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New Criteria for Selecting Elderly Patients for Breast Cancer Adjuvant Treatment Studies

SILVIA DELLAPASQUA,[a] MARCO COLLEONI,[a] MONICA CASTIGLIONE,[b] ARON GOLDHIRSCH[a,c]

[a]Medical Senology Research Unit & Division of Medical Oncology, Department of Medicine, European Institute of Oncology, Milan, Italy; [b]International Breast Cancer Study Group (IBCSG) Coordinating Center, Bern, Switzerland; [c]Oncology Institute of Southern Switzerland, Bellinzona & Lugano, Switzerland

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. List the factors that should be considered when choosing the appropriate adjuvant treatment for an elderly women with operable breast cancer.
2. Discuss the possible explanations that account for the underrepresentation of elderly patients in breast cancer clinical trials.
3. Describe the clinical trials that are being specifically conducted in elderly patients with early breast cancer to evaluate different forms of adjuvant treatments.

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ABSTRACT

About 50% of breast cancers occur in women aged 65 years and older, and both the incidence and prevalence of breast cancer among older women are expected to increase in the future. Aging implies a reduction in life expectancy and tolerance to treatments that should be considered in elderly patients with early breast cancer. In fact, treatment options often carry short-term risks and toxicities that might be tempered by long-term survival gains. The choice of adjuvant treatment for elderly patients should be based on the same criteria that are currently used for younger patients: endocrine responsiveness and assessment of risk of relapse. Adjuvant endocrine therapy should be considered for women with endocrine-responsive disease, regardless of age. The value of adjuvant chemotherapy is controversial. Older women are frequently undertreated with adjuvant chemotherapy and are underrepresented in clinical trials. In particular, no convincing data are available on the role of adjuvant chemotherapy in endocrine nonresponsive tumors, partly because most of the time these tumors represent a relatively small subset in adjuvant studies focusing on the elderly population. Several phase III trials are currently ongoing in elderly patients with early breast cancer to evaluate different options of adjuvant treatments. Only one trial, coordinated by the International Breast Cancer Study Group, is investigating the role of adjuvant chemotherapy for postmenopausal women of advanced age with endocrine nonresponsive early breast cancer. *The Oncologist* 2007; 12:952–959

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Correspondence: Silvia Dellapasqua, M.D., European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy. Telephone: 39-02-57489502; Fax: 39-02-57489571; e-mail: silvia.dellapasqua@ieo.it Received February 8, 2007; accepted for publication June 20, 2007.
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Introduction

Breast cancer incidence increases with age, with an estimated risk for new breast cancer of one in 14 women aged 60–79 compared with one in 24 women aged 40–59. About 50% of breast cancers occur in women aged 65 years and older, and the incidence and prevalence of breast cancer among older women are expected to increase in the future as a result of an increase in the aged population. Persons aged 65 years and older comprised 11.3% of the population in 1980, and are expected to account for 20% by 2030 [1].

Adjuvant endocrine therapies may be offered to patients with endocrine-responsive disease, regardless of age, axillary node involvement, or tumor size. Tamoxifen has historically been one of the most commonly used endocrine therapies, with data supporting a 1- to 5-year course of treatment in elderly patients [2]. Recent results from trials comparing tamoxifen with aromatase inhibitors (anastrozole, letrozole, and exemestane), given at different time points, reported superior results of the latter over tamoxifen in terms of disease-free survival (DFS). In one of these trials [3], this also translated into a modest improvement in overall survival (OS), while in another trial longer OS was seen only in node-positive patients [4] and in patients with both estrogen receptor (ER)- and progesterone receptor (PgR)-positive tumors [5]. According to the St. Gallen Consensus Conference, tamoxifen can still be considered an adequate treatment for selected low-risk patients, while for the majority of patients, the introduction of an aromatase inhibitor, either upfront or sequentially after tamoxifen treatment, should be considered [6, 7].

