

Adjuvant chemotherapy for older women with breast cancer

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Abstract Many older women today with early-stage breast cancer have estimated survivals exceeding 5–10 years at the time of diagnosis and should be considered for systemic adjuvant chemotherapy. When available and if eligible, such patients should be offered clinical trials participation. Given the median age for onset of breast cancer, trials should also be developed to specifically investigate the disease in this age group. Oncologists caring for elders need to educate their colleagues as well as their patients concerning the pitfalls of age bias and the potential hazard of under-treatment and poorer outcomes.

Keywords: Adjuvant therapy; Chemotherapy; Elderly; Primary breast cancer

Introduction

There will be 1 437 000 new cancer cases and 566 000 cancer deaths in the United States in 2008 [1]. The incidence of cancer in the US dramatically increases with age with a median age at diagnosis of 67 years and a median age at death of 73 years. Breast cancer is the most common cancer in women, and in the US is second only to lung cancer as the leading cause of cancer death. About 182 000 new cases of invasive breast cancer and 41 000 breast cancer deaths are estimated for 2008 [1]. The median age at diagnosis of breast cancer in the US is 61 years and median age at death is 69 years. The median age of incidence of breast cancer is similar to other affluent nations, making breast cancer a major cause of cancer morbidity and mortality for much of the world's older women. Although older breast cancer patients have slightly

better tumor characteristics than younger women (they are more likely to be hormone receptor-positive, have lower-grade tumors, node-negative, and HER-2-negative tumors) [2], survival is similar or possibly even worse than for younger patients after adjusting for stage and receptor status [3,4].

Major advances have been made in the adjuvant systemic therapy of breast cancer, with both endocrine therapy and chemotherapy playing a major role in improving survival [5]. Nevertheless, older patients continue to be under-represented in adjuvant breast cancer trials [6,7], especially in randomized trials involving chemotherapy [5]. Increasing evidence suggests that healthy older patients get similar benefits as younger patients with newer state-of-the-art chemotherapy treatments [8,9] although with greater treatment-related morbidity and mortality [9,10]. Anthracycline therapy specifically has been associated with increased risks of congestive heart failure [11] and leukemia [12]. This review focuses on adjuvant chemotherapy.

Age, comorbidity, and life expectancy

Older patients are less likely to be considered for adjuvant chemotherapy based on age bias alone

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but older women in good health can have a considerable life expectancy. For example, a healthy 65-year-old woman has an average remaining life expectancy of 20 years, a healthy 75-year old of 13 years, and a healthy 85-year old of 7 years [13]. These data indicate that adjuvant chemotherapy should be considered for many healthy older women with a breast cancer at high risk of recurrence over a 10-year period. Factoring in how other comorbid illness competes with breast cancer in lowering life expectancy can be estimated using computer models such as Adjuvant! [14] (see also www.adjuvantonline.com). Estimates of the severity of comorbidity can be added to the model and greatly help in decision making.

Selecting patients for treatment

Historically, patients have been selected for treatment based on clinical trial designs that categorized patients by nodal status (node-negative or node-positive) and hormone receptor status (positive or negative). New insights into the biology of breast cancer [15] have suggested that patients might be better selected by dividing them into three specific groups: (1) those with hormone receptor-positive, HER-2-negative tumors (by far the largest group and comprising the majority of older women), (2) those with HER-2-positive tumors irrespective of hormone receptor status (about 10–15% of older women), and (3) those with hormone receptor-negative, HER-2-negative tumors – ‘triple-negatives’ (about 15% of older patients). Such a division allows one to apply data from more recent trials in making the best treatment decision.

For the group with hormone receptor-positive, HER-2-negative tumors, adjuvant therapy with either tamoxifen or aromatase inhibitors is the adjuvant therapy of choice, and the major decision concerning the role of chemotherapy is calculating its potential added value to endocrine therapy. For elders with node-negative, estrogen receptor (ER)-positive tumors who are candidates for 5 years of tamoxifen, the recently developed OncotypeDx assay [16,17] can estimate the added value of chemotherapy and can be of great help in decision making; few older patients are likely to benefit from chemotherapy in this setting but a small percentage might derive major benefit [9]. The TAILORx trial (ECOG-PACCT-1; <http://www.cancer.gov>) in the US and the MINDACT trial (EORTC 10041 (BIG 3-04; <http://www.eortc.be>) in Europe use tumor genetic assessments to randomize patients at moderate risk of recurrence to chemotherapy or not; older patients eligible for these trials should be offered participation. A flaw in the MINDACT trial is an

age restriction of 18–70 years. For women in this group with positive lymph nodes, the decision is more complicated; use of Adjuvant! can help with these decisions, and factoring in comorbidity is an essential element assessing the value of chemotherapy on improving survival.

