Adjuvant Chemotherapy of Breast Cancer in the Older Patient

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Although increasing age is the major risk factor for breast cancer incidence and mortality, when adjusted for disease stage, breast cancer mortality is similar among younger vs older patients. Importantly, about 90% of older women with breast cancer present with early-stage disease. The biologic characteristics of breast tumors in older patients suggest they would derive benefit from adjuvant therapy, particularly endocrine therapy, but older women are still frequently undertreated, resulting in poorer survival. Studies suggest that focusing on comorbidity rather than “chronologic age” as a surrogate for life-expectancy is a key aspect of adjuvant decision-making for older patients. Morbidity and mortality from cancer in vulnerable patients with poorer health can be accurately predicted by the Comprehensive Geriatric Assessment (CGA), which evaluates comorbidities, functional status, cognition, social support, psychological state, nutritional status, and polypharmacy. Use of the CGA and newer versions of this tool can lead to interventions that maintain function and improve quality of life in older patients with breast cancer.

FIGURE 1

Age, Incidence, and Mortality of Breast Cancer

Breast cancer, a disease of aging, is the most common cancer in American women, and increasing age is the major risk factor for breast cancer incidence and mortality (Figure 1).[1] Except for the very old and very young, breast cancer mortality (when stage-adjusted) is similar among older and younger patients.[2,3] Although older women are diagnosed with breast cancer at a later stage than younger women, about 90% of older women present with stage I or II disease.[4]

The biologic characteristics of breast cancers change with increasing age; tumors in older patients are more likely to be lower grade and have lower proliferation indices, and they tend to be hormone receptor-positive, node negative, p53 negative, and HER2 negative.[5,6] There does not appear to be any difference in angiogenic markers with aging.[6] Major improvements in life expectancy during the second half of the 20th century have resulted in an older population that is healthier and more long-lived. Today, the estimated further life expectancy of a 65-year-old woman is about 20 additional years and for a 75-year-old woman is about 12 years.[7] In spite of an extensive body of literature showing the benefits of adjuvant therapy in older women, especially endocrine therapy, ageism persists—and older women are frequently undertreated, resulting in poorer survival.[4,8-10] This review will focus on issues and controversies related to the use of adjuvant chemotherapy in older women; other reviews of this topic are also available.[11,12]

Comorbidity in the Older Patient With Breast Cancer

The probability of having another illness (comorbidity) increases with increasing age and is a major factor in treatment selection and likelihood of treatment-related toxicity. In one major study of 1,800 postmenopausal women with breast cancer, patient factors including diabetes, renal failure, stroke, liver disease, a previous malignant tumor, and smoking significantly predicted shortened survival even when accounting for age and breast cancer stage. In the 15% of patients who died over a 30-month period, breast cancer was the cause of death in 51%, heart disease in 17%, and previous cancers in 8%.[13] Patients 65 to 74 years of age in this study had a median of about three comorbidities, those 75 to 84 years had a median of about four, and those 85 years and older had a
median of five. In another study of 936 women 40 to 84 years of age with breast cancer, patients with three or more of seven selected comorbidities had a 20-fold higher rate of mortality from non-breast cancer causes and a four-fold higher rate of all-cause mortality compared with those without any comorbidity.[14] A Surveillance Epidemiology and End Results (SEER)-based trial with a 28-year follow-up showed that for women 70 years and older, death from non-breast cancer causes was noted in more than 80% of those with node-negative tumors, in about 60% of those with node-positive tumors, and even in about 20% of those with metastases.[15] Focusing on comorbidity as a surrogate for life-expectancy as opposed to “chronologic age” is a key aspect of adjuvant therapy decision-making for older patients.

