Breast Cancer in the Elderly

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ABSTRACT

Screening and adjuvant postoperative therapies have increased survival among women with breast cancer. These tools are seldom applied in elderly patients, although the usually reported incidence of breast cancer is close to 50% in women 65 years or older, reaching 47% after 70 years in the updated Surveillance, Epidemiology, and End Results (SEER) database. Elderly breast cancer patients, even if in good medical health, were frequently excluded from adjuvant clinical trials. Women age 70 years who are fit actually have a median life expectancy of 15.5 years, ie, half of them will live much longer and will remain exposed for enough time to the potentially preventable risks of a relapse and specific death. In the last few years, a new concern about this issue has developed. Treatment now faces two major end points, as in younger women: to improve disease-free survival in the early stages, and to palliate symptoms in advanced disease. However, in both settings, the absolute benefit of treatment is critical because protecting quality of life and all its related aspects (especially functional status and independence), is crucial in older persons who have more limited life expectancy. Furthermore, the new hormonal compounds (aromatase inhibitors) and chemotherapeutic drugs (capecitabine, liposomal doxorubicin), are potentially less toxic than and equally as effective as older more established therapies. These new treatments bring new challenges including higher cost, and defining their benefit in elderly breast cancer must include an analysis of the cost/benefit ratio. These issues emphasize the urgent need to develop and support clinical trials for this older population of breast cancer patients both in the adjuvant and metastatic settings, a move that will take us from a prejudiced, age-based medicine to an evidence-based medicine.

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INTRODUCTION

Although breast cancer is extremely common in elderly women, there is substantial evidence that older women are less likely to receive standard care for their disease.1-4 This undertreatment has been linked to higher rates of breast cancer recurrence and mortality, especially in the oldest group of patients.8 Relatively few elderly patients are accrued in clinical trials. Barriers to accrual of elders include “physician bias” based on the fear that the patient will not tolerate or will not benefit from the treatment and “patient and family members bias” based on the belief that treatment is not worthwhile or is too toxic.

The choice of an adjuvant treatment is particularly difficult because the oncologist has to balance the benefits of treatment on lowering the risk of recurrence with other important factors that are more common in the elderly population, such as natural life expectancy and a greater risk of toxicity linked to a particular treatment. Many studies of breast cancer biology show that older women are more likely to have estrogen receptor (ER)–positive tumors that result in an endocrine-responsive disease5 and, hence, a lesser role for chemotherapy. The presence of other favorable biologic characteristics as well as concurrent comorbid illnesses that represent potentially competing causes of mortality7 must also be considered as to identify those women who are unlikely to die of breast cancer and for whom an abstention from adjuvant treatment may be the best management option. Until recently, only a few trials specifically evaluated problems related to the use of chemotherapy in older patients. In fact, in previous clinical trials that did not have an age limit for eligibility (usually 65 or 70 years in many trials), only very healthy elderly women were treated; extrapolation of data from these trials to the entire elderly population must be done with caution because the results only apply to very “fit” patients. As older and younger women with operable breast cancer have a similar prognosis, elders have a higher rate of metastasis at diagnosis,9 further evidence of the different biologic behavior of breast tumors in elderly. These differences lead to challenging...
Although breast cancer presentation in an older woman may occur at a more advanced stage, both clinical and pathologic data are consistent with a less aggressive disease in elders. Studies of breast cancer biology, deriving from large databases such as the San Antonio and SEER programs show that older women are more likely to have ER-positive tumors that result in an endocrine-responsive disease.6–10

The results of the largest biologic study, confirming the clinical impression of a more indolent disease and a favorable outcome in the elderly, were reported by Diab.6 These data were recently confirmed by analyses of two large Italian databases.13,14 These analyses showed that elderly women had a more favorable biologic phenotype as demonstrated by lower rates of tumor cell proliferation, a lower expression of the human epidermal growth factor receptor 2 (HER2), a higher content of ER and/or progesterone receptors (PgRs), a higher frequency of diploidy, a lower frequency of p53 accumulation, and, most important, a better outcome. A similar favorable biologic profile was reported in 146 patients older than 75 years that were part of a cohort of patients from the European Institute of Oncology. In this older group, tumor stage at diagnosis was more a favorable outcome than in patients younger than 65 (PT4, 6.7% vs 2.4%; and involved axillary lymph nodes, 62.5% vs 51.3%; in older and younger patients, respectively).15

This is in agreement with data on 2,136 elderly women who were treated with surgery without adjuvant systemic therapy at the University of Chicago (Chicago, IL) in a period of 60 years.16 The authors showed that even if the biologic behavior is similar to that of younger patients, the ultimate likelihood of developing distant metastases was significantly higher among elderly women.

