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State of the art therapy for elderly patients with early-stage and locally advanced breast cancer

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ABSTRACT

The global incidence of cancer is expected to increase dramatically in the coming years, due in part to ageing populations. Historically, elderly women with breast cancer have been excluded from clinical trials, making it difficult to develop evidence-based treatment guidelines. Ageing is a highly individualised process and age alone should not be used to deny treatment to otherwise appropriate patients. Comprehensive geriatric assessment (CGA), routinely used by geriatricians, is becoming increasingly relevant to oncology practice. CGA may have a direct effect on treatment decisions in breast cancer. While the role of adjuvant radiotherapy remains debated, surgery remains the best option for fit older patients. Data support the use of adjuvant tamoxifen for hormone receptor-positive disease, and the additional benefit of aromatase inhibitors remains to be fully determined. The benefits of adjuvant polychemotherapy, capecitabine or pegylated liposomal doxorubicin monotherapy are under evaluation in on-going phase III trials.

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1. Introduction

The World Health Organisation estimates that the global incidence of cancer will double to 20 million new cases per year by the year 2020.¹ The ageing of the population is a major contributing factor to the anticipated increase in cancer rates, both in developed as well as resource-constrained countries, where the majority of elderly cancer patients live. Oncologists will be increasingly involved in the care of older patients with cancer as this epidemiologic shift occurs. Although recognition of these issues has increased in recent years and studies of older patients with cancer are now being conducted, substantial work remains to be done to generate a sufficient evidence-base from which to make treatment decisions for elderly patients with cancer.

This review focuses on the care of older patients with early-stage or locally advanced breast cancer, the most common cancer in elderly women. Until recently, elderly patients with breast cancer were either excluded from clinical trials or, when eligible, were only enrolled if they were very fit which makes it difficult to generalise results to a larger, heterogeneous population. Moreover, older women are less likely to receive standard therapy than their younger counterparts with breast cancer, including less breast-conserving surgery, less axillary node dissection and less adjuvant chemo- and radiotherapy.^{2,3} When one considers that the average life expectancy in the Western world is 83 years, it becomes clear that the treatment goals for older women with operable breast cancer should, in many cases, be identical to those for younger women: prolong disease-free and overall survival.

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What is less clear is how to achieve these ends in older women, who may have comorbidities, age-related physiologic changes and reduced performance status.

1.1. Geriatric evaluation

Definitions of 'elderly' vary widely. From a political perspective, governments worldwide continue to increase the age at which one is called 'elderly' or 'senior citizen' and can therefore retire and claim pension benefits. From a regulatory perspective, the age of 65 years has been the cutoff to define 'elderly' for over a decade.⁴ From a clinical perspective, arbitrary age cutoffs are meaningless because ageing is a highly individual process.⁵ In order to evaluate objectively the impact of comorbidities on the life expectancy of older patients, geriatricians have developed a multidisciplinary approach to the assessment of the health status of older individuals. The tools used in this approach are known collectively as the comprehensive geriatric assessment (CGA). Components of a CGA include functional status, cognitive function, nutritional status, psychological state, comorbid medical conditions, medication review and social support.^{5,6}

Comprehensive geriatric assessment can be integrated into the practice of oncology and studies demonstrate that CGA provides important clinical information beyond traditional oncology parameters such as performance status (PS).^{7,8} For example, routine CGA monitoring was not only feasible in a pilot study enrolling 15 women with breast cancer but for several patients, it had a direct influence on the cancer treatment.⁹ Indirect effects, such as improved coordination of care and refinement of medication regimens, were also observed.

The International Society of Geriatric Oncology (SIOG) performed a systematic review and published recommendations for the use of CGA in oncology in 2005.⁵ The SIOG task force concluded that a CGA improves function and reduces hospitalisation in elderly cancer patients. Data regarding the impact of CGAs on survival are mixed, but it is likely that the correction of several comorbidities can lead to an extended survival. These and other similar findings remain to be verified in large randomised trials.

