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Postoperative adjuvant chemotherapy followed by adjuvant tamoxifen *versus* nil for patients with operable breast cancer: A randomised phase III trial of the European Organisation for Research and Treatment of Cancer Breast Group

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ABSTRACT

Background: The contribution of adjuvant tamoxifen in breast cancer patients after receiving adjuvant chemotherapy is not fully established. We investigated the impact of tamoxifen, given sequentially after completion of adjuvant chemotherapy in patients with operable breast cancer.

Patients and methods: Between March 1991 and June 1999, 1863 women with stages I–IIIA operable breast cancer who had undergone surgery and completed six cycles of adjuvant combination chemotherapy with either CMF, CAF, CEF, FAC or FEC were randomised to receive either tamoxifen 20 mg daily for 3 years or no further treatment. Irrespective of menstrual status and hormone receptor content of the primary tumour, patients were stratified by institute, chemotherapy scheme and age (above 50 years or younger). The main end-point was to detect a 5% increase in the 5 year survival (from 80% to 85%) in favour of antioestrogen therapy. Secondary end-points were relapse free survival (RFS), local control, incidence of second primary breast cancer and correlation of results with hormone receptor content.

Results: After exclusion of all patients from three sites because of inadequate documentation, a total of 1724 patients (93%) were analysed (Tam 861 and Control 863). At a median follow-up of 6.5 years, 5-year RFS on tamoxifen was 73% *versus* 67% in controls ($p = 0.035$). No difference was seen in overall survival. The benefit of tamoxifen therapy

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was mainly seen in the subgroup of patients with histologically documented positive axillary nodes (5-year RFS on tamoxifen 71% *versus* 64% in the control group, $p = 0.044$) and in patients with tumours expressing the ER and PR positive phenotype (5-year RFS on tamoxifen 77% *versus* 70% in the control group, $p = 0.014$).

Conclusions: Tamoxifen administered for 3 years after completion of adjuvant chemotherapy in this otherwise unselected group of patients for endocrine sensitivity had a limited impact on relapse and had no detectable effect on overall survival. The beneficial effect of tamoxifen is mainly confined to the subgroup of patients with node-positive disease and to patients with tumours expressing the ER and PR positive phenotype.

1. Introduction

Adjuvant tamoxifen as monotherapy reduces recurrence and mortality in patients with hormone receptor-positive operable breast cancer. This effect is well demonstrated in the recent overview by the Early Breast Cancer Trialists' Collaborative Group showing that in oestrogen receptor-positive disease, about 5 years of tamoxifen reduces the annual breast cancer death rate by 31%.[1] However, the contribution of tamoxifen is less established in patients receiving adjuvant chemotherapy. In the past, concurrent administration of cytotoxics and tamoxifen was used on the assumption that their effects were independent. The concurrent use of chemotherapy and tamoxifen did improve the results achieved by chemotherapy alone, particularly in postmenopausal women and in those with four or more involved nodes.[2] However, experimental data suggest that tamoxifen and chemotherapy may be partially antagonistic,[3] and clinical trials confirm that concomitant administration of tamoxifen with chemotherapy yields inferior results than chemotherapy alone.[4,5] This antagonistic effect was particularly apparent in premenopausal women where concomitant administration of adjuvant chemotherapy and hormonal treatment generally did not improve outcome and sometimes led to a less favourable outcome than either therapy given alone.[6] Given the possibility of negative interactions with concomitant administration, this trial which was initiated by the European Organisation for Research and Treatment of Cancer (EORTC) Breast Group in 1991 investigated the impact of tamoxifen administered sequentially after completion of adjuvant chemotherapy in patients with operable breast cancer. At the time this study was designed, the role of hormone receptors in predicting the value of tamoxifen therapy was not yet fully established. It was thought that tamoxifen could have some beneficial effects irrespective of the presence of hormone receptors in the tumour. Therefore, tamoxifen was given to all eligible patients regardless of endocrine sensitivity.

2. Patients and methods

2.1. Study design

Between March 1991 and June 1999, 1863 women with stages I–IIIA operable breast cancer were included in this study. The women had undergone mastectomy or breast conserving surgery ± radiotherapy and completed six cycles of adjuvant combination chemotherapy with either CMF (cyclophosphamide, methotrexate, 5-fluorouracil), or 4–6 cycles of an anthracycline based regimen including CAF (cyclophosphamide, adriamycin, 5-fluorouracil), CEF (cyclophosphamide, epirubicin, 5-fluorouracil), FAC (5-fluorouracil, adriamycin, cyclophosphamide) or FEC (5-fluorouracil, epirubicin, cyclophosphamide). A minimum of four cycles of anthracycline based chemotherapy was allowed on the basis that four cycles of AC is at least as effective as six cycles of CMF.[7] Patients were accrued irrespective of their menstrual status and of the hormone receptor content of their primary tumour.

Investigations before randomisation included chest X-ray, contralateral mammogram, and if clinically indicated, screening for distant bone metastasis with isotope scanning and ultrasound or CT scanning of the liver. Patients were excluded from the study if they had signs of relapse or residual disease at study entry, and those with any other malignant disease including contralateral breast cancer, other than adequately treated *in situ*/microinvasive cervix carcinoma or basal cell carcinoma of the skin.

Patients consenting to participate were stratified by institute, chemotherapy scheme and age (above 50 years or younger). Randomisation took place at the start of the last cycle of chemotherapy to either tamoxifen 20 mg daily for 3 years or no further treatment. Tamoxifen was started within two weeks of the end of the last cycle of chemotherapy. At the time this trial was initiated in 1991, the optimal dose and duration of adjuvant tamoxifen was not known. The above dosage and duration of treatment was chosen as the most suitable at that time. Informed consent was required according to the criteria established within the individual countries at the time of patient accrual and the protocol was approved by institutional review boards.

Patients were reviewed at least every 4 months during the first 3 years and at least every 6 months thereafter. Clinical, haematologic, and biochemical assessments were required on each visit, chest X-ray and contralateral mammography were performed yearly, while other tests such as bone isotope scanning and ultrasound or CT scan of the liver were required only when clinically indicated.

2.2. End-points and statistical considerations

This study was designed to detect a 5% increase in the 5 year survival from 80% to 85% in favour of antioestrogen therapy