Of note, 20% to 30% of older patients have an aggressive biologic phenotype characterized by negative ER and PgR expression for which endocrine treatment is inadequate. The use of chemotheraphy should be discussed for these patients whatever in the adjuvant or metastatic setting. Prognostic factors retain the same significant value in older and younger postmenopausal patients. Tumor size, lymph node status, histologic grade, the presence or absence of vascular invasion, ER and PgR status, HER2 status, and the tumor proliferative rate are all important and need to be considered in the calculation of the risk of a relapse.

**ASSESSMENT OF OLDER PATIENTS**

A likely reason for nonparticipation in screening programs and clinical trials is the number of coexisting illnesses, which tend to increase with advancing age.

Life expectancy at 70 years may range from 15.5 years in healthy women to almost half that (8.6 years) in women who have significant comorbidity such as a previous myocardial infarction.19 Ravdin et al20 have developed a computer program (www.adjuvantonline.com) that accurately estimates the benefits of endocrine therapy, chemotherapy, or both according to standard clinical and biologic variables and age. In this program, life span is estimated on the basis of age, and the clinician can also estimate the effects of comorbidity and its effect on relapse-free and overall survival. Yancik et al21 found that comorbidity was the main factor limiting the ability to obtain sufficient prognostic information with the consequence of an increase of the risk of death from causes other than breast cancer.

The main challenge remains how to identify those patients who appear to be healthy, but who are at higher risk of functional decline or even death.

The Comprehensive Geriatric Assessment (CGA) is a tool initially studied by geriatricians that helps to identify frail patients who may be best treated by supportive care alone.22 Unfortunately, CGA is rarely obtained by medical oncologists. There is strong evidence that interventions based on CGA improve function and reduce hospitalizations in elders, but it is still controversial whether interventions based on CGA can improve survival and whether CGA is cost effective. The need for more rapid and equally effective tests is an important part of the ongoing research. Shorter, less costly CGA screening tools exist and have been successfully used in different settings, but the expert Task Force of the International Society of Geriatric Oncology (SIOG) could not recommend any one tool for general use.23

**TREATMENT**

**Surgery**

Most older women tolerate breast-conserving surgery and mastectomy as well as younger patients do,24 and advanced age, per se, is not a risk factor for surgical treatment. Operative mortality rates in the range of 1% to 2% were reported in old studies using older anesthesia procedures.25,26 With the progress in anaesthesiology during the last decade, the surgical mortality rate in older women with breast cancer in reasonable health is almost negligible.27 The main factor influencing surgical morbidity and mortality remains the presence of coexistent diseases and not age.28

Axillary surgery has historically had an established role in the staging and cure of breast cancer, but the recent and widespread use of sentinel node biopsy has led to questions concerning its continued use. Axillary dissection prolongs the time of surgery and anesthetic period and has a greater complication rate than does sentinel node biopsy. Moreover, the magnitude of the therapeutic benefit of removing axillary lymph nodes is now debated.29 A trial was conducted by the

therapeutic choices and make it difficult to apply the same treatment guidelines to older and younger populations.

**SCREENING**

Many nations have an upper age limit of 70 years for screening for breast cancer. However taking into account the biologic and clinical presentation of breast cancer in the elderly, the positive predictive value of mammography, and the sensitivity of mammography, which increases with age, some public health experts have suggested that the screening invitations might be usefully extended up to age 75 years, at least for those women in good health.17,18 Because prospective randomized trials of screening are unlikely to be performed in this period of economic constraints, a reasonable recommendation would be to offer yearly mammography to older women without severe comorbidities and an estimated life span of at least 5 years. This would allow for the collection of data that would further define the cost-effectiveness of screening in this older population and lead to more evidence-based health care policy decisions.
International Breast Cancer Study Group in women older than 60 years with clinically node-negative, operable breast cancer, compared outcome with axillary clearance versus no axillary dissection. All endocrine-responsive patients also received 5 years of tamoxifen. Unfortunately, because of a slow accrual rate, the primary end point was revised to assess differences in quality of life. The results of this trial based on the 447 patients enrolled (median age in both arms, 74 years)\(^9\) are reassuring and show a very low local relapse risk (2% at median follow-up of 5 years) in endocrine-responsive patients treated with tamoxifen. The trial further questions the role of standard axillary dissection as a routine practice in this elderly population.