The presence of comorbidities is not the only factor that is important to consider in evaluating our older patients. The Comprehensive Geriatric Assessment (CGA) includes evaluation of functional status, cognition, social support, psychological state, nutritional status, and medication (polypharmacy), in addition to comorbidities, and it can accurately predict morbidity and mortality from cancer.[16] For older cancer patients in excellent health, CGA probably adds little to routine evaluation, but it can be of great value in vulnerable patients, for whom its use can lead to interventions that maintain function and improve quality of life.[17] The scarcity of gerontologists and the time needed for a traditional CGA make it impractical to perform for all older patients. Shorter, validated CGA instruments are now being tested in older cancer patients and hold great promise for screening the increasing numbers of vulnerable elders with cancer who could then benefit from a more detailed CGA.[18-20] These shorter instruments are also being tested to see if they can predict which patients are at greatest risk for treatment-related toxicity. The International Society of Geriatric Oncology (SIOG) has developed useful recommendations for performing CGA.[21]

**Adjuvant Systemic Therapy: General Considerations**

Selection of adjuvant chemotherapy in older patients depends on two main factors: 1) the patient’s stage and the tumor’s biologic characteristics (grade, hormone receptor, and HER2 [human epidermal growth factor receptor 2] status), and 2) the patient’s life expectancy. Historically, nonmetastatic breast cancer treatment was selected on the basis of nodal status and hormone receptor expression, and more recently by HER2 status. Clinical trials and gene microarray studies have suggested that treatment benefit is better predicted based on several defined biologic characteristics.[22] For clinical purposes, breast cancer patients can be divided into three major subgroups: 1) hormone receptor (HR) positive (HR+) and HER2 negative; 2) HER2 positive irrespective of HR status; and 3) hormone receptor negative (HR−) and HER2 negative (“triple-negative” tumors). Estimates of recurrence and the benefits of both endocrine therapy and chemotherapy in these subgroups can be accurately made using Adjuvant! (www.adjuvontonline.com), a web-based program that can also assess the likely effects of age and comorbidity on treatment benefit. A drawback of the current version is that the program lumps all estrogen receptor (ER)-positive patients into one group and does not easily allow for estimating the benefit of trastuzumab (Herceptin) in HER2-positive tumors. A major benefit of the program is that it accounts for life expectancy in estimating the effects of treatment.

**Selection of Treatment in Older Patients With Hormone Receptor–Positive, HER2-Negative Tumors**

This tumor type comprises the largest group of breast cancer patients and makes up approximately 70% or more of breast cancers in elders.[5] Gene microarray studies suggest that these patients include two overlapping subgroups: luminal A tumors that derive a large benefit from endocrine therapy but modest, if any, benefit from chemotherapy, and luminal B tumors that derive some benefit from endocrine therapy and a substantial benefit from chemotherapy. Clinically these groups can be defined by ER and progesterone receptor (PR) expression and tumor grade. For example, luminal A tumors are likely to be those with high ER and PR expression and lower tumor grade (and/or low Ki-67 expression), whereas luminal B tumors have low HR expression and are likely to be intermediate or high grade (and/or have high Ki-67 expression).

At present all patients in this group should first be considered for treatment with an aromatase inhibitor or tamoxifen followed by an aromatase inhibitor.[23] As a rule, patients in this group who have node-negative tumors derive little, if any, benefit from chemotherapy, although genetically based assays will likely identify a small group who will benefit. The potential added value of chemotherapy in patients with HR+/node-negative tumors and perhaps patients with minimal nodal
involvement can be estimated with several gene assays including Onco\textsuperscript{type} DX\cite{24} and MammaPrint.\cite{25} Two large clinical trials testing the value of these assays and more precisely defining chemotherapy benefits when added to endocrine therapy in these patients are now in progress; these are the TAILORx trial in North America (http://www.cancer.gov/clinicaltrials/digestpage/TAILORx) and the MINDACT trial in Europe (http://www.eortc.be/services/unit/mindact/MINDACT_websiteii.asp).

