Systemic Therapy for Older Women With Breast Cancer

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Breast cancer is a common problem in older women. As the number of medical illnesses increases with age and the life expectancy decreases, the benefits of systemic therapy for women with breast cancer become questionable. All women over age 65 years are at high enough risk of breast cancer to consider the risk/benefit ratio of preventive therapy with tamoxifen (Nolvadex) or participation in the Study of Tamoxifen and Raloxifene (STAR) trial. Adjuvant chemotherapy and hormonal therapies for early breast cancer significantly improve disease-free and overall survival; recommendations for their use are based on risk of tumor recurrence. Use of tamoxifen in the adjuvant setting in women with receptor-positive tumors is a relatively simple decision in light of its favorable toxicity profile. The delivery of adjuvant chemotherapy is a more complicated decision, and the patient’s wishes, estimated life expectancy, presence of comorbid conditions, and estimated benefit from treatment should be considered. The primary goal of the treatment of metastatic breast cancer is palliation. We discuss trials specific to older women and make appropriate treatment recommendations. Unfortunately, there is a paucity of data from clinical trials in women over age 70 years. However, because the clinical trial is the primary scientific mechanism for testing the efficacy of a treatment, every effort should be made to enter older women into treatment protocols. [ONCOLOGY 15(3):280-299, 2001]

Introduction

Cancer is a common and more frequent problem in older persons.[1,2] Currently, about 50% of breast cancer cases occur in women aged 65 years and older. Illnesses that were disabling and often fatal in the past are now treated effectively, and people are living longer. Treatments for cancer are also evolving, and prolonging the lives of cancer patients is now possible for many malignancies, including breast cancer.

The incidence of breast cancer in the United States has begun to decrease.[3] Mortality rates have also been decreasing in recent years,[4] and with increased use of mammographic screening, breast cancers are being detected at earlier, more curable stages. Moreover, adjuvant therapies have become more successful, and new drugs (such as the taxanes) have improved response rates and tolerability of therapy for patients with metastatic disease.

Regardless of age, the treatment of breast cancer involves complex decisions about risks vs benefits for each patient. As age increases, the number of comorbidities increases,[2] making the potential risks of systemic therapy greater and the potential benefits smaller. Preventing breast cancer and its recurrence and/or progression, however, becomes more important as we are able to help people with many diseases live longer.

This article will discuss the use of hormonal therapy and chemotherapy in older women. There is no unanimously accepted definition of "older," but most clinicians consider patients aged 65 years and over to be in this category.

Decreasing the Incidence of Breast Cancer

The incidence of breast cancer increases with age.[5] Potential strategies to decrease the risk of breast cancer in the geriatric population include changes in life-style such as increasing exercise, dietary modifications such as following a low-fat diet, and drug therapy with selective estrogen-receptor modulators. The data suggesting that life-style and dietary changes may lower breast cancer risk are controversial and far from compelling. Since most women with breast cancer are likely to die of other causes, exercise and dietary modification are prudent recommendations for most patients, irrespective of breast cancer risk.
At present, the use of selective estrogen-receptor modulators is the most exciting option for breast cancer prevention. These agents include tamoxifen (Nolvadex), raloxifene (Evista), and toremifene (Fareston).[6] Only tamoxifen has been approved by the Food and Drug Administration (FDA) to decrease the incidence of breast cancer. Raloxifene has been approved for the treatment of osteoporosis, and preliminary data suggest that it may also significantly decrease the incidence of breast cancer.[7,8]

**Trials of Tamoxifen**

Three published trials have evaluated the potential preventive benefit of tamoxifen: the National Surgical Adjuvant Breast and Bowel Project Prevention trial (NSABP P-1),[9] the Royal Marsden Hospital chemoprevention trial,[10] and an Italian randomized trial in women who had undergone a hysterectomy (Table 1).[11] The major differences between these trials have been discussed in detail elsewhere.[12] The NSABP P-1 trial was the only one of the three with a large cohort of older women. It showed a 50% reduction in the incidence of invasive and noninvasive breast cancer among women who took tamoxifen.

**NSABP P-1 Trial:** In NSABP P-1, 30% of participants were 60 years of age and older and 6% were over the age of 70 years.[9] Women with a 1.67% risk of developing breast cancer within 5 years were eligible for the trial. All women aged 60 years or older in the United States meet these criteria, irrespective of other risk factors. Tamoxifen lowered the incidence of both in situ and invasive lesions. There was a 55% reduction in the incidence of invasive breast cancer associated with tamoxifen use in older women; the 5-year probability of invasive breast cancer developing in women 60 years of age and older decreased from almost 4% to about 2%.