**Primary Medical Treatment**

Nonrandomized studies published in the early 1980s suggested that tamoxifen was as effective surgery as the unique primary treatment of operable breast cancer in elderly patients and suggested that tamoxifen could be employed instead of surgery for most patients. Randomized trials subsequently showed similar results, but drew different conclusions. These randomized trials included designs in which patients were randomly assigned to receive either tamoxifen alone or surgery alone, or tamoxifen alone versus surgery followed by tamoxifen. The main studies are summarized in Table 1.

The first study, from St Georges Hospital,\(^31\) concluded that surgery should be reserved for tamoxifen failure. The Nottingham Hospital study\(^32\) showed that women treated with surgery plus tamoxifen had a 70% relapse-free survival compared with 47% for those treated with tamoxifen alone. The randomized trial of the Elderly Breast Cancer Working Party showed that quality of life and survival were not similar for patients treated with tamoxifen alone or surgery alone, but that more women treated with tamoxifen required a change of treatment, usually because of local or locoregional progression.\(^33\) A joint analysis of Italian and United Kingdom trials (Group for Research on Endocrine Therapy in the Elderly and European Organisation for Research and Treatment of Cancer 10851 trials)\(^34\) showed that disease-free survival and time-to-progression rates were worse in women treated with tamoxifen alone, whereas breast cancer–related and overall survival rates were similar for both groups.

Extensive data strongly suggest that disease-free survival and quality of life are the principal end points of breast cancer treatment in the elderly population. Quality of life may differ greatly whether a woman lives with or without a growing cancer, and symptomatic local progression or relapse has to be considered when deciding which initial therapy is optimal. We believe that surgery remains the standard of care for the treatment of early breast cancer and that alternative therapies should be reserved for those patients too ill or frail for surgery, or those who refuse it. Our conclusions are supported by a retrospective review of the Geneva Cancer Registry on the prognostic impact of refusing surgery; women who refused had a significantly shorter survival, with a 2.1-fold increased risk of dying of breast cancer compared with women who elected surgery.\(^35\)

Finally, and most convincingly, a Cochrane review\(^35\) concluded that primary endocrine therapy was inferior to surgery (with or without endocrine therapy) for the local control of breast cancer in medically fit older women, even if the surgery does not result in a significantly better overall survival. This suggests that primary endocrine therapy should be offered only to women with ER-positive tumors who are unfit for or who refuse surgery. With the advent of the new generation of aromatase inhibitors, agents more effective than tamoxifen in both the adjuvant and metastatic setting,\(^36\)–\(^39\) especially in older women and/or in those who have an overexpression of c-erbB2,\(^40\) primary endocrine therapy may need to be reassessed. It is unlikely, however, that these agents will be as effective as initial surgery in healthy patients.

**Radiotherapy**

Postoperative radiotherapy decreases local recurrences after breast-conserving surgery.\(^41\) A randomized Italian trial in 579 women with tumor smaller than 2.5 cm,\(^42\) compared quadrantectomy axillary dissection and breast radiation with the same surgical approach without radiotherapy. The number of intrabreast tumor recurrences were significantly higher (23.5%) in nonirradiated patients in comparison with those who received radiotherapy (5.8%). However, the difference among groups was greatest in women up to the age of 45 years, tending to decrease with increasing age and showing no apparent difference in women older than 65 years. Moreover, overall survival for both groups was similar (\(P = .326\)), although a limited survival advantage was seen in node-positive women.

Two recent trials evaluated the role of breast radiation in older women. A Canadian trial included patients older than 50 years with tumors up to 5 cm (T1 to T2). The local recurrence rate at 5 years was 0.6% in patients treated with surgery, tamoxifen, and breast radiation versus 7.7% in the group treated with surgery plus tamoxifen only (\(P < .001\)).\(^43\) A second trial was limited to breast ER-positive tumors up to 2 cm (T1 N0) in women older than 70 years.\(^44\) Patients receiving breast radiation had a 3% lower risk of breast recurrence; hence, there may be a group of women at sufficiently low risk for local recurrence who do not require breast irradiation. At the present time, however,

<table>
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<th>Trial</th>
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<td>GRETA(^34)</td>
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<td>EORTC 10851(^34)</td>
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<td>10</td>
<td>9</td>
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</table>