There is more uncertainty regarding the role of chemotherapy in this group for patients with node-positive tumors. Data from the SEER database have suggested minimal benefit for chemotherapy in node-positive, HR-positive patients.\cite{26} The Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis of randomized trials in early-stage breast cancer, however, suggests that some of these patients may benefit from treatment.\cite{27} After 15 years of follow-up, 5 years of tamoxifen therapy in ER-positive patients reduced the annual breast cancer mortality rate by 31\% irrespective of age.\cite{27} Of note was that about 6 months of treatment with an anthracycline-containing regimen was superior to CMF (cyclophosphamide, methotrexate, and fluorouracil [5-FU]) and reduced the annual breast cancer death rate by about 20\% in women 50 to 69 years of age irrespective of tamoxifen use. Unfortunately, only about 1,200 patients 70 years and older were entered into trials comparing chemotherapy vs no chemotherapy, making an accurate assessment of chemotherapy effects in these older patients uncertain. It is likely that node-negative and node-positive patients with substantial comorbidity in this group will not derive any major benefit from chemotherapy.

The benefits of adjuvant chemotherapy in HR-positive patients in the EBCTCG analysis were seen only after extended follow-up, making life expectancy the key issue when considering chemotherapy for HR+/HER2-negative older patients. For patients with remaining life expectancies of 10 years or more and who have a high risk of recurrence even with endocrine therapy, use of nonanthracycline-containing regimens such as docetaxel (Taxotere) and cyclophosphamide (TC) that negate the risk of cardiac toxicity should be considered.\cite{28} This regimen is superior to doxorubicin and cyclophosphamide and likely CMF. For those with very high risk features such as four or more positive nodes, more aggressive taxane-containing regimens should be considered because they provide similar reductions in mortality risk in older and younger patients,\cite{29} though with greater toxicity in elders.\cite{30} Patients with HR+ tumors that involve 1–3 lymph nodes might benefit from having Onco\textsuperscript{type} DX testing, as preliminary data show that chemotherapy is of little to no value in women with low recurrence scores.\cite{31,32}

**Treatment of Older Patients With HER2-Positive Tumors**

Overexpression of HER2 is associated with a higher risk of recurrence and a phenotype that provides a target for trastuzumab therapy. Addition of trastuzumab to chemotherapy in patients with HER2-positive tumors causes a further 50\% proportional reduction in the risk of recurrence and breast cancer death compared with chemotherapy alone.\cite{33,34} Older women with HER2-positive breast cancer should be considered for both trastuzumab and chemotherapy, which is likely to be beneficial in most patients except those with small, HR+, node-negative tumors and life expectancies less than 5 years. Hormone receptor status is important in defining prognosis and those with both HR+ and HER2-positive tumors have a better prognosis than those with HR-/HER2-positive cancers (this latter group having the highest risk of recurrence of any breast cancer phenotype when trastuzumab is not used). Trastuzumab is usually well tolerated but is associated with an age-related risk of cardiac toxicity.\cite{35} Prior to administration of trastuzumab in elders, hypertension should be controlled if present and optimal management of any pre-existing cardiac disease should be instituted. To minimize the risk of cardiac toxicity, non-anthracycline-containing regimens such as docetaxel (Taxotere) plus carboplatin should be considered.\cite{36} This regimen has demonstrated similar efficacy to anthracycline-containing regimens but with minimal risk of cardiac toxicity. Cardiac monitoring is similar for younger and older patients; patients’ left ventricular ejection fraction should be measured every 3 months while they are being treated with trastuzumab.

**Treatment of Older Patients With ER-, PR- and HER2-Negative (Triple-Negative) Tumors**

About 15\% of older patients have triple-negative tumors, a phenotype that confers a major increase in risk of recurrence within 5 years of diagnosis.\cite{11} Except for those with limited life expectancy and
very small tumors, older women with triple-negative breast cancer should be offered chemotherapy.

**FIGURE 2**

Algorithm for Selecting Adjuvant Chemotherapy for Older Patients With Breast Cancer Who Have Estimated Survival Times of at Least 5 Years.