This effect was limited to estrogen-receptor (ER)-positive invasive tumors; ER-negative tumors were found with similar frequency in the tamoxifen and placebo-treated groups. Risks associated with the use of tamoxifen in older women included a significantly higher incidence of endometrial cancer and thromboembolic events. In addition, tamoxifen use increased the frequency of vasomotor and gynecologic symptoms and problems with sexual function.[13]

**Royal Marsden Hospital Trial:** The Royal Marsden Hospital chemoprevention trial included women at increased risk of breast cancer based on family history.[10] As such, the majority of women in this trial (61%) were younger than age 50 years; women over age 70 years were ineligible. At a median follow-up of 70 months, the use of tamoxifen did not decrease the incidence of breast cancer.

**Italian Trial:** The Italian randomized trial included any woman who had undergone a hysterectomy.[11] Approximately one-third of women in the Italian trial were over age 55 years, and only 11.7% were age 60 or older; women over age 70 were ineligible. No decrease in the incidence of breast cancer was associated with the use of tamoxifen, but women in this trial were at lower risk for breast cancer compared to women in the other two reported trials.

Both the Royal Marsden Hospital chemoprevention trial and the Italian randomized trial allowed women who were taking hormone replacement therapy to participate. In the Italian trial, the rate of breast cancer was lower among women taking hormone replacement therapy plus tamoxifen than in the cohort taking replacement therapy alone (log rank $P = .0216$). This is not currently accepted practice in the United States.

**Trials of Raloxifene**

Raloxifene is another selective estrogen-receptor modulator with a toxicity profile similar to tamoxifen that allegedly causes fewer endometrial changes.[14] In the Multiple Outcomes of Raloxifene (MORE) trial, 7,705 women with osteoporosis were randomly assigned to receive one of two different doses of raloxifene or placebo for 3 years.[8] Participants were primarily white (95%) and over age 62 years (82%). At 40 months of follow-up, women taking raloxifene had 43% fewer vertebral fractures and a 76% lower incidence of invasive breast cancer.

The rate of breast cancer for all arms of this trial was low (10.5 per 1,000 women given placebo and
2.5 per 1,000 women given raloxifene), but the difference was still statistically significant (response rate [RR] = 0.24; 95% confidence interval [CI] = 0.13-0.44). Hormone-receptor-positive tumors were preferentially prevented, and thrombotic events were more prevalent in women receiving raloxifene in this trial as well, but no increase in endometrial cancer was seen.

A second prevention trial (NSABP P-2) comparing tamoxifen with raloxifene, the STAR trial, is underway. Targeted accrual is approximately 22,000 postmenopausal women.

Calculating Breast Cancer Risk

All women over age 60 years were eligible for NSABP P-1 based on their calculated risk of breast cancer. Breast cancer risk assessment is becoming a routine part of general medical care, and many women are reviewing the risks and benefits of "preventive" tamoxifen with their doctors. The risk of developing breast cancer can be easily calculated using the Gail model. An updated version of this risk assessment tool is available on the Internet at http://cancertrials.nci.nih.gov.

Moreover, Gail and his colleagues have recently provided detailed clinical data on how to calculate the potential benefits and risks of tamoxifen therapy, factoring in available epidemiologic data on the risks of thromboembolic complications and endometrial cancer (Table 2).[15] For example, in a 65-year-old white woman with an intact uterus and a thromboembolic risk similar to that of patients in the NSABP P-1 trial, the 5-year risk of invasive breast cancer needs to exceed 7.0% in order for the benefits of tamoxifen therapy to outweigh the risks. The benefits of tamoxifen would outweigh the risks in the same woman who had a hysterectomy and whose risk was 3.5%.

In older women, the preventive benefits of tamoxifen may outweigh the risks, but these women should be counseled about the risks and benefits of preventive tamoxifen. They should also be encouraged to participate in the STAR trial.

Systemic Adjuvant Therapy

Adjuvant chemotherapy and hormonal therapy in early breast cancer significantly improve disease-free and overall survival.[16,17] In older women with hormone-receptor-positive tumors, tamoxifen’s favorable toxicity profile, benefits on bone density and cholesterol levels, and reduction of contralateral cancer risk make its use worthy of consideration. Adjuvant chemotherapy presents a more complicated decision; it is more toxic in the short term and may have less absolute benefit for older women (Table 3). Likewise, the decision to treat older women at low risk for recurrence is difficult.

