, similarly there were no difference in objective responses for anastrozole and tamoxifen (39% vs. 35%; $p = 0.29$) [15]. Concurrent neoadjuvant chemotherapy was permitted in this study and was received 137 of the 451 patients. In those patients not treated with chemotherapy there was a significant improvement in actual surgical favouring the anastrozole arm (43% vs. 31%; $p = 0.04$).

The Z1031 trial was a randomised 3-arm study comparing neoadjuvant exemestane, anastrozole and letrozole for 16–18 weeks in 377 woman with ER positive breast cancer who were considered either marginal candidates for breast conservation, requiring upfront mastectomy, or inoperable [10]. The clinical response rates for exemestane, anastrozole and letrozole were 63%, 69% and 75% respectively. There was no significant difference between the groups for surgical downstaging or pathological findings.

Treatment duration

Over the past two decades most of the clinical trial experience of NET has offered between three and four months of therapy, pragmatically chosen to standardise regimes and to avoid progressions on treatment. However as shown in Table 2, emerging literature suggests that maximal response may be well beyond this four month duration, waiting 6–7 months before gaining maximal tumour shrinkage [16–18]. In a prospective series of 182 patients with large operable or locally advanced ER positive breast cancer treated with neoadjuvant letrozole, Dixon et al. identified 63 patients who continued letrozole beyond 3 months [19] of whom 38 patients took letrozole for more than a year and 23 for more than 2 years. At three months, 70% of the 182 patients had a partial or complete response which increased to 83% when those patients