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Original Research

A randomised study of tailored toxicity-based dosage of fluorouracil-epirubicin-cyclophosphamide chemotherapy for early breast cancer (SBG 2000-1)

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Abstract ***Study aim:*** Retrospective studies have demonstrated a worse outcome in breast cancer patients not developing leukopenia during adjuvant chemotherapy. The SBG 2000-1 is the first randomised trial designed to compare individually dosed chemotherapy without

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Breast cancer;
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G-CSF support based on grade of toxicity to standard-dosed chemotherapy based on body surface area (BSA).

Methods: Patients with early breast cancer were included and received the first cycle of standard FEC (fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2). Patients with nadir leukopenia grade 0–2 after first cycle were randomised between either 6 additional courses of tailored FEC with increased doses (E 75–90 mg/m^2, C 900–1200 mg/m^2) or fixed treatment with 6 standard FEC. Patients with grade 3–4 leukopenia were registered and treated with 6 standard FEC. Primary end-point was distant disease-free survival (DDFS).

Results: The study enrolled 1535 patients, of which 1052 patients were randomised to tailored FEC ($N = 524$) or standard FEC ($N = 528$), whereas 401 patients with leukopenia grade 3–4 continued standard FEC and formed the registered cohort. Dose escalation did not statistically significantly improve 10-year DDFS (79% and 77%, HR 0.87, CI 0.67–1.14, $P = 0.32$) or OS (82% and 78%, respectively, HR 0.89, CI 0.57–1.16, $P = 0.38$). Corresponding estimates for the registered group of patients were DDFS 79% and OS 82%, respectively.

Conclusions: The SBG 2000-1 study failed to show a statistically significant improvement of escalated and tailored-dosed chemotherapy compared with standard BSA-based chemotherapy in patients with low haematological toxicity, although all efficacy parameters showed a numerical advantage for tailored treatment.

1. Introduction

The use of body surface area (BSA) in dosing chemotherapy has been questioned repeatedly due to large inter-individual variation in drug clearance and sensitivity to given agents [1–3]. These variations will result in under-dosing in some patients and over-dosing in others and might explain the large differences in tolerance noticed in daily practice. Five retrospective analyses of adjuvant chemotherapy in breast cancer found a relation between lack of haematological toxicity and worse survival [4–8] indicating that inter-individual variations may also result in differences in treatment efficacy.

Tailoring dosage based on toxicity may handle not only differences in pharmacokinetics but also individual differences in pharmacodynamics and might reduce the risk of under-as well as over-dosing. Several randomised trials have demonstrated a benefit of increased doses of anthracyclines in the adjuvant treatment of breast cancer [9–11]. Two previous multicentre randomised trials explored tailored dosage using granulocyte-stimulating factors and dose adjustment according to haematological tolerance as a means to achieve maximally tolerated chemotherapy doses [12,13]. Both trials demonstrated dose tailoring to be feasible but did not include a randomised comparison between tailored- and conventional dosing of an identical chemotherapy regimen.

The SBG 2000-1 study was a designed to compare the efficacy and safety of toxicity-based tailored dosage of FEC to standard BSA-based FEC dosage in women with early breast cancer and experiencing limited haematological toxicity (leukopenia grade 0–2) after a first course of standard dosed FEC. We have previously reported that tailored dosage based on haematological tolerance was well tolerated, and haematological toxicity was consistent and predictable throughout all subsequent 6 courses of adjuvant FEC [14]. Here, we report the first and final efficacy results from the first randomised study exploring tailored toxicity-based dosage of chemotherapy compared with standard BSA-based dosage.

2. Methods

The design of the study was described previously together with information on feasibility including dose intensity, tolerability and toxicity [14].

In short, women in Sweden and Denmark (in Denmark only premenopausal) with early operable node-positive or high-risk node-negative breast cancer aged 18–60 years and with an ECOG performance status 0–1, normal haematologic function, and no prior malignant diseases, received the first cycle of adjuvant chemotherapy within 8 weeks after mastectomy or lumpectomy and axillary node clearance. The chemotherapy regimen was seven cycles of FEC given IV every 3 weeks. Doses for all patients in the first cycle were fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. Blood counts including white blood cells (WBCs) were measured on days 10, 12 or 13 and 15 after cycle 1. After cycles 2–7, WBC nadirs were measured on the day when the lowest WBC was measured after cycle 1. Patients who had WBC nadir grade 4 after the first cycle received further six cycles with reduced FEC at dose level 0 and patients with WBC nadir grade 3 had six cycles with standard FEC dose level 1 (Table 1). Patients with