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Clinical Trial

Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients – A phase II trial ☆

Duveken B.Y. Fontein [a,1], Ayoub Charehbili [a,b,1], Johan W.R. Nortier [b], Elma Meershoek-Klein Kranenbarg [a], Judith R. Kroep [b], H. Putter [c], Yvonne van Riet [d], Grard A.P. Nieuwenhuijzen [d], Bart de Valk [e,f], Jetske M. Meerum Terwogt [f], Gijs D. Algie [g], Gerrit-Jan Liefers [a], Sabine Linn [h,i], Cornelis J.H. van de Velde [a,*]

[a] *Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands*
[b] *Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands*
[c] *Department of Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands*
[d] *Department of Surgery, Catharina Ziekenhuis, Eindhoven, The Netherlands*
[e] *Department of Medical Oncology, Spaarne Ziekenhuis, Hoofddorp, The Netherlands*
[f] *Department of Medical Oncology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands*
[g] *Department of Surgery, MC Zuiderzee, Lelystad, The Netherlands*
[h] *Department of Medical Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*
[i] *Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands*

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Abstract ***Background:*** Neoadjuvant hormonal therapy (NHT) is playing an increasing role in the clinical management of breast cancer (BC) and may improve surgical outcomes for postmenopausal, oestrogen receptor (ER)-positive BC patients. However, there is currently no consensus on the optimal duration of NHT before surgery. Here, we present the outcomes of the TEAM IIA trial, a multicentre, phase II trial investigating the efficacy of six months of neoadjuvant exemestane in postmenopausal, strong ER-positive (ER+, $\geqslant 50\%$) BC patients.
Methods: 102 patients (stage T2-T4ac) were included in the study after exclusion of ineligible patients. Primary end-point was clinical response at 3 and 6 months as measured by palpation. Secondary end-point was radiological response as measured by magnetic resonance imaging

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* *Corresponding author:* Address: Department of Surgery, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31 (0)71 526 2309; fax: +31 (0)71 526 6744.
E-mail address: c.j.h.van_de_velde@lumc.nl (C.J.H. van de Velde).
[1] Both authors contributed equally.

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(MRI), mammography and/or ultrasound. Linear mixed models (95% confidence interval (CI)) were used to compare changes in mean tumour size (in mm) between baseline, 3 and 6 months after the start of endocrine therapy. Conversion rates from mastectomy to breast conserving surgery (BCS) were evaluated.

Results: Median age of all patients was 72 years (range 53–88). Overall response rate by clinical palpation was 64.5% in all patients with a final palpation measurement. Four patients had clinically progressive disease. 63 patients had both 3-month and >3-month palpation measurements. Overall response was 58.7% at 3 months and 68.3% at final palpation (>3 months). Mean tumour size by clinical palpation at $T = 0$ was 39.1 mm (95% CI 34.8–43.4 mm), and decreased to 23.0 mm (95% CI 18.7–27.2 mm) and 16.7 mm (95% CI 12.6–20.8) at $T = 3$ and $T > 3$ months, respectively ($p = 0.001$). Final radiological response rates at the end of treatment for MRI ($n = 37$), ultrasound ($n = 77$) and mammography ($n = 56$) were 70.3%, 41.6% and 48.2%, respectively. Feasibility of BCS improved from 61.8% to 70.6% (McNemar $p = 0.012$).

Conclusion: 6 months of neoadjuvant exemestane therapy helps reduce mean tumour size further in strongly ER-positive BC patients without significant side-effects compared to 3 months. Nevertheless, some patients still experience disease progression under exemestane. Feasibility of breast conservation rates improved by almost 10%.

1. Introduction

Neoadjuvant hormonal therapy (NHT) with aromatase inhibitors has been gaining recognition due to its ability to improve surgical outcomes for hormone sensitive breast cancer (BC) patients with stage II or III BC. In recent years, NHT has come to play a major role in the treatment of large breast tumours, attesting its ability to render inoperable tumours suitable for mastectomy and for breast conservation in patients who would otherwise undergo ablative surgery [1]. Moreover, NHT provides the prospect of investigating the effects of endocrine treatment, with or without new targeted antitumour agents, on biochemical, molecular and histological tumour response features, which can help guide subsequent treatment decisions [2].

Although long-term survival benefit of adjuvant chemotherapy do not differ between ER+ and ER-negative (ER–) tumours based on an Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis [3], neoadjuvant studies have demonstrated that ER+ tumours are less sensitive to chemotherapy than ER– tumours in terms of pathological Complete Response (pCR) [4–7].

In oestrogen receptor-positive (ER+), postmenopausal BC patients, NHT is an appropriate option for patients who are considered unfit for neoadjuvant chemotherapy. Not infrequently, NHT is also prescribed for long-term treatment in elderly patients who are too fragile to undergo surgical intervention. During the 13th St. Gallen International Breast Cancer Consensus Conference, the majority of the breast cancer experts' consensus panel voted in favour of the use of NHT for postmenopausal patients with highly endocrine responsive disease [8].

Currently, the most commonly applied treatment duration of NHT in early BC patients with large inoperable tumours is three months. Arguably, however, this may be too short a period for aromatase inhibitors to work to their full potential, as tumour response may continue if treatment is extended [9,10]. Importantly, the St. Gallen 2013 preliminary summary of the consensus discussion reported that 62.2% of panellists were in favour of continuing neoadjuvant endocrine treatment until maximal response [8], with only 11% of panellists recommending a treatment duration of 3–4 months [11]. 26.7% of panellists were in favour of a treatment duration of 4–8 months [11]. Clinical studies investigating the optimal duration of NHT in order to optimise operability of large tumours otherwise unsuitable for breast conservation are still relatively lacking [2,12]. We report the results of the TEAM IIA study, a nationwide, multi-institutional, phase II trial that investigated six months of neoadjuvant therapy with exemestane on tumour response in strongly endocrine sensitive BC patients, which was developed to address the optimal duration of NHT.

2. Materials and methods

2.1. Trial design

The TEAM IIA trial was originally designed as a phase III, randomised clinical trial investigating three versus six months of neoadjuvant exemestane therapy on clinical response. Due to unexpectedly slow accrual, the TEAM IIA trial protocol was changed to a phase II single-arm study investigating six months of endocrine therapy on clinical response following an amendment in June 2009. The TEAM IIA trial was