Adjuvant chemotherapy improves survival for women with early breast cancer. Women aged 50–69 years with breast cancer achieve a 20% proportional reduction in the risk for recurrence and an 11% proportional reduction in the risk for death with adjuvant chemotherapy. However, limited data exist on the benefit of chemotherapy in women aged 70 years or older. Very few patients in the oldest age groups have been included in clinical trials to date for several reasons: exclusion criteria for age in some clinical trials; physician (or even patient) bias based on the notion that older patients will not benefit from adjuvant chemotherapy, will not tolerate it as well as younger patients, or both. In the Early Breast Cancer Trialists Collaborative Group (EBCTCG) 2005 meta-analysis, as few as 1,529 patients aged >70 years were included, compared with >31,000 patients <70 years, thus failing to show a statistically significant benefit of adjuvant chemotherapy in terms of disease recurrence and survival after the age of 70 years. The meta-analysis found a nonstatistically significant 13% reduction in all-cause mortality among women aged 70 years and older who received adjuvant chemotherapy. Moreover, the small sample size precluded subgroup analysis by hormone receptor status [8]. Despite the small number of patients >70 years old included in the Oxford Overview, the benefits of chemotherapy appear to decline with increasing age. This could also possibly be explained by a shorter life expectancy, a reduction in dose intensity, pathogenetic pathways resulting in reduced chemosensitivity, and the reduced benefit of chemotherapy in endocrine-responsive tumors [9].

However, an analysis conducted to define a threshold relapse risk above which adjuvant treatment could be worth prescribing in patients aged 65–85 concluded that older breast cancer patients could expect a reduction in relapse fairly similar to that of younger patients [10].

Criteria for Selecting Adjuvant Treatment in Elderly Patients

The choice of adjuvant treatment for elderly patients should be based on the same criteria that are currently used for patients in other age groups: endocrine responsiveness and assessment of risk of relapse. According to the St. Gallen Consensus Conference [6], endocrine monotherapy may be offered to selected patients with clearly endocrine-responsive disease, while chemotherapy alone is offered to patients with endocrine nonresponsive disease. Patients with tumors of uncertain endocrine responsiveness (i.e., low levels of steroid hormone receptor immunoreactivity, or lack of PgRs irrespective of the expression of ERs) and traits of potential resistance to certain endocrine therapies (e.g., human epidermal growth factor receptor [HER-2]/neu overexpression and tamoxifen), or large micrometastatic burden of disease, are theoretically suited to combinations of chemotherapy and endocrine therapy, although the value of this combination in elderly patients is less clear if compared with the younger population.

However, additional factors should be considered when choosing the appropriate adjuvant treatment for an elderly woman with operable breast cancer. These include life expectancy, benefits and possible toxicity of treatments, functional status, comorbid conditions, cognitive status, economic means, social support, and the viewpoints of both the physician and the patient. All these geriatric parameters do not have a direct relationship with chronological age and therefore have to be assessed separately using a multidimensional geriatric assessment [11]. As early as 2001, the St. Gallen Consensus Conference eliminated the category of "elderly" because it was believed to be arbitrary and not

useful [12], and, more recently, acknowledged that life expectancy and comorbid conditions must be considered in treatment decisions, without setting an upper age limit for the use of chemotherapy [6], as did guidelines from the National Comprehensive Cancer Network [13].

Aging implies a reduction in life expectancy and in tolerance to treatments; both factors should be considered when an elderly woman presents to the oncologist after surgery for early breast cancer.

Life expectancy represents a central concept in decision making in the elderly patient with breast cancer, because treatment options now available to the patient with breast cancer often carry short-term risks and toxicities in older women that are tempered by long-term survival gains. There is a nonlinear relationship between age and life expectancy that is crucial in clinical decision making: women aged 65, 75, and 85 years in generally good health can expect to live, on average, an additional 20, 12, and 6 years, respectively [14].