Abbreviations: BC, breast cancer; Surg, surgery; TAM, tamoxifen; CRC, Cancer Research Campaign; GRETA, Group for Research on Endocrine Therapy in the Elderly; EORTC, European Organisation for Research and Treatment of Cancer.
breast irradiation after breast-conserving surgery remains the standard of care. Even using modern high-energy radiation, one must carefully balance life expectancy and eventual serious adverse effects (usually <1%), including radiation pneumonitis, pericarditis, risk of coronary vessel damage, and rib fractures, when recommending postoperative radiotherapy for older women. A recent report evaluating the effect of radiotherapy omission on survival in older breast cancer patients treated with breast-conserving surgery highlights the fact that some of the studies that suggested no impact on survival but only an increased risk of local failure might have had a too-short follow-up. These authors also noted that the frequency of radiotherapy omission significantly increased with advancing age (7%, 9%, and 26% in age 50 to 64, 65 to 74, and ≥75 years, respectively; P < .0001), and that omission of radiation was associated with significantly reduced local control, breast cancer–specific survival, and overall survival. These data suggest that inadequate local therapy is associated with reduced survival in elderly women treated with breast-conserving therapy. Another recent study derived from the SEER database focused on the effects of comorbidity on the potential benefits of radiation therapy in 8,724 women 70 years and older treated with breast-conserving surgery for small, lymph node–negative, ER-positive (or unknown) breast cancer. The authors showed that radiation therapy was most likely to benefit those ages 70 to 79 years without comorbidity, but not those 80 years or older with moderate to severe comorbidity. A population-based cohort study showed that after mastectomy, chest-wall radiation improved survival in women 70 years or older with high-risk breast cancer (T3-T4, N2-N3). Ongoing trials such as PRIME (Postoperative Radiotherapy in Minimum-Risk Elderly) are addressing issues of local control, morbidity, and quality of life in older, low-risk patients and will help define which patients do not benefit from radiotherapy. Intraoperative radiotherapy (IORT), which consists of a single-fraction treatment targeted to the tumor bed, immediately after the lesion removal and which has been shown to yield results that compare favorably with those observed with conventional external radiotherapy, seems an approach extremely appealing, especially in the elderly, for whom the risk of recurrence outside the index quadrant is very low.

**Hormonal Treatment**

Adjuvant setting. The 2005 St Gallen meeting classified early-stage breast cancer as either endocrine responsive, endocrine nonresponsive, or endocrine responsive uncertain (uncertainty was defined as <10% of tumor cells hormone receptor–positive, and ER-positive but PgR-negative tumor, a tumor with a high proliferative index or a HER2/neu positive tumor). Until recently, tamoxifen has been the most commonly used hormonal therapy for endocrine-responsive patients in adjuvant setting, with data supporting a 5-year course rather than shorter periods. The 2000 overview of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) confirmed the benefit of tamoxifen after 15 years of follow-up for all patients with hormone receptor–positive tumors, a finding that is particularly important for elderly women, of whom more than 80% are likely to be ER positive and endocrine-responsive. Serious toxicities of tamoxifen include endometrial carcinoma and thromboembolic disease, and remain in the range of 1%. Older patients who have small (<1 cm), node-negative tumors or have serious comorbidity with an estimated survival less than 10 years are unlikely to derive any survival benefit from tamoxifen or other endocrine treatments.

Of note, in a recent update of International Breast Cancer Study Group trial IV, only 1 year of tamoxifen resulted in a significant and prolonged improvement in disease-free and overall survival that carried over for 21 years in the elderly population. The advent of the new aromata inhibitors (anastrozole, letrozole, exemestane) has opened a new era. Data on 9,366 patients accrued in the ATAC trial (Arimidex, Tamoxifen, Alone or in Combination as adjuvant therapy in postmenopausal women) were initially published in 2002 and recently updated. The results show a disease-free survival advantage for anastrozole over tamoxifen, with a hazard ratio (HR) of 0.83 (P = .005) and a longer time to recurrence (HR, 0.74; P = .0002) in hormone receptor–positive patients. Compared with tamoxifen, anastrozole treatment was associated with fewer thromboembolic events, and ischemic cerebrovascular events, and less endometrial cancer, vaginal bleeding, hot flushes, and vaginal discharge; arthralgia, myalgia and bone loss were more common with anastrozole. The median age of these patients was 64 years, but no data are available evaluating outcome and tolerance in elderly patients.

