# Taxanes in adjuvant chemotherapy for early breast cancer

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'The Early Breast Cancer Trialists' Collaborative Group study found that allocation to approximately 6 months of anthracycline-based polychemotherapy reduced the yearly death rate from breast cancer by approximately 38% for women younger than 50 years of age at diagnosis and by approximately 20% for women aged 50–69 years at diagnosis.'

Adjuvant polychemotherapy improves disease-free survival and overall survival in women with early breast cancer. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported that over 15 years there had been a reduction in recurrence and death in women younger than 50 years who had received adjuvant polychemotherapy [1]. A smaller but still highly significant reduction in the risk of recurrence and death was observed for women aged 50–69 years who received the same treatment. The effect of adjuvant chemotherapy on recurrence was noted mainly during the first 5 years after randomization. The magnitude of effect within this 5-year period was 2.5-times greater for women aged under 50 years compared with women aged 50–59 years. The EBCTCG meta-analysis also compared regimens that contain anthracyclines with no chemotherapy or with the oral combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) [1]. The most widely investigated regimens that contain anthracyclines were a combination of cyclophosphamide and 5-fluorouracil with either doxorubicin or epirubicin. The EBCTCG study found that allocation to approximately 6 months of anthracycline-based polychemotherapy reduced the yearly death rate from breast cancer by approximately 38% for women younger than 50 years of age at diagnosis and by approximately 20% for women aged 50–69 years at diagnosis.

The Cancer And Leukemia Group B (CALGB) 9741 study randomly assigned patients to one of four groups to assess variations in the use of a regimen of doxorubicin, cyclophosphamide and paclitaxel [2]. Two groups assessed differences between sequential and concurrent use of these agents with a dose-dense, 2-weekly schedule (with filgrastim). The other two groups investigated the same issues of concurrent versus sequential use with a standard 3-weekly schedule. The CALGB 9741 study compared the combined results of patients who received dose-dense doxorubicin and cyclophosphamide followed by paclitaxel with the combined results of those who received standard-dose doxorubicin and cyclophosphamide followed by paclitaxel [2]. At a median follow-up of 36 months, disease-free survival was 82% for the dose-dense group compared with 75% for the standard-dose group, and overall survival was 92 versus 90%, respectively. When a Cox proportional hazard model was applied to adjust for baseline characteristics, the risk ratio was 0.74 ($p = 0.01$) for recurrence and 0.69 ($p = 0.013$) for death.

The dose-dense regimen most commonly used in clinical practice combines four cycles of doxorubicin/cyclophosphamide (AC)60 followed by four cycles of 175 mg/m$^2$ paclitaxel infused over 3 h given every 2 weeks with filgrastim. Differences between the combined dose-dense group and standard-dose groups might have been overemphasized in this trial due to the 2 × 2 factorial design, which combined the outcomes of all four groups, including the less effective, nonstandard 3-weekly sequential group, with the group given 3-weekly doxorubicin and cyclophosphamide followed by paclitaxel. Furthermore, sufficient follow-up has not yet been reached for this study, and further follow-up is needed to establish whether the 20% proportional reduction in death rate at 3 years is maintained at 5 years. Indirect comparisons across heterogeneous populations should be made with caution. However, they can be helpful in the absence of direct randomized comparisons. Of the two regimens that demonstrate significant 5-year

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reductions in mortality compared with oral CMF or AC, the greatest proportional reduction was noted for the cyclophosphamide, epirubicin and 5-fluorouracil (CEF) regimen (23%). The AC60 followed by 175 mg/m$^2$ paclitaxel regimen showed a 13% reduction in the death rate. Six cycles of a standard-dose anthracycline regimen has been proven to be more effective than CMF (yearly deaths from breast cancer decreased by 38% for women aged under 50 years and by 20% for women aged 50 years or older) [1]. Of the two regimens compared with six cycles of a standard-dose anthracycline, the docetaxel, doxorubicin and cyclophosphamide (TAC) regimen resulted in the greatest proportional increase in survival (32%); the 5-fluorouracil, epirubicin and cyclophosphamide (FEC)100 regimen showed an increase of 25%. Thus, on the basis of survival outcomes alone, the TAC regimen and the FEC100 regimen would be recommended for adjuvant treatment of node-positive breast cancer. Between these two regimens, it is not possible to establish which is preferred, due to the lack of randomized trials comparing the two regimens. However, on the basis of the results in terms of reduction of risk of death, TAC should probably be the first option for fit patients.