The toxicity of adjuvant chemotherapy may be greater in older women. Because some physiologic changes (including reduced glomerular filtration rate and marrow reserve and increased susceptibility to mucositis, cardiac toxicity, and neurotoxicity) are more common in persons aged 65 years and older, age is associated with a lower tolerance to adjuvant chemotherapy with a consequent reduction in dose intensity [15]. In the International Breast Cancer Study Group (IBCSG) trial VII, cyclophosphamide, methotrexate, and fluorouracil (CMF) tolerability and effectiveness were both lower for older patients than for younger postmenopausal node-positive breast cancer patients who received tamoxifen for 5 years [16].

A multidimensional comprehensive geriatric assessment (CGA) provides the most reliable information regarding life expectancy, treatment tolerance, and unsuspected conditions (e.g., dementia, depression, comorbidity) that may interfere with cancer treatment. The CGA includes assessment of functional status, comorbidities and pharmacology, cognitive status and emotional conditions, economic means and social support, and nutrition [17]. Some form of assessment should be performed for all patients >70 years of age because age-related changes occur more rapidly in this age group [18, 19].

Despite progresses in geriatric oncology, and recommendations for the widespread use of a CGA [20], the appropriate use of adjuvant chemotherapy for elderly women with breast cancer still remains controversial, with a lack of clear guidelines for patients in this age group.

Undertreatment of Elderly Patients

Elderly patients have always been undertreated for fear of possible side effects of adjuvant chemotherapy [21]. Several studies have demonstrated a decreasing use of chemotherapy with age, with no age-related differences in either the drug regimens recommended or patient acceptance rates for adjuvant therapy.

In a retrospective review of data from four Cancer and Leukemia Group B (CALGB) randomized trials that accrued 6,487 node-positive breast cancer patients between 1975 and 1999, 8% of patients were aged 65 years or older and 2% were at least 70 years old. There was no association between age and DFS, whereas OS was worse for patients over 65 because of death from causes other than breast cancer ($p < .001$). The overall treatment mortality was 0.5% (95% confidence interval [CI], 0.4%–0.7%), with a significant relationship between age and mortality resulting from protocol therapy (0.2% for patients ≤50 years old, 0.7% for patients 51–64 years old, and 1.5% for patients ≥65 years old; $p < .001$). Older women (in good general health) and younger women derived similar reductions in breast cancer mortality and recurrence from regimens containing more chemotherapy, suggesting that age alone should not be a contraindication to chemotherapy [22].

In a population-based observational cohort study, Elkin and colleagues identified 5,081 women age 66 and older diagnosed with receptor-negative early breast cancer from 1992 to 1999, of whom 1,711 (34%) received adjuvant chemotherapy. Chemotherapy use decreased with increasing age (from >52% of women aged 66–69 to approximately 5% of women aged 85 and older) and comorbidity, and increased with year of diagnosis (from 25% in 1992 to 45% in 1999), tumor size, number of positive nodes, and higher tumor grade. Adjuvant chemotherapy was associated with a mortality reduction of approximately 15%, with the greatest survival benefit in node-positive and in high-risk node-negative breast cancer patients [23].

These results are consistent with those reported by Giordano et al. [24], who determined patterns of chemotherapy use in a population-based cohort of 41,390 women >65 years old diagnosed with early breast cancer between 1991 and 1999, of whom 4,500 (10.9%) received adjuvant chemotherapy. 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 significant shift toward anthracycline use, despite time trends toward earlier stage disease and older age at diagnosis, thus reflecting both the increasing use of adjuvant chemotherapy for all breast cancer patients and a greater willingness to offer chemotherapy to older patients. Women who were younger, white, and with lower comorbidity scores, more advanced stage disease,

and receptor-negative disease were significantly more likely to receive chemotherapy. Chemotherapy did not improve survival among women with either node-negative disease or node-positive, receptor-positive disease (hazard ratio [HR], 1.05; 95% CI, 0.85–1.31); however, among women with node-positive, receptor-negative breast cancer, chemotherapy was associated with a significant reduction in breast cancer mortality (HR, 0.72; 95% CI, 0.54–0.96). A similar significant benefit of chemotherapy was seen in the subset of women aged 70 years or older (HR, 0.74; 95% CI, 0.56–0.97) [24].