The Breast International Group (BIG) 1-98 trial compared letrozole with tamoxifen and recent data from 8,010 patients (median age, 61 years) at a median follow-up of approximately 2 years (25.8 months) showed a significant benefit in favor of letrozole (2.6% reduction in event-free survival at 5 years with an HR of 0.8; P = .003). This benefit was seen for local failure, distant recurrence, and contralateral breast cancer. An analysis of adverse events based on 7,949 patients who received at least one dose of trial treatment showed similar toxicity for letrozole to that noted for anastrozole in the ATAC trial, with fewer thromboembolic events but more frequent bone fractures. Cardiovascular events were more common with letrozole, and further follow-up of trials involving aromatase inhibitors is needed. An evaluation of the risks and benefits of treatment in elderly patients in the BIG 1-98 trial is now in progress. The optimal strategy for the use of endocrine therapy in postmenopausal patients, including elderly patients, remains controversial. An American Society of Clinical Oncology (ASCO) Technology Assessment Group recommended that aromatase inhibitors be included in the treatment of postmenopausal women with ER-positive breast cancer, but this group did not define the optimal timing or duration of aromatase-inhibitor therapy. Trials of switching to an aromatase inhibitor after 2 to 3 years of tamoxifen showed larger reductions in hazard ratios than did trials comparing tamoxifen and letrozole as initial therapy, raising the question of whether a sequential approach may be a superior approach that reduces the adverse effects of both tamoxifen and aromatase inhibitors, especially in the older group of patients.

Also of note, the use of letrozole after 5 years of tamoxifen showed significant benefit for letrozole in improving event-free survival when compared with placebo, especially in node-positive patents, and this benefit was seen in all age groups. Because bone density decreases with age, older women are at higher risk of osteoporosis and complicating fractures, and in older patients, hip fractures are associated with a high risk of long-term complications as well as excess mortality.

Optimal use of endocrine therapy will require longer follow-up of trials currently in progress as well as yet-unpublished data from the BIG 1-98 for the treatment groups randomly assigned to the sequence of tamoxifen and letrozole or the inverse, and the TEAM (Tamoxifen Exemestane Multinational) trial, which compared exemestane followed by tamoxifen with exemestane alone.
Careful evaluation of concomitant comorbidities and the different spectrum of toxicity of tamoxifen versus aromatase inhibitors (cardiovascular events, lipid metabolism, pre-existing osteoporosis, cognitive functions) has also to be taken into account when recommending adjuvant endocrine therapy in the elderly population.64

Metastatic setting. Most older patients that relapse after a long disease-free interval and have received previous adjuvant treatment with tamoxifen are candidates for treatment with aromatase inhibitors.65 New agents like fulvestrant are also particularly appealing in this setting because of its low toxicity profile.66,67 As the therapeutic window becomes wider with the advent of new hormonal drugs and targeted therapies,68 new options will need to be studied in elderly patients. For example, a randomized phase II trial compared letrozole with or without oral metronomic cyclophosphamide in 114 elderly breast cancer patients.69 Metronomic scheduling of oral cyclophosphamide associated with letrozole yielded a superior response rate (87.7%) compared with letrozole alone (71.9%) in an ER-positive subgroup. Endocrine therapy should be continued for as long as possible in older patients, until their metastases are convincingly refractory to such treatment, delaying the use of chemotherapy.

Bisphosphonates are recommended for all patients with lytic bone metastases and should be part of the treatment irrespective of age. This is true especially in women who cannot be treated with other agents because of poor general health. The choice between the various intravenous and oral forms is still a matter of debate70,71 and is addressed in ongoing trials such as the German ICE (Ibandronic With or Without Capecitabine in Elderly Patients With Early Breast Cancer) study.

Chemotherapy

Adjuvant setting. Among the 23,053 women 65 years or older evaluated in the SEER registry,6 approximately 20% had one to three positive nodes, and a further 15% had four or more nodes involved; 10% to 24% had other poor prognostic factors such as large tumor size, ER negativity, or high S-phase fraction. There is, therefore, a potential population of elderly breast cancer patients with a substantial risk of recurrence who should be considered for adjuvant chemotherapy.