In the absence of systemic therapy, the 5-year survival of patients with primary breast cancer and histologic evidence of axillary node involvement is approximately 50%, and the rationale for initiating systemic adjuvant therapy to reduce this high recurrence rate is clear.[18] Table 3 lists the statistically significant reductions in recurrence and mortality rates at 10 years after adjuvant tamoxifen or chemotherapy.[16,17] Notably, in the meta-analysis used to derive these data, there were an insufficient number of patients more than 70 years old who had been treated with chemotherapy to make the analysis meaningful.

There is a statistically significant benefit from chemotherapy in women aged 50 to 69 years with node-negative breast cancer; the absolute reductions in recurrence and death rates are 5.7% ± 2.3% and 6.4% ± 2.3%, respectively.[16] The absolute benefit in recurrence and death rates for women in this age group with axillary node involvement was lower but still statistically significant—ie, 5.4% ± 1.3% and 2.3% ± 1.3%, respectively.

Risk of Cancer Recurrence

As in younger women, larger tumor size, the presence of and a higher number of involved axillary lymph nodes, the presence of lymphatic vessel invasion, high histologic grade, negative hormone-receptor status, and a high proliferative rate are the major predictors of disease recurrence.[19] Older women, as a group, may have a lower risk of recurrence. In a study of 274
women aged 65 years and older who were part of a cohort of 1,267 women with locoregional breast cancer, Lyman et al found that the older women were more likely to have early-stage cancer, a lower histologic grade, higher hormone-receptor levels, and lower S-phase fractions.[20] These good prognostic factors inferred a better prognosis; ie, older women experienced a longer time to disease recurrence and a longer overall survival than did younger women.

Likewise, in a study of more than 307,000 breast cancer patients, Diab et al found that there was an association between increasing age at diagnosis and the presence of more favorable biological characteristics.[21] With older age, there were more tumors that expressed steroid receptors, lower proliferative rates, more diploid tumors, more normal p53 genes, and no expression of epidermal growth-factor receptor and c-erbB2. As a group, the observed survival in women with node-negative breast cancer was not different than the expected survival of age-matched women in the general population. Individual prognosticators, however, should be considered for each patient; not every older woman has indolent disease.

Life Expectancy and Comorbidity

A major issue in determining the benefit of adjuvant therapy in older women relates to anticipated survival and the presence of comorbid disease. Estimates of the life expectancy of women who are healthy, of average health, or sick are presented in Figure 1.[22,23] The presence of comorbid disease may not have as great an effect on overall life expectancy as is commonly believed. Welch et al estimated the effect of competing risks on mortality, based on age.[24] As life expectancy diminished with increasing age, the effect of a new, potentially fatal disease had a smaller effect on overall life expectancy (Figure 2).

Fish et al found that among women with breast cancer, those over the age of 65 years have more non-breast cancer-related deaths than those younger than age 65 years (20% vs 3%, \( P < .001 \)).[25] Satariano and colleagues performed several landmark analyses of the effect of comorbidities on mortality in women with breast cancer. In two separate analyses of a population of women with breast cancer, Satariano et al found that comorbidity had an adverse effect on both overall and breast cancer-related survival.[26,27] As the number of comorbid conditions increased, so did the risk of death. Moreover, the number of comorbid conditions increased the risk of death from all causes, independently of age or stage of disease.

After 4 years of follow-up, women with two or more comorbid conditions were 2.2 times more likely than women without comorbid conditions to die from breast cancer (95% CI = 1.13-4.18) after adjusting for other factors.[27] In examining the prognostic significance of individual conditions, it was found that symptomatic heart disease increased the risk of death from breast cancer 2.4 times (95% CI = 1.07-5.52). In another study, women with three or more comorbid conditions had a 20-fold higher rate of mortality from causes other than breast cancer.[2]

Adjuvant Therapy Decision-Making

Two models have been generated to determine the relative benefit of adjuvant therapy and to assist in deciding whether to initiate such therapy in older women. One was an analysis of cost-effectiveness in hormone-receptor-negative, node-negative patients aged 60 to 80 years.[28] For an estimated baseline risk of relapse of 5% per year (39% at 10 years), the model showed that chemotherapy produced only a small survival benefit in older women vs younger women. The cost-benefit ratio of adjuvant chemotherapy was high but within the range of other commonly reimbursed procedures; at age 75 years, the model indicated that chemotherapy was associated with a 1.8-month average gain in quality-adjusted months, and an absolute decrease in risk of relapse at 5 years of 3%, at a cost of $44,400 per year of life saved.