A retrospective analysis conducted by Brunello et al. [9], comparing elderly (≥70 years) with younger postmenopausal (control) early breast cancer patients, concluded that the former receive much less adjuvant chemotherapy, according to each prognostic factor. Of 188 patients presenting one or more risk factors (pT2–3, G3, node-positive, receptor-negative), 48.4% were not proposed for adjuvant chemotherapy (compared with 7.2% in the control group). Among the patients who did not receive the option of adjuvant chemotherapy, 39.8% had nodal involvement (compared with 4.3% of controls; $p < .0001$), and 22.7% were receptor-negative (compared with 0.0% of controls; $p = .0002$). The 2-year DFS rate was significantly lower in node-positive, receptor-negative patients than in the remaining elderly patients (49.9% compared with 90.9%; $p = .0006$), suggesting that this small group of patients should probably receive adjuvant chemotherapy whenever allowed by CGA [9].

Finally, in a retrospective study analyzing 1,568 patients aged 55 years and older who were treated for early breast cancer, older women were less likely to receive treatment in concordance with guidelines for definitive surgical therapy ($p < .001$), radiation ($p = .03$), adjuvant chemotherapy ($p < .001$), and adjuvant hormonal therapy ($p < .001$). In a multivariate analysis, age ≥75 years predicted a deviation from guidelines for definitive surgical therapy, adjuvant chemotherapy, and adjuvant hormonal therapy [25].

Underrepresentation of Elderly Patients in Clinical Trials

Elderly patients have been excluded from or underrepresented in most cancer clinical trials. For adjuvant chemotherapy, low percentages of patients >70 years of age were included in few trials, and always in a proportion much lower than the prevalence of cancer in that age group [26]. Whereas one half of breast cancers occur in patients >65 years old and one fourth occur in patients >75 years old, only 17% and 3%, respectively, of patients included in cooperative trials were in these age ranges [27].

Of 12,813 patients who were included in IBCSG Trials I to 14, only 1,666 (13%) were >65 years old at trial entry, and as few as 717 (5.6%) were >70 years of age (Dr. Diana Crivellari, personal communication) [28].

Hutchins and colleagues analyzed data on 16,396 patients consecutively enrolled in 164 Southwest Oncology Group (SWOG) trials between 1993 and 1996 according to age. Overall, patients >65 years old accounted for 25% of patients in SWOG trials, as compared with 63% in the U.S. population of cancer patients ($p < .001$). When the age cutoff was set at 70 years, the proportions of patients enrolled in SWOG trials and those in the U.S. population of cancer patients were 13% and 47%, respectively ($p < .001$). Underenrollment of elderly patients was particularly striking in breast cancer trials: in the U.S. population of cancer patients, 49% of breast cancers occurred in patients who were 65 years old or older, whereas only 9% of patients enrolled in SWOG breast cancer trials were 65 or older [29].

Kemeny and colleagues have shown that age bias remains a significant independent cause of oncologists' reluctance to offer participation in clinical trials to older patients: in a retrospective case–control design in 10 CALGB institutions, only 34% of women aged 65 years or older with stage II breast cancer and eligible for a clinical trial were offered participation, compared with 68% of women younger than 65 years ($p = .0004$). In multivariate analyses, age remained highly significant in predicting trial offering ($p = .0008$). Of those offered a trial, there was no significant difference in the participation rate between younger (56%) and older (50%) patients ($p = .67$). Thus, age was not a significant predictor of whether a patient would participate, once they had been offered a trial. Consequently, the principal barriers to accruing older patients to trials seem to be physician- and not patient-related issues [30].