However, little evidence exists about the benefits and risks of systemic chemotherapy in patients older than 70 years. The EBCTCG overview72 clearly shows a lesser proportional and absolute benefit from chemotherapy with increasing age, but only few women age 70 years and older were accrued to these chemotherapy trials (1,224 of 28,764 women; 4.3%), with an even smaller number in those addressing the role of anthracyclines (213 of 14,971; 1.4%). This paucity of data prevents the investigators from making firm conclusions about the benefits of treatment or developing guidelines for the elderly population. Of note, a survival benefit from adjuvant chemotherapy in endocrine unresponsive patients aged 66 years or older, was described by the Memorial Sloan-Kettering Cancer Center Group who evaluated data derived from the SEER cancer registries.73 The authors identified 1,711 women with ER-negative, stage I to III breast cancer treated from 1992 to 1999 and showed a dramatic reduction in the use of chemotherapy with the increase of age (32.3% in 66 to 69 years vs 5.3% in ≥ 85 years; P < .0001). The overall survival probability at 5 years was 62%, after adjusting for the likelihood of receiving treatment. Chemotherapy was associated with a statistically significant 15% reduction in all-cause mortality for this ER-negative elderly population. The survival benefit seen in the entire cohort was largely but not exclusively driven by the benefit shown in node-positive patients. These data are in agreement with those of Giordano et al,74 who evaluated the benefit of adjuvant chemotherapy in patients older than 65 years with stage I to III breast cancer, irrespective of ER status, in the same database. The significant reduction in mortality was confined to older women with ER-negative and node-positive disease (HR, 0.72; 95% CI, 0.54 to 0.96) and maintained in those older than 70 years. They also showed that the use of adjuvant chemotherapy more than doubled during the 1990s, from 7.4% in 1991 to 16.3% in 1999 (P < .0001), with a shift toward anthracycline use. Both of these retrospective analyses are consistent with data from the Cancer and Leukemia Group B (CALGB) and US Breast Cancer Intergroup, which showed that the main benefits from chemotherapy were in the hormone receptor–negative population.75

Despite these major advances in adjuvant chemotherapy treatment, optimal chemotherapy regimens and doses and schedules for elderly breast cancer patients have not yet been defined, and concerns persist regarding the potential toxicity of cytotoxic therapies in elders. In a recent study from the CALGB,76 the efficacy and tolerability of different and progressively more intensive adjuvant chemotherapy regimens in node-positive older patients were analyzed. Although benefits from modern schedules of chemotherapy did not differ across age groups, older patients were found to have a worse overall survival compared with younger patients, mainly because of competing causes of death, and older patients also had a higher rate of treatment-related mortality of 1.5%. Of note among the 6,487 women analyzed, only 542 (8%) and 159 (2%) were older than 65 or 70 years, respectively. The conclusions that older and younger women derive similar reductions in breast cancer mortality and recurrence from current chemotherapy regimens must be taken with caution, as these data were not only derived from a small minority of elderly patients, but, more importantly, they were derived from patients who were highly selected and, therefore, probably not representative of the overall elderly population.

Many factors, such as changes in the pharmacokinetics of drugs, polypharmacy and potential drug interactions, dose reductions, and poor compliance with oral agents, may contribute to increased toxicity from chemotherapy in elderly patients.

Previously, nonanthracycline-containing regimens were preferred in elders because of the fear of anthracycline-induced cardiac toxicity; however, short-duration adjuvant chemotherapy with regimens such as CMF (cyclophosphamide, methotrexate, fluorouracil) showed no significant advantage over tamoxifen in different trials involving older women.77,78

Doxorubicin-based chemotherapy was more effective in the overview analysis. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B–16,79 four cycles of doxorubicin and cyclophosphamide (AC) combined with tamoxifen proved superior to tamoxifen alone. The International Collaborative Cancer Group reported an improvement in disease-free survival with the use of adjuvant epirubicin in a trial of 604 patients.80 The potential benefit of low-dose, less toxic anthracyclines therapy for elderly patients was specifically demonstrated in a French study that enrolled 338 elderly node-positive women over a 10-year period. With a 6-year median follow-up, this trial, which randomly assigned patients to tamoxifen alone or tamoxifen and low-dose weekly epirubicin, showed a significant improvement in disease-free survival that was related to a lower...
rate of locoregional relapse. Unfortunately, this trial was underpowered to conclusively show a benefit for low-dose anthracycline chemotherapy, but the data suggest that further studies of this regimen are indicated, especially in the ER-negative subgroup.