A second study used a Markov model to assist in decisions regarding delivery of adjuvant therapy to older women with primarily hormone-receptor-positive tumors, while considering age, risk of recurrence, and comorbidity.[29] This model evaluated the threshold risk of relapse at 10 years necessary in order for treatment to provide an absolute reduction of 1% in 10-year risk of relapse and an absolute reduction of 1% in mortality risk at 5 and 10 years.
It was assumed that a patient had an ER-positive tumor and had received either 5 years of tamoxifen or standard chemotherapy, the benefits of which were extrapolated from the 1998 overview analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG).[16,17] That earlier analysis showed that the benefits of adjuvant therapy on relapse and mortality diverged widely in older patients; the benefit on mortality was strongly influenced by age and comorbidity.

**Adjuvant Tamoxifen**

The 1998 updated meta-analysis by the EBCTCG of randomized trials initiated before 1990 showed a major benefit for adjuvant tamoxifen in older women.[30] Women of all ages who received 5 years of adjuvant tamoxifen had a significant, proportional reduction in the rates of breast cancer recurrence and death (Table 4). The proportional reduction in breast cancer relapse and mortality were similar for women with node-negative and node-positive tumors.

Patients with ER-positive tumors benefited from tamoxifen, as did women with unrecorded ER status. Women with tumors devoid of estrogen receptors derived no benefit from tamoxifen therapy, regardless of age. Adjuvant tamoxifen is fairly nontoxic and extremely effective. Its use is widely accepted in women with hormone-receptor-positive tumors who have no history of thrombotic events and whose tumor is 1 cm or greater.

**Adjuvant Chemotherapy**

The decision to use adjuvant chemotherapy in older women is more complex. Among the factors that must be taken into consideration are: (1) the risk/benefit ratio of delivering chemotherapy, (2) the risk of cancer recurrence, (3) life expectancy, and (4) the presence of other potentially life-limiting comorbid illnesses.

**Risk/Benefit Ratio of Delivering Chemotherapy:** In the 47 adjuvant chemotherapy trials included in the meta-analysis encompassing approximately 18,000 women, only about 600 (3%) were age 70 years or older.[16] This sample size was not sufficient to determine the benefits of chemotherapy in this age group, although the meta-analysis did show statistically significant benefits in the relapse-free and overall survival of women of all ages (Table 5). The benefits, though, were greater for younger women.

For recurrence, the proportional reductions in risk were smaller in women aged 60 to 69 years (18% ± 4%) than in women under 40 years old (37% ± 7%; trend test: χ² = 17.7, 2p = .00003). A trend for mortality was also seen, with less benefit from chemotherapy for older women. The proportional reduction in risk of mortality for women aged 60 to 69 (8% ± 4%) was smaller than for women less than 60 years old (27% ± 8%; trend test: χ² = 11.6, 2p = .0007). Interestingly, a consideration of deaths that occurred before recurrence found that, in the absence of breast cancer, about 96% of women aged less than 69 years would have survived 10 years from randomization. Chemotherapy, therefore, had little effect on the number of deaths not related to cancer.

The majority of the benefits of chemotherapy were seen within 4 years of therapy, at which time there was a statistically significant benefit in relapse-free and overall survival (Table 5). At 5 or more years of follow-up after chemotherapy, there was no further benefit to treatment in terms of relapse, but there was a further improvement in survival. This implies that the benefits of chemotherapy are greatest in women whose life expectancy is at least 4 years.

Women with hormone-receptor-negative tumors gain substantial benefit from chemotherapy (30% ± 5% reduction in recurrence and 17% ± 6% reduction in mortality). Although still a debated issue, the overview analyses showed that women with hormone-receptor-positive tumors also benefited from chemotherapy, and that the combination of tamoxifen and chemotherapy was significantly better than either modality alone (Table 5).[16,17] With regard to polychemotherapy, the proportional reductions in recurrence and death for women aged 50 to 69 years were 22% ± 4% and 12% ± 4% for chemotherapy vs no adjuvant therapy, and 19% ± 3% and 11% ± 4% for chemotherapy plus tamoxifen vs tamoxifen alone.[16] In addition, for chemotherapy plus tamoxifen vs chemotherapy alone, the proportional reductions in recurrence and death rates in this age group were 52% ± 8% and 47% ± 9%, respectively.[17]
**CMF-Based Regimens:** Which adjuvant chemotherapy regimen should be recommended for older patients remains an important issue. In the meta-analysis, anthracycline-containing chemotherapy was associated with a small but significant further reduction in the risk of recurrence (12% ± 4%) and a marginal reduction in mortality (11% ± 5%, \( P = .02 \)), compared to CMF chemotherapy (cyclophosphamide [Cytoxan, Neosar], methotrexate, fluorouracil [5-FU]). Although these differences were significant, they were small, and data were not generated for benefit across age groups. Non-anthracycline-containing regimens might be preferable in older patients whose risk of anthracycline cardiac toxicity is higher than in younger patients.[31]

