Mammography Screening and Treatment of Breast Cancer in the Elderly

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Key Words

Breast cancer · Elderly · Geriatric assessment · Creatinine clearance · Comorbidity

Summary

Breast cancer patients of an advanced age will suffer from ailments related to both senescence and cancer. Some will have been denied access to screening programmes and will present with an advanced disease. Many will need the expertise of the geriatrician and the oncologist who will participate in specific case discussions to look at social and medical issues that will affect the treatment plan (with questions regarding surgery, radiation, drug therapy, rehabilitation, supportive care, and palliative care often intertwined). This paper reviews recommendations by the International Society of Geriatric Oncology (SIOG) task force which recently assessed the available evidence on breast cancer in elderly individuals, and provided evidence-based recommendations for the diagnosis and treatment of breast cancer in such individuals. Recommendations on the topics of screening, surgery, radiotherapy, (neo)adjuvant hormone treatment, and chemotherapy, and on metastatic disease have been given. Oncologists are now learning to take into account the physiological age of their patient, which is the reflection of a normal and sometimes abnormally accelerated loss of body reserves which is certainly related to chronological age but not precisely dictated by it. Understanding the biology of breast cancer will allow to optimally adapt the treatment of the elderly patient.

Schlüsselwörter

Brustkrebs · Ältere Menschen · Geriatrische Bewertung · Kreatinin-Clearance · Komorbidität

Zusammenfassung

Brustkrebspatientinnen im fortgeschrittenen Alter leiden an Beschwerden bedingt sowohl durch Seneszenz als auch durch die Krebserkrankung. In manchen Fällen besteht kein Zugang zu Screening-Programmen, so dass die Patientinnen erst im fortgeschrittenen Krankheitsstadium vorstellig werden. Viele Fälle erfordern das Fachwissen von sowohl Geriatrikern als auch Onkologen, welche in spezifischen Falldiskussionen soziale und medizinische Aspekte in Betracht ziehen, die den Behandlungsplan beeinflussen (oftmals ineinander greifende Fragen der chirurgischen Behandlung, Radiotherapie, Medikation, Rehabilitation, unterstützenden Pflege und Palliativpflege). Dieser Artikel gibt einen Überblick über Empfehlungen der International Society of Geriatric Oncology (SIOG)-Arbeitsgruppe, welche vor kurzem die verfügbare Evidenz zu Brustkrebs bei älteren Menschen bewertet und evidenzbasierte Empfehlungen zur Brustkrebsdiagnose und -behandlung in dieser Patientengruppe erstellt hat. Letztere umfassen die Bereiche Screening, chirurgische Behandlung, Radiotherapie, (neo)adjuvante Hormontherapie und Chemotherapie sowie metastasierte Erkrankung. Onkologen haben gelernt, das physiologische Alter ihrer Patienten zu berücksichtigen. Dieses reflektiert den normalen und manchmal ungewöhnlich beschleunigten Verlust von körperlichen Reserven, der sicher mit dem chronologischen Alter zusammenhängt, aber nicht unbedingt von ihm diktiert wird. Durch das Verstehen der Biologie von Brustkrebs kann die Behandlung älterer Patientinnen optimal gestaltet werden.

Introduction

Worldwide, nearly a third of breast cancer cases occur in patients over the age of 65 years. For those aged 65 years and older, crude incidence rates are 432.7 per 100,000 women in North America and 295.0 per 100,000 in northern and western Europe [1]. Advanced age at diagnosis of breast cancer is associated with more favourable tumour biology as indicated by increased hormone sensitivity, less frequent HER-2 overexpression, and lower grades and proliferative indices. However, elderly patients are more likely to present with larger and more advanced tumours, and involvement of lymph nodes increases with age [2, 3].

