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Review

Neoadjuvant endocrine treatment in early breast cancer: An overlooked alternative?

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Abstract

During the last decade neoadjuvant endocrine therapy (NET) has moved from being reserved for elderly and frail non-chemotherapy candidates to a primary systemic modality in selected patients with hormone sensitive breast cancer. Neoadjuvant hormonal treatment in patients with hormone receptor positive, HER-2 negative early breast cancer is proven to be an effective and safe option; it is associated with a higher rate of breast conserving surgery (BCS), may reduce the need for adjuvant chemotherapy and enables a delay of surgery for medical or practical reasons. Clinical responses range from 13% to 100% with at least 3 months of NET. Methods of assessing response should include MRI of the breast, particularly in lobular tumours. In studies comparing tamoxifen with aromatase inhibitors (AI), AI proved to be superior in terms of tumour response and rates of BCS. Change in Ki67 is accepted as a validated endpoint for comparing endocrine neoadjuvant agents. Levels of Ki67 during treatment are more closely related to long-term prognosis than pretreatment Ki67. Neoadjuvant endocrine therapy provides a unique opportunity for studies of endocrine responsiveness and the development of new experimental drugs combined with systemic hormonal treatment.

Keywords: Breast cancer; Neoadjuvant treatment; Tamoxifen; Aromatase inhibitors; Fulvestrant; Oestrogen receptor positive

Introduction

Surgery followed by adjuvant treatment has been the gold standard for breast cancer treatment for a long time. During recent decades neoadjuvant treatment has been recognized as an important strategy in biomarker and target evaluation.[1] In particular, preoperative chemotherapy has been widely studied and used[2]; it is generally considered to be a more active and better-documented neoadjuvant regimen compared to NET, although it is clearly more toxic.[3] Endocrine therapy has been far less popular due to a slow response rate, requiring prolonged therapy and risking the benefit of an early surgical intervention.[4] Assessing response to NET to explore the prediction of long-term relapse-free survival is also less obvious as the prognosis of patients with hormone sensitive tumours is generally good.[5] Therefore, NET has been tested initially in postmenopausal women who were not fit for chemotherapy or surgery due to medical co-morbidities, or in patients who aimed to change the extent of the surgical procedure from mastectomy to a breast conserving surgery (BCS). The development of highly effective aromatase inhibitors (AIs; which inhibit the action of the enzyme aromatase to convert androgens into oestrogens) has resulted in a wider use of endocrine therapy in this setting.[6]

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Safety of NET in hormone sensitive breast cancer

In the 1980s the potential benefit of endocrine monotherapy was suggested in early studies with tamoxifen (a partial oestrogen antagonist), used as primary treatment in elderly women with breast cancer who were too frail to undergo other forms of treatment.[7–10] Response rates were in the range of 30% or higher, while long lasting responses were observed in some patients.[8,10] Randomised trials on the use of tamoxifen as the only treatment modality versus surgery followed by adjuvant tamoxifen showed that surgery is important to optimize the local control of the disease, but has no impact on the overall survival (OS).[11–14] A meta-analysis comparing primary surgery with primary endocrine therapy using tamoxifen in women older than 70 years of age was unable to find a significant difference in OS (HR 0.98; p = 0.9) although patients receiving surgery did experience a superior progression-free survival (HR 0.55; p = 0.0006).[13] Current evidence therefore suggests that the use of NET is safe in elderly women with hormone receptor positive (HR+) disease, but in the long term is ineffective to achieve permanent local control in the absence of definitive surgery.[15] These findings led to the design of subsequent neoadjuvant studies, using more potent AIs in younger postmenopausal women with bulky HR+ disease in an attempt to improve surgical outcome.[7]

Optimal duration of neoadjuvant endocrine treatment

As the response to endocrine treatment is slow, duration of neoadjuvant treatment in most clinical trials is usually between 3 and 6 months.[16] Volume reductions continue to occur beyond that time in a large proportion of cases and in routine clinical practice one could consider treating preoperatively until maximum response is achieved. This relatively slow emergence of downstaging relates to the absence of any increase of apoptosis with endocrine therapy and dependence of responses on the antiproliferative effects of oestrogen withdrawal.[16,17] Increased angiogenesis detected in responders to AIs as NET may represent a stromal response to cell death as part of tumour–stroma interaction following oestrogen depletion.[18] However, the optimal duration of NET is not unequivocally defined. Fontein et al. found an overall response rate of 58.7% at 3 months and 68.3% at final assessment by palpation in 102 patients treated with neoadjuvant exemestane for 6 months.[19] Llombart-Cussac conducted a prospective phase II trial with letrozole 2.5 mg daily to maximum response as primary systemic therapy in 70 postmenopausal (over 65 years old) with oestrogen receptor/progesterone receptor positive (ER+/PR+) operable breast cancer.[20] A total of 43 out of 65 (76.8%) evaluable patients achieved an objective response, 29 (51.8%) being partial (PR) and 14 (25%) complete response (CR). The median time to objective response was 3.9 months (CI 3.3–4.5) and the median time to maximum response was 4.2 months (CI 4.0–4.5), although 20 (37.1%) patients achieved maximal response within 6–12 months. A prospective randomised trial, comparing 4–6 months of preoperative treatment with exemestane 25 mg daily, found that responses were comparative, although it should be mentioned that patient numbers were relatively small.[21] Similar observations were made by Krainick-Strobel et al. treating patients for 4–8 months with neoadjuvant letrozole.[4] Rusz et al. performed a retrospective analysis of 46 patients with stage I–III invasive HR+ breast cancer who received 1 year of NET.[22] Due to local progression, NET was replaced by neoadjuvant chemotherapy in 3 patients; pathological complete response (pCR) was seen in 13% of the premenopausal patients. These authors concluded that long-duration NET is effective and safe. Pragmatically, 4–6 months AI as NET seems an optimum duration, but with modest persistent benefits thereafter.

Assessing response to NET by clinical examination and/or imaging

The majority of studies use a combination of physical examination and imaging modalities to assess response to NET. As some hormone sensitive tumours, such as lobular carcinomas, do not have well circumscribed borders (Fig. 1 left and right), response measurements may vary depending on the imaging technique used and do not always correlate with clinical findings. In addition, as responses can be slow it can take several months to confirm the definitive response status of an individual patient. It is commonly accepted that a combination of physical examination, ultrasound scanning, mammography and/or MRI scanning are appropriate for response evaluation (Fig. 2 left and right).[23] Clinical assessment and imaging should be performed at predefined fixed time points to detect patients progressing under NET as soon as possible. Several studies tested feasibility of BCS after NET in patients who were considered for mastectomy as surgical treatment at initial presentation. However, it is clear that this is a highly subjective criterion to measure response. Ueda et al. performed an interesting study including 12 patients with ER+ breast cancer in order to validate the role of PET-CT as response evaluation after 12 weeks neoadjuvant daily letrozole 2.5 mg.[24] Sequential FDG PET/CT scans were made at baseline, at 4 weeks (PET2) and prior to surgery (PET3). Metabolic responders showed a marked decrease in Ki67 labelling index (LI) at 2 weeks after the initiation of treatment (62.9%, p = 0.04) and at surgery (91.7%, p = 0.03). Cell cycle response monitored by Ki67 correlated with metabolic response monitored by tumour maximal standardized-uptake values (SUV max) and therefore it seems feasible to use FDG PET/CT to predict cell-cycle response after 4 weeks of NET. Due to the high cost of FDG PET/CT this modality is currently not used in the vast majority of NET study protocols and in clinical practice.