These findings suggest that the attitudes and preferences of physicians who treat older women also require examination [31]. We lack information on physician–patient interactions and on the preferences and attitudes of older women and their physicians. For example, we do not know how many older women were referred to a medical oncologist for a discussion about adjuvant chemotherapy or how often chemotherapy was recommended and refused [32]. Data on the preferences and attitudes of older women with respect to adjuvant chemotherapy are limited, but older women may differ from younger women in this regard [33]. A prospective study concluded that patients with cancer are much more likely to opt for radical treatment with minimal chance of benefit than people who do not have cancer. Up to one half of cancer patients consider a 1% chance of cure as a reasonable justification for undertaking chemotherapy.

This should be taken into account when discussing treatment options with patients and their relatives [34].

From Treatments "Over the Board" Toward Tailored Adjuvant Treatments

The importance of hormone receptor status as a major factor related to response to chemotherapy is being recognized with increasing frequency. In an analysis of more than 6,000 node-positive patients treated during the last 20 years in CALGB trials, adjuvant chemotherapy had a consistently greater impact on those patients with ER-negative than with ER-positive disease [35]. Similarly, as seen above, chemotherapy determined a significant reduction in breast cancer mortality in women with node-positive, receptor-negative breast cancer [24].

However, no clinical trials have been specifically conducted in the past in elderly women with endocrine nonresponsive early breast cancer to define the best adjuvant treatment in this subpopulation. In particular, no data are available on the adjuvant treatment of endocrine nonresponsive tumors in the elderly cohort, partly because most of the time receptor-negative tumors represent a relatively small subset in adjuvant studies in the elderly. For these reasons, a therapeutic dilemma exists when a woman of advanced age presents with endocrine nonresponsive early breast cancer. The physician may decide not to offer a relatively frail patient any treatment, for fear of possible subjective or severe toxic effects of chemotherapy. Typically, however, these patients are treated in a rather heterogeneous way by arbitrarily reducing doses or modifying schedules of adjuvant chemotherapy regimens that were studied in younger women [36–40].

Furthermore, relapses of breast cancer may occur earlier in patients with endocrine nonresponsive disease than in those with hormone receptor–expressing tumors, thus providing a rationale for reducing the risk of relapse even when life expectancy is less than decades [9].

Approximately 15%–20% of patients >70 years of age have aggressive, hormone receptor poor tumors. Therefore, this represents a substantial subpopulation of patients at elevated risk. Focusing on this population of endocrine nonresponsive breast cancer women when drawing adjuvant chemotherapy trials for elderly breast cancer patients should be advantageous because the magnitude of chemotherapy effect for this postmenopausal cohort is likely to be quite large, similar to the effect observed for premenopausal patients with similar biological tumor characteristics. Moreover, avoiding dilution with patients having endocrine-responsive tumors (even those with a high number of axillary lymph nodes involved) maximizes the chance to observe a benefit in the shortest time with the lowest number of patients: because these patients do not benefit from hormonal therapy, use of such therapy is unlikely to confound the relationship between chemotherapy and survival.

Ongoing Clinical Trials in Elderly Early Breast Cancer Patients

In 2000, the National Institutes of Health Consensus Conference emphasized the urgent need for randomized clinical trials of adjuvant chemotherapy in women aged >70 years, and trials specifically designed for this population are under way [41]. In particular, four phase III trials are being specifically conducted in elderly patients with early breast cancer to evaluate different forms of adjuvant treatments (Table 1).