1.2. Surgery

Advanced age is an insufficient criterion to preclude surgical treatment for an older patient with operable breast cancer.¹⁰ However, the higher prevalence of co-morbidities and functional impairment in elderly patients increases the risk of surgical complications, which may deter physicians from offering optimal management to oncogeriatric patients. The ability to predict short-term postoperative outcomes could facilitate patient selection for surgery, and recent data show that this goal might be achievable. The Preoperative Assessment of Cancer in the Elderly (PACE) questionnaire comprises several validated assessment tools and has been evaluated as a predictor of postoperative outcomes in elderly cancer patients.¹¹ A total of 460 consecutively recruited elderly cancer patients undergoing elective surgery were surveyed preoperatively in this trial. Mortality, postoperative complications

(morbidity) and length of hospital stay were recorded up to 30 days after surgery and correlated with the various PACE components. Poor health in relation to disability (assessed using the IADL, Instrumental Activities of Daily Living tool), fatigue (assessed using the brief fatigue inventory, BFI) and impaired PS were associated with a 50% increase in the relative risk of postoperative complications. Multivariate analysis identified moderate/severe fatigue, dependent IADL and abnormal PS as the most important independent predictors of postoperative complications, while disability assessed by Activities of Daily Living (ADL), IADL and PS were associated with an extended hospital stay. No component, however, predicted mortality, which may have been due to the small number of events (3.6%).

Another research question, which has been addressed in several clinical trials, is whether elderly women with operable breast cancer benefit from surgery. These patients appear to have a more indolent form of breast cancer than younger women.² In 70–80% of the cases, the disease is hormone receptor-positive (HR+), making these patients candidates for endocrine therapy. Thus, it has been hypothesised that hormonal therapy alone may be sufficient in this population. Numerous randomised trials have compared tamoxifen to surgery (with or without adjuvant tamoxifen) and found that while effective, tamoxifen monotherapy tends to be associated with higher rates of local progression.^{12–16} Moreover, operative mortality rates for fit older women with breast cancer have dropped significantly with recent anaesthesiology advances.¹⁷ For women who are surgical candidates, surgery is generally safe and should be considered standard for the treatment of early-stage disease. Primary endocrine therapy may be appropriate for women with HR+ disease who refuse or are too ill or unfit for surgery.

1.3. Radiation therapy

The benefits of adjuvant radiotherapy (RT) for elderly patients with breast cancer are less clear. In a pivotal study demonstrating that adjuvant RT significantly reduces ipsilateral disease recurrence after breast-conserving surgery, the benefit was greatest for women under the age of 45. After age 65, there was no apparent benefit to adjuvant RT.¹⁸ Indeed, EORTC 22881/10882 demonstrated that age is an independent prognostic factor for local control in early-stage breast cancer.¹⁹ Five-year local control rates increased from 82% for patients 35 years and younger to 97% for patients over the age of 60 in this study ($p < 0.0001$). Boost RT significantly reduced the risk of local recurrence in only the younger patients in the initial analysis.²⁰ With longer follow-up, the effect of boost RT on local control reached significance in elderly patients as well, decreasing the 10-year cumulative incidence of local recurrence from 7.3% to 3.8% in patients over the age of 60 ($p = 0.0008$).²¹ No impact was seen on overall survival, however.

Subsequent trials have aimed to identify specific populations of elderly women who can safely avoid adjuvant RT. For women age 50 years and older with T1–T2, node-negative disease, the addition of RT to surgery plus tamoxifen decreased local recurrence rates from 7.7% to 0.6% ($p < 0.001$)

and improved 5-year disease-free survival rates (91% versus 84%; $p = 0.004$) in one trial.²² In women over the age of 70 with smaller tumours (T1N0), adjuvant RT produced a small but statistically significant reduction in locoregional recurrence rates compared with surgery plus tamoxifen alone (1% versus 4%; $p < 0.001$).²³ There were no differences in rates of mastectomy due to recurrence, distant metastases or overall survival, and the authors questioned the clinical significance of the RT treatment effect, given the greater incidence of adverse events and inferior physician-rated cosmesis in the RT group. Two trials, PRIME I and PRIME II (post-operative radiotherapy in minimum-risk elderly), are currently evaluating whether RT is truly necessary after breast-conserving treatment for elderly women with low-risk, node-negative disease. PRIME I focuses on quality of life, while PRIME II focuses on local control and survival.

1.4. Hormonal therapy

Most older patients with breast cancer have hormone receptor-positive disease and can be expected to respond to hormonal therapy in both the adjuvant and metastatic settings. In the adjuvant setting, 5 years of tamoxifen is as effective for reducing the risk of recurrence and cancer-related mortality in women over 70 years of age as it is for younger women.²⁴ For postmenopausal women, aromatase inhibitors (AI) have consistently shown superiority to tamoxifen in randomised trials in the adjuvant setting. Women over the age of 70 were included in ATAC, BIG 1-98, and the IES trials, and subsequent subgroup analyses have provided some evidence of efficacy in elderly women.^{25–27} However, side-effects associated with AI therapy, such as osteoporosis and hip fractures, might become significant in elderly women, possibly leading to excess morbidity and mortality, even if a recent review of BIG 1-98 indicates that these and other side-effects such as thromboembolic and cardiovascular events follow the same pattern as in younger patients.²⁸ More data are needed to draw firm conclusions about the role of adjuvant AI therapy in this population.

