Adjuvant chemotherapy in older patients with breast cancer

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A prospective, randomised trial has shown that standard adjuvant chemotherapy is superior to capecitabine in the treatment of women with breast cancer aged 65 years or older; on the basis of the results of this study, capecitabine cannot be recommended in this setting.

One of the major successes in oncology is the improvement of overall survival as a result of adjuvant chemotherapy in patients with localised breast cancer. The benefit of adjuvant chemotherapy has only been robustly shown for patients who are younger than 70 years of age. In a meta-analysis, adjuvant chemotherapy was found to improve overall survival compared with no chemotherapy in patients aged 50–69 years, irrespective of oestrogen receptor status.[1] Firm conclusions could not be drawn, however, for women older than 70 years of age, because of the small number of patients (n=1200), the heterogeneity of the disease, and different treatments. Furthermore, two large, observational studies[2,3] suggested that adjuvant chemotherapy in patients over 65 years of age might only benefit those with oestrogen-receptor-negative and lymph-node-positive tumours, and not those with oestrogen-receptor-positive disease.[2]

Consequently, adjuvant chemotherapy is administered to only 8% of patients over the age of 69, and to 21% of those aged 65–69.[2] The main concern associated with the use of adjuvant chemotherapy in older patients, in or outside clinical trials, is severe chemotherapy-induced toxic effects. Withholding adjuvant chemotherapy from elderly patients might explain the equivalent stage-adjusted mortality rates for breast cancer in elderly and younger patients (except for those <35 and >80 years of age, both associated with increased mortality),[4] even though improved outcomes for older patients may be expected, as tumours in older women generally have a more favourable biology.[5]

Many patients with breast cancer are over 70 years of age and this number will continue to rise in the future owing to aging of the population; therefore, there is an obvious need for the evaluation of adjuvant chemotherapy in elderly patients. Muss et al.[6] performed a randomised trial to test the noninferiority of oral capecitabine compared with standard combination chemotherapy (CMF: cyclophosphamide, methotrexate, fluorouracil, or AC: doxorubicin and cyclophosphamide) in women with breast cancer aged 65 or older. The results showed inferiority of capecitabine for relapse-free survival (three-years relapse-free survival 68% vs

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85%; HR 2.09, $P<0.001$) and overall survival (three-year overall survival 86% vs 91%; HR 1.85, $P=0.02$) compared with standard chemotherapy. Importantly, a subgroup analysis showed a significant interaction between treatment and hormone status. The superiority of standard chemotherapy in terms of overall survival was only present in patients with oestrogen-receptor-negative tumours (HR 3.8 [2.2–6.3] compared with capecitabine). This, however, was an unplanned analysis and thereby prone to bias, which could hinder firm conclusions.

As capecitabine is unlikely to negatively affect survival in patients with localised breast cancer, this study demonstrated that adjuvant combination chemotherapy was effective in older women, emphasising that age alone should not be a reason for withholding adjuvant chemotherapy. The reasons for the inferiority of capecitabine remain to be defined. It might be that capecitabine is a less active drug than CMF and AC, although in the metastatic setting capecitabine is considered equivalent to CMF. Findings have shown that a substantial number of patients with cancer are not fully compliant to dosing schedules with oral antitumour agents. Similar observations have been noted with tamoxifen in the adjuvant setting,[7] where there is an uncertainty about the necessity of adjuvant therapy. In the study by Muss et al.,[6] only 76% of patients took more than 80% of the planned oral doses, which might have led to an underestimation of efficacy. This finding demonstrates that adherence of patients to oral antitumour drugs deserves more attention.

In addition to providing pivotal insight into the value of adjuvant chemotherapy in older patients with breast cancer, this study also sheds more light on the widespread concern of increased toxic effects from chemotherapy in the elderly. Although age is frequently used to determine who qualifies for chemotherapy, physiology rather than age affects drug pharmacokinetics and toxicity. It is well known that physiological changes related to age are highly individual. Unfortunately, pharmaco-kinetic data on chemotherapy in elderly patients are limited and are derived from small, highly-selected populations of patients with advanced breast cancer. Pharmacokinetic analyses in older women with breast cancer indicate no age-related changes in drug clearance or volume of distribution for AC, CMF or capecitabine regimens; therefore, chemotherapy should not be withheld from patients solely on the basis of age. In the study by Muss et al.[6] nonhaematological toxic effects were similar in both treatment arms. As expected, a much higher percentage (53%) of patients treated with standard-dose chemotherapy experienced severe (grade 3 and 4) haematological toxic effects compared with capecitabine-treated patients (2%). Importantly, however, the incidence of febrile neutropenia in patients who received CMF and AC chemotherapy was low (8%–9%). The only reported treatment-related deaths occurred in the capecitabine arm. The occurrence of toxic effects led to discontinuation of therapy in 38%, 8% and 20% of patients who received CMF, AC and capecitabine, respectively. These findings are similar to previous data showing reduced tolerability and reduced dose intensity for CMF in older patients with breast cancer compared with younger patients.[8] The reduced dose intensity of CMF may have led to an underestimation of efficacy. Tolerance to AC seems to be independent of age, thereby rendering AC an acceptable regimen for elderly patients.

The study by Muss and colleagues emphasised that age should no longer be a reason for withholding adjuvant chemotherapy from elderly patients with breast cancer, particularly from those with oestrogen-receptor-negative disease. In this context, the use of validated comprehensive geriatric assessments, comorbidity scores and functional performance status will enable well-founded decisions on the eligibility of elderly patients with breast cancer for chemotherapy. Moreover, the outcomes of this study can serve as a basis to assess potentially more-effective chemotherapy combinations, for instance docetaxel and cyclophosphamide, which, when compared with AC, showed superiority for the taxane-based regimen in a subgroup of elderly patients.[9] Future clinical trials in older patients should be stratified by hormone receptor status. Together with the application of novel prognostic and predictive models based on tumour characteristics, this will lead to a more tailored approach for the treatment of elderly patients.[10]

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

Practice point

Similar to young women with localised breast cancer, elderly patients in good clinical health gain benefit from adjuvant chemotherapy.

Capecitabine is inferior to standard chemotherapy and is therefore not recommended in the adjuvant setting.

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