An observational study recently reported at the 2006 ASCO meeting showed that even in healthy women aged 66 to 70 years treated with anthracycline-containing regimens, the rates of congestive heart failure (CHF) were significantly higher than with non-anthracycline-containing regimens (HR, 1.45 for anthracyclines vs others). Of note, there was no reported increase for patients older than 70 years. In a series of 5,575 patients extracted from the SEER database, cardiac toxicity continued to increase through 10 years of follow-up, stressing that identifying and minimizing the late effects of treatment remain extremely important as the number of long-term survivors grows.

A National Cancer Institute–supported randomized trial comparing standard adjuvant chemotherapy (CMF or AC) with the oral agent capecitabine is ongoing for women age 65 years or older with high-risk node-negative and node-positive breast cancer, and other trials recently started in German, British, and IBCSG Groups will help answer many of the questions related to the safety and effectiveness of chemotherapy in elders. Trials ongoing or ready to start are summarized in Table 2.

**Metastatic setting.** All treatment in the metastatic setting is palliative and the goals are to control the cancer, improve any cancer-related symptoms, and maintain or improve quality of life.

Whether to use combination versus sequential single-agent therapy remains an open question for treating women with metastatic breast cancer. Sequential therapy allows for the optimal delivery of single drugs, potentially reducing the risk of toxicities, and maintaining or improving quality of life. Combination therapy is associated with higher response rates and time to progression and also higher toxicity, but not improved survival.

Age is the main risk factor for doxorubicin-related CHF with older patients (> 65 years) showing a greater incidence of CHF after a cumulative doxorubicin dose of 400 mg/m². This cumulative dose is higher than what is delivered with four standard doses of adjuvant treatment, but Li et al have recently shown that the initial concentrations of doxorubicin after intravenous administration are higher in older people because of a decrease in the distribution clearance, related to an alteration in the regional blood flow, and these changes could contribute to age-related doxorubicin-induced cardiotoxicity. In addition, older patients, even healthier ones, are more likely to have underlying atherosclerotic cardiovascular disease and less cardiac reserve.

Many drugs such as idarubicin, capecitabine, taxanes, gemcitabine, and vinorelbine have been studied in elderly patients with metastases and show different response and toxicity profiles compared with younger patients. Capecitabine was studied by Bajetta et al in 73 elderly patients with a median age of 73 years. This study consisted of two phases, each using a different capecitabine dosage. With the standard dose, two patients (7%) had lethal toxicity (one age 75 and one age 80) resulting from grade 4 diarrhea and severe dehydration. At a lower dosage, there was better compliance and an equivalent response rate of 34.9% (95% CI, 21.0% to 50.9%) but three patients discontinued treatment for acute myocardial infarction, CHF, or grade 4 diarrhea. The authors concluded that lower-dose capecitabine was safe and effective in elderly women with metastatic breast cancer. Better response rates were reported by Del Mastro et al using weekly paclitaxel 80 mg/m² for three consecutive weeks every 28 days. Among 41 assessable patients, two complete and 20 partial responses were noted, for an overall response rate of 53.7% (95% CI, 38.7% to 67.9%). This high response rate is probably partly due to the inclusion of patients with locally advanced disease in the trial (stage IIIA/IIIB in nine patients). A CGA was performed as part of this study to see whether CGA assessment would be predictive of toxicity. Unacceptable toxicity was, however, reported in seven (15.2%) of 46 patients assessable for tolerance, and included two toxic deaths resulting from pulmonary embolism and CHF. Five cases of cardiac toxicity, one case of febrile neutropenia, and one severe allergic reaction were also reported. In none of these patients was CGA predictive of these severe and unacceptable toxicities. More recently, a trial performed in women older than 60 years randomly assigned gemcitabine versus epirubicin as first-line chemotherapy. Epirubicin proved superior to gemcitabine for all end points: time to progression (6.1 vs 3.4 months), overall

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<th>Table 2. Ongoing (or pending) Randomized Trials of Chemotherapy As Treatment for Early Breast Cancer in Older Women</th>
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<td><strong>Name of the Trial</strong></td>
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Abbreviations: ER, estrogen receptor; NSABP, National Surgical Adjuvant Breast and Bowel Project; IBCSG, International Breast Cancer Study Group; BIG, Breast International Group; CM, cyclophosphamide, methotrexate; NCI, National Cancer Institute; GCSF, granulocyte colony-stimulating factor; AC, doxorubicin, cyclophosphamide; EC, epirubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, fluorouracil; TAM, tamoxifen.