The Chemotherapy Adjuvant Study for women at advanced Age (CASA) study is the unique phase III trial evaluating the role of adjuvant pegylated liposomal doxorubicin (PLD; Caelyx®, Schering Plough, Kenilworth, NJ; Doxil®, Ortho-Biotech, Bridgewater, NJ) for women (age 66 years or older) with endocrine nonresponsive breast cancer who are not suitable for being offered a "standard chemotherapy regimen." The trial, coordinated by the IBCSG, has two individual complementary randomization options that are tailored to the investigator's decision and/or the patient's preference about what would constitute an appropriate control treatment group for the individual patient. Option 1, PLD versus nil, is designed for patients who, according to the treating physician and/or the patient's preferences, are candidates to receive no adjuvant therapy. Option 2, PLD versus low-dose, metronomic cyclophosphamide and methotrexate (CM), is designed for patients who, according to the treating physician and/or the patient's preferences, should receive some adjuvant treatment. The possibility to choose one of the two options gives investigators the chance to "personalize" participation in the clinical trial, reflecting the attitude toward adjuvant chemotherapy in a subpopulation of older women with receptor-negative disease [42]. Although the incidence of breast cancer in elderly women is high, only about 15%–20% have receptor-negative disease; therefore, satisfactory accrual can be reached only through international collaboration and participation around the world.

Other phase III trials are currently being conducted to determine the best adjuvant cytotoxic treatment for elderly women with early breast cancer, but none of these are specifically designed for the population of patients whose tumors are negative for steroid hormone receptors.

The CALGB 49907 trial (details of which are available at http://www.cancer.gov) is a phase III randomized study that recruited about 600 women (Prof. Hyman Muss, per-

Table 1. Ongoing phase III trials in elderly patients with early breast cancer

Trial name	Age	Expected sample size	Treatment arms	Tumor characteristics	Concomitant endocrine therapy[a]
CASA IBCSG 32-05 BIG 1-05	>65	1,296	Low-dose CM × 16 wks (cyclophosphamide, 50 mg/day p.o., and methotrexate, 2.5 mg b.i.d. p.o. twice a week) or observation versus liposomal doxorubicin (20 mg/m^2 i.v. every 2 wks × 8)	ER ± PgR <10%	No
CALGB 49907	>65	600	AC × 4 or classic CMF × 6 versus capecitabine (1,000 mg/m^2 p.o. b.i.d. 2/3 wks × 6)	Any receptor status	Tamoxifen or an aromatase inhibitor for 5 years
ICE GBG 32	≥65	1,500	Ibandronate (50 mg p.o. daily or 6 mg i.v. every 4 wks × 2 yrs) versus ibandronate (as above) plus capecitabine (1,000 mg/m^2 p.o. b.i.d. 2/3 wks × 6)	Any receptor status	Anastrozole (1 mg/day) for 5 years
ELDA	65–80	300	i.v. CMF × 4 or 6 versus docetaxel on days 1, 8, and 15 × 4 or 6	Any receptor status	Tamoxifen (20 mg/day) for 5 years

[a]Patients with endocrine-responsive tumors.
Abbreviations: AC, doxorubicin and cyclophosphamide; b.i.d., twice a day; BIG, Breast International Group; CALGB, Cancer and Leukemia Group B; CASA, Chemotherapy Adjuvant Study for women at advanced Age; CM, cyclophosphamide and methotrexate; CMF, cyclophosphamide, methotrexate, and fluorouracil; ELDA, Elderly Breast Cancer – Docetaxel in Adjuvant Treatment; ER, estrogen receptor; GBG, German Breast Group; IBCSG, International Breast Cancer Study Group; ICE, Ibandronate with or without Capecitabine in Elderly patients with early breast cancer; PgR, progesterone receptor; p.o., orally.