The cost of giving a regimen can be an important factor in treatment selection, especially when two regimens have comparable activity and safety. The chemotherapy acquisition and protocol-driven supportive-care costs varied by regimen. Actual Canadian prices as of July 2005 were used in all cost calculations and converted into US$ using an exchange rate of CDN$1 = US$0.80334. Based on costs of chemotherapy acquisition alone, the TAC regimen was the most costly (US$6825) and the FEC100 regimen was the least expensive (US$3162).

The cost of a regimen in human resources corresponds directly to the complexity of the protocol. Administration costs were calculated by multiplying a regimen's individual complexity factor, as cited on the Cancer Care Ontario website [101], by a standard wage per minute, including benefits for nursing or pharmacy care (US$0.64/min), and the total number of cycles given. The FEC100 regimen incurred the lowest administration costs (US$216), followed by the AC then paclitaxel regimen (US$221), the TAC regimen (US$239) and the CEF regimen (US$347) [3].

Supportive-care costs were divided into two categories: protocol-driven costs and incidental costs. Protocol-driven supportive-care costs are prescribed by the study protocol, whereas incidental supportive-care costs arise as a result of a treatment complication. Associated costs were calculated on the basis of protocol variables by use of Canadian pricing dated July 2005 and converted into US$. The cost attributed to incidental use of filgrastim was estimated by multiplying the cost of one cycle of filgrastim by the rate of febrile neutropenia and two-thirds the total number of associated-regimen cycles. The dose-dense AC followed by 175 mg/m$^2$ paclitaxel regimen incurred the greatest protocol-driven supportive-care costs (US$7400), and the TAC regimen had the greatest incidental supportive-care costs (US$1110) [3].

'When all factors are considered, the docetaxel, doxorubicin and cyclophosphamide (TAC) regimen, the 5-fluorouracil, epirubicin and cyclophosphamide (FEC)100 regimen and the cyclophosphamide, epirubicin and 5-fluorouracil (CEF) regimen seem to be the best available treatment options.'

The total cost of treatment was calculated by the addition of total cost of chemotherapy acquisition, protocol-driven and incidental supportive care, and administration. Overall, FEC100 incurred the lowest cost for total treatment (US$3557), followed by AC60 then 175 mg/m$^2$ paclitaxel (US$4340), CEF (US$4852), AC60 followed by 225 mg/m$^2$ paclitaxel (US$5665), TAC (US$8266), and dose-dense doxorubicin and cyclophosphamide followed by 175 mg/m$^2$ paclitaxel (US$11,741) [3].

In conclusion, of the categories being used, level-one evidence is available for the escalated-dose epirubicin and anthracycline–taxane-containing categories. Based on survival alone, the TAC regimen and the FEC100 regimen resulted in the greatest proportional reductions in mortality. Severe febrile neutropenia or severe infection, nonhematological toxic effects, cardiotoxicity and secondary leukemia occurred with all regimens, although the magnitude of the toxic effects varied by regimen. When total treatment costs were taken into

account, the FEC100 regimen and the AC60 followed by 175 mg/m$^2$ paclitaxel regimen were the least expensive, whereas the FEC100 regimen and the TAC regimens were more convenient to patients. When all factors are considered, the TAC regimen, the FEC100 regimen and the CEF regimen seem to be the best available treatment options. However, the choice of adjuvant chemotherapy regimen is often made on the basis of physician training, or patient preference and information derived from media or internet sources.

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## Website


101. Cancer Care Ontario – Drug Formulary www.cancercare.on.ca/index_drugFormulary.htm