1.5. Chemotherapy

The impact of adjuvant chemotherapy for patients over the age of 70 is less clear than that of adjuvant tamoxifen. In the EBCTCG overview, too few elderly patients had been enrolled in the included clinical trials to adequately assess the benefits of adjuvant polychemotherapy in this group, especially if one looks only at ER negative patients.²⁴ When chemotherapy is used, consideration must be given to the older patient's unique physiology to assure appropriate dosing (Table 1).²⁹ For example, renal insufficiency is relatively common in elderly patients and is best gauged through the calculated creatinine clearance rather than the serum creatinine level alone. Recently published clinical practice guidelines from the SIOG recommend that creatinine clearance be calculated for every elderly patient, even those with a serum creatinine within the normal range, as many such patients already have a decreased clearance.³⁰

Increasingly, trials are being conducted specifically in older patients with breast cancer, providing much needed data to

Table 1 – Potential age-related factors affecting chemotherapy pharmacokinetics²⁹

Parameter	Factor
Absorption	Concomitant medications Compliance Altered GI secretion, emptying, motility
Distribution	Changes in body composition <ul style="list-style-type: none"> • Increased body fat • Decreased intracellular water • Reduced serum albumin Increased volume of distribution Lower peak concentration Prolonged $t^{1/2}$
Metabolism	Altered liver function Polypharmacy/drug interactions
Excretion	Decreased renal function

guide clinical practice. The French Adjuvant Study Group (FASG) trial 08 compared weekly epirubicin plus tamoxifen to tamoxifen alone in elderly women (≥ 65 years) with node-positive breast cancer.³¹ Patients were randomly assigned after surgery to tamoxifen 30 mg/day for 3 years ($n = 164$) or epirubicin 30 mg on days 1, 8 and 15 every 28 days for six cycles plus the same tamoxifen regimen ($n = 174$). Disease-free and overall survival were similar in the two groups at 6 years (69.3% and 75.8%, respectively, with tamoxifen versus 72.6% and 75.4%, respectively, with combination therapy). However, multivariate analysis demonstrated a relative risk of relapse that was significantly reduced with chemotherapy ($HR = 1.93$; $p = 0.005$). Chemotherapy was generally well tolerated, with low rates of neutropenia (grade 2: 6%), anaemia (grade 2: 2%) and nausea and vomiting (grade 3: 5%). The ACTION trial has been initiated by Cancer Research UK in conjunction with the National Cancer Research Network to evaluate anthracycline-based therapy (EC or AC) versus no chemotherapy in patients 75 years of age and older.³² A second randomisation to dose-dense (every 2 week) therapy with G-CSF or 3-weekly administration occurs in the chemotherapy arm. The trial is expected to enroll 1000 women over the next 3 years.

Non-anthracycline-containing regimens are frequently preferred in the elderly due to concerns related to the potential for treatment-induced cardiotoxicity. The Breast International Group (BIG) conducted a survey of member oncologists and reported in 2004 that CMF was the most commonly chosen adjuvant regimen in clinical practice (Fig. 1).³³ They also found great interest amongst their members in oral therapy, which many believe may be better tolerated by elderly patients. Results from the recently closed CALGB 49907 study will shed light on the role of capecitabine monotherapy for the treatment of women age 65 and older with node-positive or high-risk node-negative breast cancer.³⁴ This Intergroup trial randomised 1800 women to either polychemotherapy with CMF or AC or monotherapy with capecitabine 2000 mg/m²/day; patients with HR+ positive disease could receive either tamoxifen or anastrozole (Fig. 2). Disease-free survival, overall survival and quality of life will be assessed. Similarly,

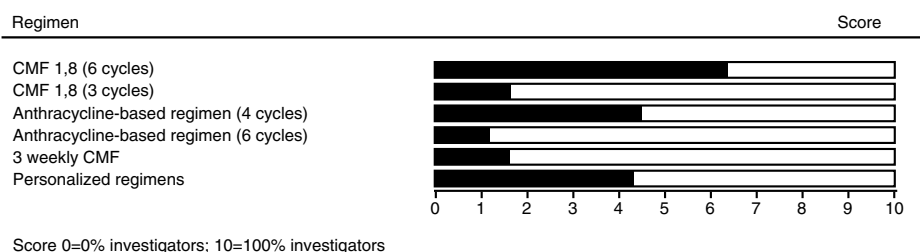


Fig. 1 – Adjuvant chemotherapy regimens used in clinical practice by BIG members.³³