There is no role for endocrine therapy in this setting. The EBCTCG analysis of chemotherapy or not in women with ER-poor tumors showed a 10-year reduction in breast cancer mortality of 6% in women aged 50 to 69 years with older chemotherapy regimens such as CMF.[37] In addition, an analysis of randomized trials of more intensive anthracycline- and taxane-containing chemotherapy regimens in patients with node-positive tumors showed that these more intensive regimens provided the greatest reductions in recurrence in women with HR− tumors.[38]

Another large retrospective review showed that current anthracycline- and taxane-containing regimens provided similar reductions in recurrence and death from breast cancer in both older and younger patients.[39] A recently published trial in those patients aged ≥ 65 years of age that compared capecitabine with standard chemotherapy (either CMF or doxorubicin and cyclophosphamide) showed superiority for standard treatment in improving both relapse-free and overall survival.[40] Of note, an unplanned subset analysis showed that the major benefit for chemotherapy was in patients with HR− tumors. Older patients with triple-negative tumors and cardiac disease should be considered for nonanthracycline regimens in this setting such as docetaxel and cyclophosphamide or CMF.[41,42] Recommendations for systemic adjuvant therapy for each of the groups summarized previously are presented in Figure 2.

**Follow-up and Survivorship**

Follow-up of older women with breast cancer should be the same as for younger patients and should follow the ASCO (American Society of Clinical Oncology) or NCCN (National Comprehensive Cancer Network) guidelines. Older patients, however, require close monitoring of toxicity during chemotherapy treatment, as even low-grade toxicity (for example grade 1-2 neuropathy) can have major effects on function. The vast majority of cancer survivors in the US are older patients, with breast cancer patients being the largest group.[43] Most of these women are likely to die of non-breast cancer causes. For many of these women, however, the oncologist remains the major caregiver. Oncologists should work closely with primary care physicians to make sure that other significant comorbid illness is optimally managed. Older patients should be offered support groups and be included in survivorship programs when available.

**Reference Guide**

**Therapeutic Agents Mentioned in This Article**

- Carboplatin
- CMF
- Cyclophosphamide
Clinical Trials

Older patients are less likely to be enrolled in clinical trials.[44,45] especially adjuvant breast cancer trials. Recent studies indicate that about 30% of accruals to all phase II and III Cancer Cooperative Group trials are patients 65 years and older.[46,47] Increasing age is an independent variable associated with a lower probability for offering breast cancer trials to older patients, yet when offered participation, older patients are as likely to partake as younger patients (about 50% for both age groups).[48] The barriers to trial participation for older patients are numerous and include age bias and concerns about toxicity.[48,49] Another major factor is eligibility criteria; it is estimated that older patients could account for up to 60% of clinical trial participants if organ and physical function exclusion criteria were relaxed.[47] Healthy older women with estimated survivals exceeding 5 years and in generally good health should be offered participation in state-of-the-art phase II and III trials. In addition, trials designed specifically for older but more vulnerable older patients are needed. Further, efforts to predict which older patients are most likely to experience treatment-related toxicity need to be expanded. Incorporation of a brief, primarily self-administered CGA is currently being tested in the Cooperative Group clinical trial setting and may provide a better means for defining loss of function and predicting which older patients are likely to experience major side effects (see CALGB 340401; [www.cancer.gov; CHNMC-06170].[18]

Conclusions

The decision to use adjuvant chemotherapy in older patients and which regimen to use is frequently challenging. Healthy elders with 5 to 10 more years of life expectancy should be managed like younger postmenopausal patients and should be considered for state-of-the-art treatment programs, including clinical trials. Recently developed nonanthracycline regimens are safer than older anthracycline regimens and appropriate for lower-risk older patients for whom chemotherapy is indicated, or in combination with trastuzumab in patients with HER2-positive tumors. For higher-risk patients in good health, newer, more intensive regimens containing both anthracyclines and taxanes are still the treatments of choice. CGA may be of great help in estimating the potential for functional loss in patients with and without recognized comorbidities. Newer, shorter, and mostly self-administered CGAs are likely to help select patients most likely to experience major toxicity. The major barrier to consideration of adjuvant chemotherapy in older breast cancer patients is physician bias. Greater efforts are needed to educate both physicians and patients about life-expectancy issues, as well as efforts aimed at identification of factors other than age that may better predict treatment-related toxicities.

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trial comparing doxorubicin and cyclophosphamide followed by docetaxel with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab in Her2neu positive early breast cancer patients (abstract 52). *Breast Ca Res Treat* 100 (suppl 1): S90, 2006.


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