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Improved outcome from substituting methotrexate with epirubicin: Results from a randomised comparison of CMF versus CEF in patients with primary breast cancer

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ABSTRACT

We compared the efficacy of CEF (cyclophosphamide, epirubicin, and fluorouracil) against CMF (cyclophosphamide, methotrexate, and fluorouracil) in moderate or high risk breast cancer patients. We randomly assigned 1224 patients with completely resected unilateral breast cancer to receive nine cycles of three-weekly intravenous CMF or CEF. Patients were encouraged to take part in a parallel trial comparing oral pamidronate 150 mg twice daily for 4 years versus control (data not shown). Substitution of methotrexate with epirubicin significantly reduced the unadjusted hazard for disease-free survival (DFS) by 16% (hazard ratio 0.84; 95% CI; 0.71–0.99) and for overall survival by 21% (hazard ratio 0.79; 95% CI; 0.66–0.94). The risk of secondary leukaemia and congestive heart failure was similar in the two groups.

Overall CEF was superior over CMF in terms of DFS and OS in patients with operable breast cancer without subsequent increase in late toxicities.

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1. Introduction

The benefits of adjuvant chemotherapy were recognised more than 25 years ago.[1–3] The predominant regimen used in these pivotal trials was later named classical CMF and consisted of four-weekly oral cylophosphamide 100 mg/m^2 days one to fourteen in combination with intravenous methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2 days one and eight.[1,2] The Milan group observed no detrimental effects switching to twelve cycles of three-weekly intravenous CMF (600 mg/m^2, 40 mg/m^2, 600 mg/m^2).[4] Based on indirect comparisons, others have, however, hypothesised that classical CMF might be superior to three-weekly intravenous CMF.[5] A direct comparison in a randomised trial has never been undertaken in the adjuvant setting, but in advanced breast cancer, classical CMF with oral cyclophosphamide has, in a single small phase III trial, been superior to three-weekly intravenous CMF.[6] The meta-analyses performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have confirmed that CMF improves disease-free survival and overall survival in patients with operable breast cancer, but have not explored the possible differences between classical and intravenous CMF.[7]

Anthracyclines are among the most active drugs in advanced breast cancer and several trials comparing CMF-like regimens with regimens including an anthracycline were published between the late 1970s and the early 1990s. Although the results of these, often quite small, trials were conflicting, a statistical overview from five of these trials demonstrated a 31% increase in time to progression and a 20% prolongation of survival time.[8] Similar results were demonstrated in the largest of these trials.[9] Similar efficacy but generally less cardiotoxicity has been observed with epirubicin compared to doxorubicin when administered at equitoxic doses.[10,11] Alongside other groups we decided to evaluate whether the results obtained with anthracyclines in advanced breast cancer could be translated into the adjuvant setting. We used a symmetrical design with randomisation to regimens both consisting of a 3-drug combination given nine times intravenously with 3 week intervals. The dose and schedule of cyclophosphamide and 5-fluorouracil was identical in both groups.

2. Patients and methods

This open-label, randomised, phase III trial involving centres nationwide in Denmark, and three health-care regions in Sweden and Iceland, was conducted in accordance with the Helsinki declaration and was approved by ethical committees with jurisdiction for the participating institutions. The Danish Breast Cancer Cooperative Group prepared the original protocol (DBCG trial 89D). Minor regional modifications were later added in the sub-protocols of the other healthcare regions. Informed consent was obtained before randomisation following oral and written information.

2.1. *Patients*

The study included women who had completely resected unilateral invasive carcinoma of the breast and no signs of distant metastases as determined by physical examination, chest radiography, and bone scintigraphy (if positive, to be confirmed by radiography), or axial bone radiography. Lower axillary clearance (level I and part of level II) in combination with breast-conserving surgery or mastectomy was required. In node positive patients, endocrine trials were run in parallel and three distinct groups of patients were therefore eligible for this trial. Group A: node negative premenopausal patients, independent of hormone receptor status but with malignancy grade II or III and a primary ductal carcinoma 5 cm or less in size; Group B: premenopausal patients with hormone-receptor negative (oestrogen (ER) and progesterone (PgR) receptor negative) or unknown tumours, and either axillary lymph node metastases or tumours with a size larger than 5 cm; and Group C: postmenopausal patients with hormone-receptor negative tumours, and either axillary lymph node metastases or tumours with a size larger than 5 cm. A patient was classified as premenopausal if she had amenorrhoea for less than 2 months, amenorrhoea for less than 12 months and FSH in the premenopausal range, or 50 years of age or younger in the case of hysterectomy.

2.2. *Pathological procedures*

Classification of histological type and grade (ductal carcinomas) according to regional guidelines e.g. WHO or Ackerman, examination of tumour margins, invasion into skin or deep fascia, measurement of gross tumour size, total number of lymph nodes identified and number of metastatic nodes was mandatory. ER and PgR were analysed using immunohistochemical assays or dextran-coated charcoal assays in frozen tissue. Tumours were considered to be receptor positive in the quality controlled and validated biochemical ligand-binding assay as defined by the laboratories in each region. Following immunohistochemical staining, tumours were considered receptor positive if the percentage of ER or PgR positive epithelial cells was 10% or above.

2.3. *Treatment*

Patients were assigned to either CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2) or CEF (cyclophosphamide 600 mg/m^2, epirubicin 60 mg/m^2 and 5-fluorouracil 600 mg/m^2) both given intravenously (i.v.) day one every 3 weeks. Loco-regional radiotherapy was administered according to regional guidelines and patients not assigned to loco-regional radiotherapy received nine cycles of CMF or CEF, while patients assigned to radiotherapy received one or two cycles of CMF or CEF before radiotherapy and one or two cycles of single agent cyclophosphamide (850 mg/m^2) concomitant with radiotherapy followed by CMF or CEF to a total of nine cycles of chemotherapy. The doses were primarily adjusted according to white cell and platelet counts ($\times 10^9$/l) day one of the scheduled cycle as follows: platelets > 100 and WBC > 3.0, 100%; platelets 50–100 or WBC 2.0–3.0, 75% of all three drugs. If platelets < 50 or WBC < 2.0, the treatment was delayed for 1 week. The protocol permitted secondary randomisation to pamidronate 150 mg given orally twice daily for 4 years against control. The use of endocrine therapies was not recommended.