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Original article

Neoadjuvant chemotherapy with sequential anthracycline–docetaxel with gemcitabine for large operable or locally advanced breast cancer: ANZ 0502 (NeoGem)☆

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ABSTRACT

Background: Neoadjuvant chemotherapy has a sound rationale for use in women with large operable breast cancer, and achievement of pathological complete response (pCR) is prognostic. Epirubicin and cyclophosphamide followed by docetaxel is a standard chemotherapy regimen for early breast cancer. In metastatic breast cancer the combination of gemcitabine and a taxane has shown promising results. This phase II study investigated the efficacy and safety of incorporating gemcitabine into neoadjuvant therapy.

Methods: Female patients with operable breast cancer that was clinically T2 (≥3 cm) or T3-4, N0-1, M0 were enrolled to receive 24 weeks of neoadjuvant chemotherapy using epirubicin and cyclophosphamide followed by docetaxel and gemcitabine, plus trastuzumab if HER2-positive. The primary endpoint was the pathological complete response (pCR) rate in the breast in separate HER2-negative and HER2-positive cohorts. Secondary endpoints included pCR in both the breast and axillary lymph nodes, clinical and radiological response rates, disease free survival and safety.

Results: 81 patients were enrolled: 63 HER2-negative and 18 HER2-positive. 67 (84%) completed all cycles of chemotherapy, and 78 (96%) proceeded to surgery. pCR was achieved by 12 (20%) patients with HER2-negative, and 9 (53%) with HER2-positive disease. At the first interim analysis, addition of prophylactic G-CSF was recommended due to excess neutropenia. The HER2-negative cohort was closed to accrual because it did not meet the pre-specified target for pCR, and the HER2-positive cohort was closed

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due to slow accrual. At a median follow-up of 24 months, 12 of 81 (15%) patients had experienced a relapse of their breast cancer.
Conclusion: Neoadjuvant gemcitabine, when added to docetaxel, after epirubicin and cyclophosphamide, did not reach the pre-specified expectations for pCR rate in HER2-negative tumours. Excess neutropenia was observed, requiring growth factor support. Addition of gemcitabine to docetaxel in this schedule cannot be recommended.
Australia and New Zealand Clinical Trials Registry (www.anzctr.org.au) registration number ACTRN12606000191594.

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Introduction

Large operable and locally advanced breast cancers are associated with a relatively poor prognosis and higher risk of micrometastatic disease [1] and require multimodality therapy. Neoadjuvant or induction chemotherapy is the standard treatment for inoperable locally advanced breast cancer and is also used for large operable cancers to help achieve breast conservation. Although a survival benefit has not been demonstrated with neoadjuvant compared with adjuvant chemotherapy, there is sound rationale for using neoadjuvant chemotherapy [2]. Apart from improving the likelihood of breast conservation [3], neoadjuvant chemotherapy provides early treatment to the primary tumour and micrometastatic disease and also provides an early indication of the effectiveness of the particular chemotherapeutic agents [4]. Furthermore, the pathologic complete response (pCR) rate following neoadjuvant chemotherapy has been shown to be a strong prognostic measure of long-term disease-free survival (DFS) and overall survival (OS) [5,6], at least in oestrogen receptor (ER) negative disease.

Anthracycline-based chemotherapy remains the core of most pre- and post-operative chemotherapy regimens for women diagnosed with high risk locally advanced breast cancer. The addition of a taxane following 4 cycles of an anthracycline-based regimen has been associated with increased pathologic complete response rate in the neoadjuvant setting [2] and further incremental survival benefit in the adjuvant setting [7]. Standard treatment for the human epidermal growth factor receptor 2 (HER2) over-expressing breast cancer subgroup now incorporates trastuzumab, most frequently given concurrently with a taxane [8]. Gemcitabine, a nucleoside analogue anti-metabolite, has established safety and efficacy in metastatic breast cancer [9]. Combining gemcitabine with docetaxel is active in patients with anthracycline pre-treated metastatic disease, without excess toxicity [10]. Trastuzumab has also been combined successfully with taxanes and gemcitabine either alone or in combination, with promising results in patients with HER2 positive metastatic disease [11,12].

We therefore sought to test the feasibility and activity of a neoadjuvant regimen consisting of a standard anthracycline-based regimen followed by a combination of gemcitabine and docetaxel, with or without trastuzumab (depending on HER2 status), in this Phase II study in women with large operable or locally advanced breast cancer.

Materials and methods

Patient selection

Patients with histologically confirmed unilateral, operable or locally advanced (at initial presentation) T2 (≥3 cm), T3-4, N0-1, M0 primary breast cancer were eligible. Other eligibility criteria included age ≥18 years, no prior chemotherapy or hormonal therapy for breast cancer or other invasive cancer and ECOG performance status 0–2. Eligible patients were required to have adequate bone marrow, neurological, hepatic, renal and cardiac function. Patients with inoperable, inflammatory or metastatic breast cancer were excluded.

Study design

This was a Phase II study with a planned enrolment of 147 patients across two cohorts, 84 HER2-negative and 63 HER2-positive. All enrolled patients were planned to receive combined epirubicin (E) and cyclophosphamide (C) followed by combined docetaxel (Taxotere®, D) and gemcitabine (Gemzar®, G) chemotherapy in the neoadjuvant setting. Patients with HER2 positive tumours also received trastuzumab (Herceptin®, H) in combination with DG followed by adjuvant H for a total of 1-year. The primary endpoint of the study was the pCR rate of the primary tumour in the breast after neoadjuvant chemotherapy, at the time of surgery. Secondary endpoints were (i) pCR rate in both the breast and axillary lymph nodes, (ii) clinical and radiological complete response rates following neoadjuvant anthracycline chemotherapy and after all neoadjuvant chemotherapy, (iii) disease-free and overall survival and (iv) safety profile of this neoadjuvant chemotherapy regimen.

The study was conducted in accordance with Good Clinical Practice guidelines and the tenets of the Declaration of Helsinki. Participants provided written, informed consent. It was approved by local Human Research Ethic Committees, underwent review by the Consumer Advisory Panel of the ANZBCTG and was registered with the Australia and New Zealand Clinical Trials Registry (www.anzctr.org.au), registration number ACTRN12606000191594.

Treatment plan

Neoadjuvant chemotherapy consisted of a first phase of E 90 mg/m [2] and C 600 mg/m [2] both intravenous (IV) on day 1 of a 21-day cycle for 4 cycles (Appendix A). This was followed by a second phase of chemotherapy starting 3 weeks after the start of the 4th cycle of EC and consisting of D 75 mg/m [2] IV on day 1 and G 1000 mg/m [2] (30 min IV infusion) on days 1 and 8 of a 21-day cycle for 4 cycles. In HER2-positive patients, H was commenced with the taxane phase of chemotherapy using a loading dose of 4 mg/kg followed by 2 mg/kg IV weekly for 12 weeks. This trastuzumab schedule was used based on the prevailing neoadjuvant literature, in which weekly trastuzumab was combined with concurrent chemotherapy [13]. After surgery, H was administered at 6 mg/kg IV every 3 weeks up to a total of one year.

Patients with oestrogen (ER) and/or progesterone receptor (PgR) positive tumours were recommended to receive adjuvant endocrine therapy, as chosen by the investigator, for a minimum of 5 years. An aromatase inhibitor, tamoxifen, or a sequential combination of the two was recommended for postmenopausal women. Tamoxifen was recommended for premenopausal women.

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