CALGB-49907: ADJUVANT CMF OR AC VERSUS CAPECITABINE IN WOMEN 65 YEARS AND OLDER

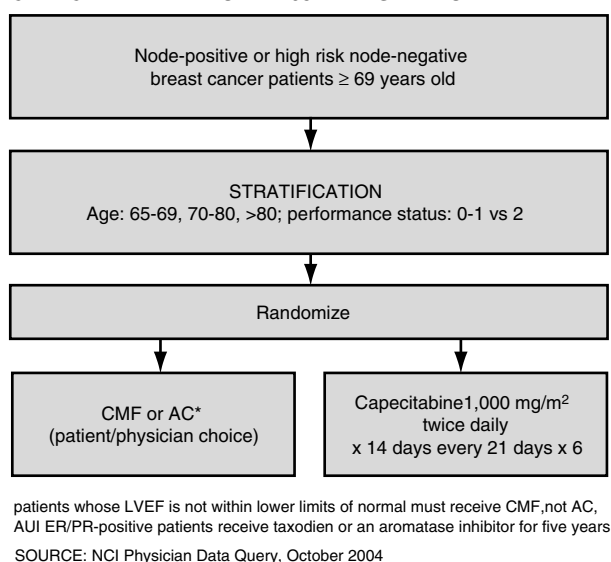


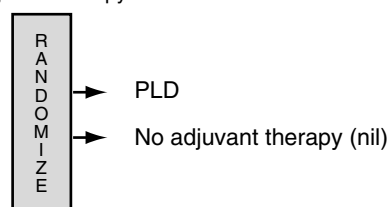
Fig. 2 – Design of Intergroup trial CALGB 49907.

the German Breast Group is conducting the phase III ICE trial, which compares capecitabine 1000 mg/m² twice a day, days 1–14, every 3 weeks for six cycles to no chemotherapy in women 65 years of age or older.³⁵ In addition, all patients receive treatment with ibandronate, given orally or intravenously. Patients with hormone-sensitive disease receive anastrozole 1 mg daily for 5 years.

Another alternative to traditional anthracycline-based therapy is pegylated liposomal doxorubicin (PLD). Compared with conventional doxorubicin, PLD has demonstrated similar efficacy in the treatment of metastatic breast cancer, with a significantly lower incidence of cardiotoxicity, myelotoxicity, vomiting and alopecia.³⁶ The reduction in the risk of cardiotoxicity was seen in all patient subgroups, including patients over the age of 65, who comprised approximately 15% of the study population. The International Breast Cancer Study Group (IBCSG) is currently conducting the CASA trial in conjunction with BIG, which compares PLD monotherapy with either no chemotherapy or a combination of cyclophosphamide/methotrexate ('metronomic chemotherapy'). Patient and physician preference determine which randomisation option is used (Fig. 3). Target accrual is nearly 1300 women over the age of 65 years with endocrine non-responsive, early-stage breast cancer.

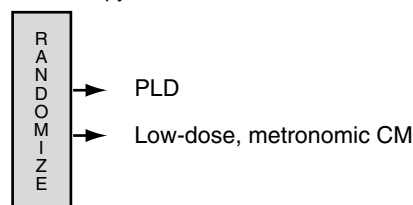
Option 1: CASA-nil

For patients who, according to the treating physician and/or to the patient's preferences, are candidates to receive no adjuvant therapy



Option 2: CASA-CM

For patients who, according to the treating physician and/or to the patient's preferences, are candidates to receive some adjuvant therapy



All regimens are 16 weeks' duration. C = cyclophosphamide 50 mg PO qd x 16 wk; M = methotrexate 2.5 mg PO bid d 1 & 4 q wk x 16 wk.

Fig. 3 – Design of the CASA Trial.

2. Conclusions

Elderly patients should not be denied effective treatment for breast cancer based on chronological age alone. Surgery remains a standard of care for many elderly women with early-stage breast cancer; however, some elderly patients may not require adjuvant RT. On-going trials are addressing whether adjuvant RT can be omitted for certain older women after surgery. Chemotherapy needs further evaluation specifically in this population and a number of adjuvant treatment trials are currently enrolling patients. Demographic shifts are increasingly requiring oncologists to consider a patient's functional age in addition to the traditional prognostic and predictive factors related directly to the patient's tumour. As such, comprehensive geriatric assessment is likely to become a component of routine oncology care in the near future.

Conflict of interest statement

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