Various groups have reported trials of CMF-based regimens added to tamoxifen vs tamoxifen alone in postmenopausal women with hormone-receptor-positive, node-positive breast cancer.[32-34] Only one regimen—standard CMF with oral cyclophosphamide repeated every 4 weeks for three cycles immediately after surgery, given with tamoxifen for 5 years—showed a benefit over tamoxifen alone.[34] The International Breast Cancer Study Group (IBCSG) assessed this regimen in a group of postmenopausal women (aged 35 to 84) with node-positive, primarily (77%) ER-positive breast cancer.[34] At a median follow-up of 60 months, the addition of CMF to tamoxifen significantly improved the 5-year disease-free survival (64% ± 2% vs 57% ± 2%; \( P = .01 \)); the benefit was seen in all age groups. There was no statistically significant benefit in terms of overall survival.

Another analysis of this trial was performed with data divided further, according to age groups, less than 65 years vs 65 years and older, at a median follow-up of 8 years.[35] Not only did the older group have significantly higher grades of toxicity compared with the younger group (\( P = .004 \)), but the older women also received less than their expected CMF dose and had lower 5-year disease-free benefits (for chemohormonal therapy vs tamoxifen: 63% vs 61%, \( P = .99 \), and 61% vs 53%, \( P = .008 \)) from the addition of chemotherapy. There were no significant differences in survival between the treatment groups, either overall or within age groups.

The test for heterogeneity of the CMF effect according to age group, however, was not statistically significant, and the decreased effectiveness of CMF in older women could not be attributed to dose reductions. Older women were at higher risk for diarrhea, cystitis, gastritis, and oral mucositis. This trial included relatively few women over age 65 (\( n = 76 \)), and the effectiveness of adjuvant CMF in the elderly is still under question.

A report by Colleoni and coworkers, however, supports the higher toxicity rate of CMF in older women.[36] These researchers reported on CMF-related deaths that occurred among 6,926 patients included in IBCSG trials I through IX.[36] All patients were prescribed the same regimen of CMF using oral cyclophosphamide, except for the preoperative chemotherapy group who were given all three drugs intravenously. Among 3,653 patients aged 50 years or less, 3 (0.8%) died; among 2,728 patients aged 51 to 64 years, 7 (0.26%) died (\( P < .0001 \)). Pulmonary embolism was the most common cause of death (5 patients). All postmenopausal patients in the series received either concomitant tamoxifen or tamoxifen after completion of CMF.

**Doxorubicin-Based Chemotherapy:** Another study of short-term therapy in hormone-receptor-positive, node-positive breast cancer found benefit from a short course of adjuvant doxubicin-based chemotherapy.[37] The NSABP B-16 trial showed that short-term chemoendocrine therapy using doxorubicin and cyclophosphamide (four courses) combined with tamoxifen was superior to tamoxifen alone in patients ≥ 50 years of age with hormone-receptor-positive breast cancer.[37] At 3 years of follow-up, disease-free survival (84% vs 67%; \( P = .0004 \)) and overall survival (93% vs 85%; \( P = .04 \)) were better with AC (doxorubicin [Adriamycin], cyclophosphamide) plus tamoxifen than with tamoxifen alone. Patients receiving doxorubicin and cyclophosphamide experienced little hematologic toxicity, but alopecia and protracted vomiting requiring antiemetics were common. There was also no significant increase in major cardiac toxicity with doxorubicin.