sonal communication) aged 65 years and over to compare the effectiveness of adjuvant chemotherapy using standard CMF (oral cyclophosphamide daily on days 1–14, i.v. methotrexate and i.v. fluorouracil on days 1 and 8, every 4 weeks) or AC (i.v. doxorubicin and i.v. cyclophosphamide on day 1 every 3 weeks) with oral capecitabine in terms of DFS, OS, quality of life, physical functioning, and toxicity in elderly women with operable breast cancer. The trial was closed in December 2006 after reaching sufficient accrual to address the study objectives. Patients were stratified according to age, performance status, and HER-2 status, and were randomized to one of two treatment arms. Arm 1 consisted of two treatment groups: in group A patients received six courses of classic CMF; in group B patients received four courses of standard AC. Patients with insufficient left ventricular ejection fraction (LVEF) were included in group A, patients with normal LVEF were assigned to group A or B based on physician/patient choice. Arm 2 consisted of six courses of oral capecitabine (given twice daily on days 1–14 every 3 weeks). Patients with ER- or PgR-positive disease received oral tamoxifen or an aromatase inhibitor daily for 5 years.

The Ibandronate with or without Capecitabine in Elderly patients with early breast cancer (ICE) study was started by the German Breast Group in 2004 to compare event-free survival in elderly patients after local treatment for primary breast cancer treated with either ibandronate alone or ibandronate plus capecitabine as adjuvant treatment. The trial is enrolling patients >65 years of age, who will be randomized after surgery to either ibandronate (given 50 mg orally daily or 6 mg i.v., every 4 weeks for 2 years) or capecitabine (given orally at a dose of 2,000 mg/m^2, days 1–14, every 3 weeks for six courses) plus ibandronate (given 50 mg orally daily or 6 mg i.v., every 4 weeks for 2 years). Patients with endocrine-responsive tumors will receive anastrozole (1 mg) for 5 years.

Finally, the Elderly Breast Cancer – Docetaxel in Adjuvant Treatment (ELDA) trial is being conducted by the National Cancer Institute, Naples. In that study, patients aged 65–80 years will be randomized to either standard adjuvant

chemotherapy with CMF (i.v. days 1 and 8 of each cycle) or experimental adjuvant chemotherapy with weekly docetaxel (given i.v. on days 1, 8, and 15 of each cycle). The trial is expected to enroll 300 patients with intermediate–high risk of recurrence according to St. Gallen criteria (ER and PgR negative, or lymph node metastasis, or tumor size >2 cm, or tumor grade 2 or 3). In both treatment strategies four cycles of chemotherapy will be administered for patients at least 10% positive for ER or PgR, and six cycles will be administered for patients expressing <10% ER or PgR. Patients with ER- or PgR-positive breast cancer will receive adjuvant tamoxifen (20 mg/day for 5 years) after chemotherapy. The primary endpoint will be DFS; secondary endpoints will be compliance, quality of life during treatment, and OS.

Conclusions

The choice of adjuvant therapy for an elderly patient in clinical practice is currently driven by age itself as well as stereotypical attitudes of medical oncologists, rather than an objective and reproducible evaluation of predictive and prognostic factors and geriatric parameters (comorbidity level, functional status, life expectancy). Toxicity issues in the absence of clear evidence of a survival benefit are not the only explanation. Physician-related issues (such as fear of inadequate compliance because of comorbidity and logistic limitations), patient concerns (related to hair loss and awareness of malignant disease), and the paternalistic attitudes of relatives (often asking physicians to connive in hiding the dismal diagnosis) may influence therapeutic choice [9, 25].

By 2030, the number of people in the U.S. over the age of 65 years will have doubled, and the number of persons over the age of 85 years will have quadrupled. Because of the relatively high risk of cancer in these populations, a high prevalence of cases of breast cancer in older members of the U.S. population can be predicted in the future.

Therefore, participation of elderly patients in clinical trials should become more acceptable to the public and the medical community. International trial cooperation is mandatory and should be focused on questions that are relevant for patient care and for understanding biological principles in older patients [29]. Focusing on issues of safety and efficacy, of quality of life and burden of subjective side effects, and of economical and personal costs should be a priority in future trials conducted by cooperative groups. The definition of appropriate tailored research in the older population is a major challenge that will have to be addressed in the years to come.

Disclosure of potential conflicts of interest

The authors indicate no potential conflicts of interest.

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