Older women and younger women with HER-2-positive tumors have higher risks of early relapse and should be considered for trastuzumab therapy in addition to chemotherapy [18,19]. For older women treated with trastuzumab, cardiac toxicity is a major concern as age is a risk factor for an increased risk of cardiac toxicity and CHF [20,21]. Older patients need to be carefully monitored, and for some with a history of hypertension or heart disease, initiation of ACE-inhibitors and beta-blockers might be considered prior to starting trastuzumab to minimize the cardiac risks. Also, elders should be considered for non-anthracycline-containing regimens with trastuzumab such as docetaxel and carboplatin [22] or docetaxel and cyclophosphamide [23] to minimize cardiac risk. Not all older patients with HER-2-positive tumors require trastuzumab. For those with small, node-negative tumors a centimeter or less, the added value of trastuzumab is small and risks may outweigh benefits.

Older women with triple-negative breast cancer and estimated non-breast cancer estimated survival greater than 5 years should be offered state-of-the-art chemotherapy including taxane-containing regimens [24,25]. This aggressive strategy is supported by a recent analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) comparing chemotherapy or not in women with ER-poor tumors, which showed a 10-year reduction in breast cancer mortality of 8% in women younger than 50 years, and 6% in women aged 50–69 years [26]. Of note, these impressive survival benefits were achieved with older, non-taxane-containing regimens, with almost half of these patients receiving cyclophosphamide, methotrexate, and fluorouracil. In an analysis of data from the Surveillance, Epidemiology and End Results Program (SEER), older women with node-positive breast cancer and those with higher risk node-negative breast cancer derived significant survival benefits from chemotherapy [27]. A first analysis of CALGB trial 49907, which compared standard chemotherapy (either CMF or doxorubicin and cyclophosphamide (AC)) with capecitabine in women aged 65 and older with early-stage breast cancer, showed that standard chemotherapy was superior to capecitabine, especially in those with receptor-negative tumors [28]. Although the HER-2 status of the patients from the CALGB analysis [24], the

Table 1. Clinical trials specifically designed for older patients with breast cancer.

Trial	Treatment	N (actual)	Status
CALGB 49907	AC/CMF vs. capecitabine	600 (600+)	Closed
ICE (BIG)	Ibandronate ± capecitabine	1400 (1350)	N±, ER+ and AI
CASA (BIG)	Caelyx vs. none Caelyx vs. po CM	Closed after 42 pts	ER– and PR–
ELDA (NCI-Naples)	Docetaxel vs. CMF	300 (just started)	mod-high risk
ACTION (UK)	AC or EC vs. none	1000 (just started)	ER–

meta-analysis of the EBCTCG [26], and the SEER database [27] was not available, it is likely that about 80% or more of these patients had triple-negative breast cancer and one would expect even better results if trastuzumab were given to the HER-2-positive patients in these trials.

Clinical trials

Older patients continue to be under-represented in clinical trials and clinicians should be encouraged to offer trial participation to older patients. Available data suggest that when offered trials, older and younger patients have similar rates of participation, approximating 50% [29]. Another strategy to improve accrual is to design trials specifically for older patients, and current trials for older women with early breast cancer are presented in Table 1. In addition, newer trials with more aggressive regimens would benefit by incorporating a CGA assessment tool for older patients as part of the trial. The shortage of trained geriatricians has led to the development of shorter instruments that can accurately predict functional decline and mortality risk [30–32]. Helping to identify which patients are at greatest risk for treatment toxicity and loss of function prior to treatment would be of great value to patients and physicians. A gap in knowledge related to management of frail patients with early breast cancer [33]. Specific trials for this group of patients are needed.

Conclusions

Many older women today with early-stage breast cancer have estimated survivals exceeding 5–10 years at the time of diagnosis and should be considered for systemic adjuvant chemotherapy. When available and if eligible, such patients should be offered clinical trials participation. Outside of a trial, management guidelines for older women with breast cancer have been recently developed by the international Society of Geriatric Oncology and provide excellent guidance for patient management [34]. In addition, several excellent recent reviews of this topic are available [35,36]. Oncologists caring

for elders need to educate their colleagues as well as their patients concerning the pitfalls of age bias and the potential hazard of under-treatment and poorer outcomes.

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