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Critical Reviews in Oncology/Hematology 58 (2006) 166–175

Critical Reviews in Oncology Hematology

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# Dose-dense adjuvant chemotherapy for node-positive breast cancer in women 60 years and older: Feasibility and tolerability in a subset of patients in a randomized trial

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Accepted 11 August 2005

## Contents



## Abstract

To evaluate the feasibility and tolerability of dose-dense adjuvant chemotherapy for older patients with node-positive breast cancer, a retrospective subset analysis compared dose delays and dose reductions for women aged ≥60 years with those of younger women. Patients

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doi:10.1016/j.critrevonc.2005.08.009

were randomized to a dose-dense (DD, 14-day cycle) or conventional-schedule (CS, 21-day cycle) regimen. DD patients ($n = 104$; 25 aged ≥60 years) received epirubicin 90 mg/m$^2$ plus paclitaxel 175 mg/m$^2$ (four cycles), then cyclophosphamide 600 mg/m$^2$, methotrexate 40 mg/m$^2$ and fluorouracil 600 mg/m$^2$ (CMF 600/40/600) (three cycles), plus filgrastim 5 μg/kg per day in every cycle. CS patients ($n = 107$; 27 aged ≥60 years) received epirubicin 90 mg/m$^2$ plus cyclophosphamide 600 mg/m$^2$ (four cycles), then CMF 600/40/600 (three cycles), plus filgrastim if required.

Delays were more common in older patients in both the DD and CS groups (DD, 17% versus 6%; CS, 11% versus 6%), as were Grades 3–4 leukopenia (26% versus 12%) and neutropenia (33% versus 25%). All older DD and 89% of older CS patients received all seven chemotherapy cycles, with 99% of cycles at full dose. This study demonstrates that a dose-dense regimen combining epirubicin and paclitaxel can be administered to patients ≥60 years of age with a tolerable safety profile.
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*Keywords:* Chemotherapy; Breast cancer; Elderly; Filgrastim

## 1. Introduction

Breast cancer is the second leading cause of death for women aged 60–79 years, and the risk of breast cancer increases with advancing age [1]. Yet, few studies have focused on the treatment of older patients with breast cancer. Evidence is limited concerning the most appropriate regimens for patients ≥60 years of age, at least in part because these patients are often underrepresented in clinical trials [2].

In many studies of patients treated for breast cancer, elderly patients receive adjuvant chemotherapy less frequently than younger patients, and the oldest patients are the least likely to receive it [3–7]. This lack of treatment may affect patient survival. In a retrospective study, Bouchardy et al. found that elderly patients who received adjuvant chemotherapy for breast cancer experienced a significantly higher rate of 5-year survival [8].

In spite of the relatively low rates of use of adjuvant chemotherapy in older patients with breast cancer, clinical trials have shown that adjuvant chemotherapy using a variety of regimens can benefit these women. In a meta-analysis of published studies, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found a substantial and highly significant reduction in recurrence of cancer in women aged 60–69 years (18%). So few women ≥70 years were represented in the study that they were not included in the analysis [9]. In a combined analysis of more than 2000 patients in the National Epirubicin Adjuvant Trial (NEAT) and Scottish Cancer Trials Breast Group (SCTBG BR9601) studies, Poole et al. found that the treatment benefit observed with a sequential regimen of epirubicin followed by cyclophosphamide/methotrexate/fluorouracil in adjuvant chemotherapy was significant among women of all ages [10]. A study by the International Breast Cancer Study Group showed that estrogen receptor-negative patients ≥60 years benefit from adjuvant chemotherapy with CMF, regardless of lymph node involvement [11].

Muss et al. performed a subgroup analysis of 6489 women from CALGB studies 7581, 8082, 8541 and 9344 of patients with node-positive breast cancers after a median 9.6 years of follow-up. Although women ≥65 years represented only 10% of patients, higher dosed chemotherapy regimens of the various agents studied provided a similar benefit to the patients ≥65 years as to younger patients in relapse-free survival [12]. A review of clinical trials of elderly women with breast cancer found that weekly administration of paclitaxel at lower doses was tolerable for most patients; this regimen was found to have lower hemotoxicity than higher dosing at longer intervals [13].

Recent evidence supports the use of regimens incorporating taxanes with anthracyclines for patients with breast cancer. In clinical studies, sequential administration of doxorubicin followed by CMF and paclitaxel in combination with doxorubicin improved survival compared to CMF alone [14]. At 5 years, the survival benefits of anthracycline–taxane combination regimens were similar for patients in all age groups, including those ≥60 years [15]. Epirubicin provides comparable response rates to those of doxorubicin, with reduced cardiotoxicity [16,17]. The survival advantages of epirubicin in various regimens have been confirmed in several clinical trials, including a large phase 3 study of 2000 patients in which patients in one treatment group received the taxane docetaxel for three cycles after three cycles of treatment with epirubicin [18].

One aspect of adjuvant chemotherapy that has emerged as a predictor of outcome is whether patients receive the full prescribed dose. In a 20-year study of patients with node-positive breast cancer, Bonadonna et al. demonstrated that patients who receive ≥85% of prescribed chemotherapy doses have a survival advantage compared to those who receive lower proportions of the prescribed dose [19]. The importance of full dose administration of chemotherapy for preventing disease progression has also been demonstrated in other studies of the treatment of node-positive breast cancer [20,21].

Additional developments in adjuvant chemotherapy may also improve survival in node-positive breast cancer, including the use of dose-dense (DD), dose-intensive and sequential regimens [20–22]. These regimens increase the amount of therapeutic agent that patients receive using higher doses, shorter intervals between cycles or two different drug combinations in sequential cycles.

In spite of these advances, many older patients with breast cancer receive reduced quantities of chemotherapeutic agents because of reduced doses, delayed or missed cycles, or both. In a retrospective study of more than 20,000 patients, Lyman et al. found that patients aged ≥65 years had a significantly

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