"HER2 positive patients will compare chemotherapy/anti-HER2 versus anti-HER2 without chemotherapy."
survival (19.1 v 11.8 months) and response rate (40.3% v 16.4%). Three possible gemcitabine-related deaths were reported in patients older than 70 years. Of note, 10 patients discontinued epirubicin treatment because of cardiac events, whereas only one patient discontinued gemcitabine for a cardiac event. Another trial that included pharmacokinetic drug monitoring evaluated low-dose idarubicin (5 mg/d for 21 consecutive days).91 The low-dose idarubicin was well tolerated in these elderly patients but did not demonstrate an improvement in efficacy in comparison with standard schedules. Pegylated liposomal doxorubicin has been clearly shown to cause less cardiotoxicity than standard doxorubicin is currently being tested in elderly women with metastatic breast cancer using two different schedules; an every-4-weeks schedule in fit elderly and a lower-than-standard dose every 2 weeks in sicker patients.

**NEW TARGETED THERAPIES**

New targeted therapies with monoclonal antibodies include trastuzumab, which targets the extracellular domain of HER2 receptor, and bevacizumab which targets vascular endothelial growth factor. These new exciting additions to the medical oncology armamentarium have shown major activity in advanced breast cancer, usually when used in combination with cytotoxic agents like taxanes92,93 or capetitabine. Only a few and highly selected elderly patients have been treated so far. This precludes us from drawing firm conclusions on the use of such agents. There is, therefore, an urgent need to study the use of these agents in elders. Trastuzumab has also shown impressive results in the adjuvant setting but is associated with CHF if administered with anthracyclines.94 Moreover, increased age was a risk factor for a greater incidence of cardiac toxicity. There is also concern about increased risk of vascular events in elders who receive bevacizumab. A pooled analysis of 1,745 patients with metastatic carcinomas (breast, colorectal and non–small-cell lung) treated in five randomized controlled trials showed that the addition of bevacizumab to chemotherapy was associated with an increased risk of arterial thromboembolic events and that history of atherosclerosis and age older than 65 years were independent risk factors.95

Of great interest are recently reported laboratory studies exploring the potential mechanisms for resistance to endocrine therapies. These experiments show crosstalk between growth factor signaling pathways and ER,96 and suggest that combining ER-targeted therapies with growth-factor inhibitors may represent a promising approach for future trials, especially in elderly patients.

**LOOKING AT THE FUTURE**

The new era of molecular biology is likely to Shortly challenge the old era of using clinical variable alone for treatment selection, whether it be surgical staging and axillary dissection or the use of radiation or adjuvant systemic therapy. Currently, stage of disease, tumor grade, hormone-receptor status (ER and PgR), and HER2 status remain the key prognostic factors for determining prognosis and treatment. It is clear, however, that much more work has to be done to define the molecular subclassifications of ER-positive breast cancer.97

The use of microarray technology, which is capable of identifying a limited number of specific genes that can predict disease-free survival, is likely to become a better way to define prognosis and select treatment than are currently used clinical and biologic variables, and is of particular interest and importance for elderly patients. One such assay can generate an accurate prediction of metastases at 10 years in node-negative, ER-positive patients treated with tamoxifen. This assay (OncoType DX, Genomic Health, Redwood City, CA) separates patients into low, intermediate, and high risk based on a 21-gene assay assesses using the polymerase chain reaction. It proved useful in determining the value of adjuvant CMF chemotherapy in the NSABP B-20 trial (node-negative, ER-positive patients randomly assigned to tamoxifen with or without CMF). Only patients with a high-risk recurrence score (> 31) benefited from addition of CMF chemotherapy, with a mean absolute decrease of 28% in the development of distant metastases at 10 years.98 This assay may be particularly useful for elderly patients, but further data are needed. Using gene array technology, a recent study showed a significant agreement among several gene sets that were predictive of recurrence.99 Such studies should eventually be able to provide accurate estimates of the risk of metastases and identify low-risk patients who would derive little to no benefit from chemotherapy.

In conclusion, the explosion in knowledge of molecular biology and the development of targeted therapies is opening a new era for improving cancer treatment. It is essential that elders be included in new trials and that they be offered the best treatments available. All oncologists need to become familiar with the issues and challenges of caring for older patients so we can provide them the best of care.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicated no potential conflicts of interest.

**AUTHOR CONTRIBUTIONS**

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