**Adjuvant Epirubicin:** Epirubicin (Ellence) alone as adjuvant therapy may be another viable option for older women. The International Collaborative Cancer Group reported benefit in terms of relapse-free survival from the addition of epirubicin to tamoxifen in postmenopausal women (median age was 59 in the epirubicin/tamoxifen arm and 60 in the tamoxifen alone arm, range: 39-75) with
node-positive breast cancer.[38] Estrogen-receptor positivity was 63% in the epirubicin/tamoxifen arm and 67% in the tamoxifen alone arm. The study compared epirubicin (50 mg/m$^2$ IV on days 1 and 8 every 4 weeks for six cycles) plus tamoxifen (20 mg/d starting within 1 month of surgery and continuing for 4 years) vs the same schedule of tamoxifen alone.

At a median follow-up of 5.7 years, the reduction in the rate of recurrence associated with the addition of epirubicin was 27.9% (SD = 12.3%, $P = .023$). Survival was similar for the two treatment groups ($P = .46$). Toxicity was more pronounced with the addition of epirubicin, but treatment was generally well tolerated and the incidence of severe toxicity was low. Of 303 women in the epirubicin arm, two developed congestive heart failure vs none in the tamoxifen alone arm ($P = NS$). Thrombotic events occurred in nine patients, and eight of these were in the epirubicin/tamoxifen arm (log rank test = 4.01; df = 1, $P = .045$).

**Summary of Recommendations for Adjuvant Therapy**

The recommendations for adjuvant therapy in women over 70 years of age are presented in Table 6; these represent the consensus of experts participating in the St. Gallen Breast Cancer Conference in 1992[39] and are not substantially modified by the 1998 overview.[16,17] In women over age 70 years, particularly women ≥ 75 years and those with significant comorbid disease, the physician and patient must carefully weigh the benefits and risks of adjuvant therapy, especially chemotherapy.

**Treatment of Metastatic Breast Cancer**

Despite advances in therapy for breast cancer, metastatic breast cancer remains incurable, and all systemic therapy should be considered palliative. The mean survival for patients with metastatic breast cancer is 18 to 24 months, with a range extending from a few months to many years.[40,41]

**Endocrine Therapy**

The treatment strategy we recommend for older women with metastatic breast cancer is outlined in Table 7.[42-47] Endocrine therapy should be considered as initial treatment for all older patients with metastatic disease. For those with hormone-receptor-positive tumors, endocrine therapy should be continued until disease progression; for responding patients or those with slowly progressing metastases, several endocrine agents should be tried in succession.

Patients in whom disease progresses on endocrine therapy after prolonged periods of remission or stable disease (i.e., 6 months or longer) should be observed for withdrawal responses. Older patients with receptor-negative tumors who are minimally symptomatic should be considered for at least one trial of endocrine therapy. In this population of patients, responses approaching 20% have been observed by some investigators.[48]

**Chemotherapy**

Strategies for the selection of chemotherapy in older patients are also outlined in Table 7.[42-47] Retrospective studies (and some prospective phase II trials) have shown that standard chemotherapy regimens are well tolerated by older patients.[49-51] Older patients may experience slightly more hematologic toxicity (but episodes of febrile neutropenia are uncommon), as well as more GI toxicity in the form of mucositis (but not nausea and vomiting), and may be at greater risk of anthracycline-related cardiac toxicity.[35,52-54] The response rates to standard chemotherapy regimens for metastatic breast cancer are also similar in younger and older women who are in reasonably good health.[49,50,53,55,56]

Detailed reviews of the pharmacology of chemotherapeutic agents in older patients have been published recently.[52,57] Most cytotoxic agents are metabolized in the liver, and only patients with major liver function abnormalities have an increased risk of toxicity, especially with anthracyclines or taxanes.
Methotrexate excretion is dependent on renal function; hence, creatinine clearance should be obtained. Gelman and colleagues modified methotrexate dosage in a CMF regimen on the basis of renal function in older women with advanced breast cancer, without compromising the drug’s therapeutic effect.[55]

The severity and duration of myelosuppression is somewhat more severe in older patients but has not resulted in major differences in mortality related to neutropenia, sepsis, or bleeding.[50,56] Nausea and vomiting may be less frequent in older patients,[54] and psychosocial adjustment to chemotherapy appears better in older rather than younger women.[58]

Chemotherapeutic agents used to treat metastatic breast cancer include anthracyclines, such as doxorubicin and epirubicin; mitoxantrone (Novantrone), an anthraquinone; the taxanes, paclitaxel (Taxol) and docetaxel (Taxotere); alkylating agents, such as cyclophosphamide and melphalan (Alkeran); antimetabolites, such as 5-FU, capecitabine (Xeloda), and methotrexate; and vinorelbine (Navelbine). Recent studies support the use of sequential single-agent therapy for metastatic breast cancer because this strategy is generally less toxic and yields survival rates similar to those achieved with multiagent regimens.[59-61]

