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Doxorubicin/cyclophosphamide with concurrent versus sequential docetaxel as neoadjuvant treatment in patients with breast cancer ☆

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Abstract ***Background:*** This study was designed to determine whether delivering neo-adjuvant chemotherapy at a higher dose in a shorter period of time improves outcome of breast cancer patients.

Patients and methods: Women with newly diagnosed breast cancer were randomly assigned to neoadjuvant chemotherapy of four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel (AC 60/600 – T 100 mg/m^2) or six cycles of TAC (75/50/500 mg/m^2) every 3 weeks. The primary endpoint was the pathologic complete response (pCR) rate, defined as no invasive tumour present in the breast.

Results: In total, 201 patients were included. Baseline characteristics were well balanced. AC-T resulted in pCR in 21% and TAC in 16% of patients (odds ratio 1.44 (95% confidence interval (CI) 0.67–3.10). AC-T without primary granulocyte-colony stimulating factor (G-CSF)

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prophylaxis was associated with more febrile neutropenia compared to TAC with primary G-CSF prophylaxis (23% versus 9%), and with more grade 3/4 sensory neuropathy (5% versus 0%).

Conclusions: With a higher cumulative dose for the concurrent arm, no differences were observed between the two treatment arms with respect to pCR rate. The differential toxicity profile could partly be explained by different use of primary G-CSF prophylaxis.

1. Introduction

Neoadjuvant chemotherapy has become the standard of care in patients with locally advanced or borderline resectable breast cancer.[1] Interest has developed in extending this approach to patients with less advanced disease. Neoadjuvant chemotherapy allows observation of clinical response to systemic treatment, has the potential to down-stage the primary tumour which may facilitate breast conserving therapy, and bears the opportunity of down staging the axilla obviating the need of axillary treatment in some patients.[2] In a trial setting, a neoadjuvant approach is attractive as with far less patients a more rapid outcome is available in comparison to adjuvant trials.

Currently, anthracyclines, cyclophosphamide and taxanes are considered to represent the most potent drugs in breast cancer.[3,4] The NSABP-B28 and the CALGB-9344 trials were the first and largest studies to show a significant improvement in 5-year disease-free survival (72% versus 76% and 65% versus 70%, respectively), and the CALGB-9344 also in 5-year overall survival, for the addition of 3-weekly paclitaxel in sequence to four cycles of adjuvant doxorubicin and cyclophosphamide.[5,6] Subsequently, the upfront combination of docetaxel with doxorubicin and cyclophosphamide (TAC) was shown to outperform the combination of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) as adjuvant treatment in node-positive and node-negative breast cancer patients.[7–9]

In the neoadjuvant setting, the sequential administration of docetaxel after anthracycline-based therapy versus the anthracycline regimen alone was studied in two randomised studies.[10,11] In the Aberdeen study, patients received four cycles of anthracycline-based chemotherapy; responders were randomised to receive another four cycles of anthracycline-based chemotherapy or four cycles of docetaxel.[10] Switch to docetaxel showed a substantial improvement in response rate and an increased rate of breast conserving therapy. The NSABP-B27 trial also showed that addition of docetaxel after neoadjuvant anthracycline-based chemotherapy improved outcome with a significant increase in the pathological complete response (pCR) rate (14% versus 26%).[11,12] Furthermore, relapse-free survival was moderately improved in the neoadjuvant docetaxel-containing arm.

Hence, both the upfront combination of docetaxel with anthracyclines and cyclophosphamide and the sequential use of docetaxel have shown to improve breast cancer outcome. In this study, we hypothesised that the planned chemotherapy dose and dose-intensity may be a critical factor for predicting outcome. This is supported by the hypothesis that delivering chemotherapy within a shorter time frame prevents tumour outgrowth and development of resistance and should thus be more efficacious than sequential regimens in which the chemotherapy is given in a larger time frame.[13]

2. Patients and methods

2.1. Study design

This was a multicentre, open-label, phase III study in women with newly diagnosed breast cancer. Patients were randomly assigned to neoadjuvant sequential chemotherapy or combination chemotherapy consisting of doxorubicin, cyclophosphamide and docetaxel.

Patients provided written informed consent before enrolment. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study was approved by the Ethics Committee in agreement with the Dutch law code for medical research on humans.

2.2. Patient eligibility

Women eligible for the study were between 18 and 70 years with a Karnofsky performance score of at least 70%. Eligible patients had a primary tumour size of 3 cm or more and/or presence of positive regional lymph nodes. Patients were required to have optimal haematologic, renal and liver functions. No prior history of malignancy or anti-tumour therapy was allowed.

2.3. Treatment

Patients in the AC-T arm received four 3-weekly cycles of doxorubicin and cyclophosphamide at a dose of 60 and 600 mg/m^2, respectively, followed by four 3-weekly cycles of docetaxel (100 mg/m^2). Patients who were assigned to TAC chemotherapy received six cycles of doxorubicin, cyclophosphamide and docetaxel at doses of 75, 500 and 50 mg/m^2, respectively, every 3