**Toxicity of the Anthracyclines:** The cardiotoxicity of the anthracyclines, especially doxorubicin, remains a concern in older patients.[31] The risk of anthracycline-related cardiotoxicity does not seem to be higher in otherwise healthy older women. In one series, deaths due to cardiopulmonary causes were noted in 6% of women over the age of 65 years, compared with 5% of women aged 50 to 64 years.[56] Another retrospective review with 16.8 years of follow-up determined the cumulative probability of developing doxorubicin-induced congestive heart failure in women aged 50 to 64 years and those over age 65 years.[62] The rate of doxorubicin-induced congestive heart failure was similar in the younger and older groups—33/528 (6%) and 13/144 (9%), at cumulative doses of 410 mg/m² and 400 mg/m², respectively.

In a report from the same institution, time to progression, and overall survival in older and younger women treated with doxorubicin-based chemotherapy were also similar.[56] These trials indicate that for generally healthy older women, anthracyclines do not pose a major cardiac risk. More recently, liposomal preparations of anthracyclines have been used in this setting with response rates similar to those achieved with conventional anthracycline treatment and with almost no cardiac toxicity.[63] Nevertheless, the left ventricular ejection fraction should be measured prior to administering anthracyclines to older persons.

**Mitoxantrone Dose:** Repetto et al administered escalating doses of mitoxantrone (8, 10, 12, 14 mg/m²) every 21 days as first-line therapy for locally advanced or metastatic breast cancer in 13 women with good performance status who were older than age 70 years (median age: 73, range: 70-80).[64] Pharmacokinetic studies showed that there was a linear relationship between the administered dose of mitoxantrone and mitoxantrone exposure (ie, the area under the concentration-time curve, or AUC) in the plasma (r = .856, P < .001). At a dose of 12 mg/m², the peak level of mitoxantrone in the plasma was 839 ± 134 mg/L, the AUC was 0.73 ± 0.12 mg/L h, and the half-life was 0.15 ± 0.03 hours. These pharmacokinetic parameters were similar to those reported previously in the literature for conventional IV administration of mitoxantrone.[65]

After four cycles of treatment, a significant decrease in bone marrow cellularity (P = .0067) and hematopoietic progenitor cell content (ie, burst-forming units-erythroid [BFU-E], P = .0077) was observed. There was also a large, but not statistically significant, decrease in circulating hematopoietic progenitor cells (colony-forming units-granulocyte-macrophage [CFU-GM]), and this decrease was still present 8 to 12 months after termination of treatment. Treatment was generally well tolerated. No febrile events were reported, and the blood count of all patients recovered within 1 week. No clinical or subclinical cardiotoxicity (≥15% reduction in left ventricular ejection fraction by echocardiogram) was seen.

**Vinorelbine as First-, Second-, or Third-Line Therapy:** There have been two reports demonstrating acceptable tolerability of vinorelbine in older women with metastatic breast cancer.[66,67] A study of vinorelbine as first-, second-, or third-line therapy in women older than 65 years with metastatic breast cancer was conducted by Sorio and coworkers.[68] No alterations in the
pharmacokinetics were observed in this age group in comparison with younger patients. With an initial dose of 30 mg/m² administered on days 1 and 8 every 3 weeks, responses were seen in 6 of 20 evaluable patients despite a relatively low dose intensity (67%). Severe neutropenia occurred in 37% of patients; other toxicities were acceptable.

Vogel and colleagues reported a prospective phase II multicenter study that evaluated the safety and efficacy of vinorelbine as first-line chemotherapy for advanced breast cancer in women ≥ 60 years old.[67] The initial weekly dose of vinorelbine was 30 mg/m², with a median dose intensity of 20.6 mg/m². Doses were delayed during the first course in 71% of patients (a median of two dose delays per patient).

The objective response rate in this study was 38% (95% CI: 24%-51%) with two (4%) complete responses and 19 (34%) partial responses.[67] The major dose-limiting toxicity was hematologic, which was primarily manifested as granulocytopenia without neutropenic fever. At least one episode of grade 3/4 granulocytopenia occurred in 80% of patients, lasted a mean of 9 days, and occurred at week 3 in 49% of patients.

In patients with HER2-positive tumors, trastuzumab (Herceptin) is associated with a response rate of approximately 15%, with higher response rates seen in patients with strong HER2 positivity.[45,69] Trastuzumab is also effective when combined with chemotherapy either a taxane[46,70] or vinorelbine.[47] Cardiac function must be monitored in older patients receiving trastuzumab, as it has been associated with myocardial dysfunction.

Supportive Therapies

Supportive treatments such as pamidronate (Aredia) and erythropoietin should be considered, although they have not been specifically studied in older patients. For patients with anemia, weekly doses of erythropoietin starting at 40,000 U have been shown to correct the anemia and improve quality of life.[42] The bisphosphonate pamidronate, given monthly, has been shown to decrease the rate of bony complications (eg, fractures, pain, hypercalcemia) in women with primarily lytic bone metastases.[43,44]

Clinical Trials in Older Women

Clinical trials have led to major changes in the treatment of cancer, but persons over age 65 years are significantly underrepresented in clinical trials.[71,72] The reasons posited for the lack of accrual of older persons to clinical trials, as elucidated by Trimble, include: (1) concern that aggressive therapy is considered too toxic for older cancer patients, (2) the presence of comorbid conditions in older persons, such as a prior malignancy, makes them ineligible for many clinical trials, (3) fewer trials are available for older patients, (4) physicians, relatives, and patients have limited expectations for long-term benefits, and (5) there is a lack of financial, logistic, and social support for the participation of older patients in clinical trials.[70]

Cancer and Leukemia Group B protocol 9670 investigated possible barriers to the accrual of older breast cancer patients into clinical trials.[73] In multivariate analysis, and after controlling for the number of comorbidities, physical functioning, and disease stage, age was the only factor that significantly influenced whether or not a clinical trial was offered to a patient. However, when older women (≥ 65 years) were offered participation in clinical trials, they were equally as likely as younger women (≤ 64 years) to participate.

Physicians expressed concern about the many issues related to accrual of older women in clinical trials, including transportation needs, the ability of older patients to understand complicated protocols, comorbid conditions that were not excluded by the trial but still might affect the patient's response, toxicity of treatment, and the need for assistance at home during treatment. When asked what might improve accrual of older cancer patients into trials, 42% stated that greater education of the oncologist concerning treatment-related toxicity in the older person would improve accrual, with 58% to 62% also endorsing greater education of family members and patients concerning clinical trials.
Siminoff et al also found that older patients were less likely to be referred for clinical trials for breast cancer.[74] In a large metropolitan region, 147 physicians were interviewed regarding 245 patients. Overall, only 38% of the patients were offered participation in a clinical trial. In exploring the effects of patient characteristics on physicians’ trial referrals, the only factor that predicted a significant chance of referral was the patient’s age. The older the patient, the less likely she was to be referred ($P < .05$).

Surgical and medical oncologists were also significantly more likely to refer patients to clinical trials when they knew which trials the patient was eligible for and if the patient had been involved in the decision to enter a clinical trial ($P < .01$). Oncologists in a university setting, who had formal support from a cooperative clinical trials group, were significantly more likely to refer patients to clinical trials.

Unfortunately, this lack of accrual of older persons to clinical trials decreases our ability to make educated treatment plans for them. Generalizing the results of clinical trials conducted in younger persons to the older geriatric population is questionable. With clinical trials serving as the scientific mechanism for testing treatment efficacy, accrual of older persons to protocols must be improved, not only to determine treatment efficacy in this age group, but also to provide equal access to care.[49,75,76]

**Conclusions**

Breast cancer is a major problem in older women. There are many options available for treatment, both in the adjuvant and metastatic setting, and new and evolving options to decrease the incidence of breast cancer in high-risk patients. Treatment decisions should be based on the risk/benefit ratio for each patient, taking into consideration the patient’s stage, her wishes concerning the goals of treatment, comorbid illnesses, and estimated life expectancy.

The prospect of preventing breast cancer is exciting. Each woman should discuss the risks and benefits of tamoxifen in this role with her physician. Recommendations for adjuvant therapy are based on risk of tumor recurrence. The decision to employ adjuvant tamoxifen in receptor-positive patients is relatively simple because of tamoxifen’s favorable toxicity profile.

Chemotherapy, even though it is more toxic, offers a clear benefit to selected older women. Decisions regarding the use of adjuvant combination chemotherapy in older women should be based on the estimated life expectancy, comorbid illnesses, and estimated benefit for each woman. Treatment of metastatic breast cancer is similar in all age groups and should be aimed at the palliation of symptoms and preservation of functional quality of life.

**References:**


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