Undertreatment

While emerging guidelines [4, 5] should help all to provide adequate treatment options for elderly women, the reality until now has been that many are undertreated. Undertreatment can have a strong negative effect on the survival of elderly patients [6]. A recent example is a cohort study [7] conducted within 6 US integrated healthcare delivery systems. Automated administrative databases, medical records, and tumour registries were used to identify women aged 65 years or older who underwent breast conserving surgery (BCS) or mastectomy to treat stage I or II breast cancer diagnosed from January 1 1990 through December 31 1994. The authors identified 1,837 women having operations for stage I or II breast cancer. Compared to women receiving mastectomy, those receiving BCS without radiation therapy (RT) were twice as likely to die of breast cancer (adjusted hazards ratio (HR): 2.19; 95% confidence interval (CI): 1.51–3.18). Breast cancer mortality rates were similar between women receiving BCS plus RT and women receiving mastectomy (adjusted HR: 1.08; 95% CI: 0.79–1.48). The explanation for these age-related differences in approach to treatment is complex and includes physician and patient bias, the views of relatives and caregivers, psychosocial issues, cost, and proximity to the oncology or radiotherapy centre.

Geriatric Evaluation

As patients get older, comorbidities and physiological aging processes will influence their life expectancy and ability to tolerate various treatment procedures. Therefore, during the last decade, oncologists and geriatricians have begun to work together to integrate the principles of geriatrics into oncology care. The increasing use of a comprehensive geriatric assessment (CGA) is one example of this effort. A CGA includes an evaluation of an older individual's functional status, comorbid medical conditions, cognition, nutritional

status, psychological state, and social support; and a review of the patient's medication. The reader is referred to a recent update on the studies that address the domains of a geriatric assessment applied to the oncology patient, including a review of the results of the first studies evaluating the use of a CGA in developing interventions to improve the care of older adults with cancer. It is demonstrated that a CGA can predict morbidity and mortality in older patients with cancer, and its usefulness in the setting of oncological practice is now part of prospective studies many of which aim at simplifying the procedure [8].

Mammography: Should One Screen Elderly Women for Breast Cancer?

There are simply no strong data supporting or opposing the systematic use of mammography in women over 70 years of age. Cultural differences in the approach to breast cancer screening should be taken into account. In well organised, population-based breast cancer screening programmes, mammography screening up to the age of 75 years could be appropriate [5]. In individual patients, the decision should be individualised to take into account the risks and benefits of screening, patient preference, physiological age, and life expectancy. The Dutch breast cancer screening programme extended the upper age limit from 69 to 75 years in 1998. This decision was based on microsimulation modelling that resulted in a favourable balance of benefits and harms of mammography screening up to at least 75 years. Updated results up to 2007 were recently presented [9]. In 1998–2006, 7.37 million screening examinations were performed of which 862,655 involved women aged 70–75 years. The participation rate was 81.2% for ages 50–69, and 71.9% for ages 70–75. As of 2003, the breast cancer mortality rate among women aged 75–79 (when assuming a lag time of 5 years to take effect) started to significantly decline statistically, and was 29.5% lower in 2006 than the mean rate during 1986–1997. This breast cancer mortality reduction showed a similar pattern as previously found in women aged 50–69. The results of this study thus strongly suggest that screening in women aged 70–75 years has a positive impact on breast cancer mortality, and that mammography screening of high quality is effective and appropriate up to 75 years. Of interest, another study has also indicated that screening older breast cancer survivors is of benefit [10]. The authors enrolled 1,846 stage I and II breast cancer patients who were at least 65 years old at 6 integrated healthcare delivery systems. They matched 4 controls to each breast cancer decedent to estimate the association between receipt of surveillance mammogram and breast cancer mortality. 178 women died of breast cancer during 5 years of follow-up. The authors report that each additional surveillance mammogram was associated with a 0.69-

fold decrease in the odds of breast cancer mortality (95% CI: 0.52–0.92). The protective association was strongest among women with stage I disease, those who received mastectomy, and those in the oldest age group. This large observational study thus provides support for the recommendations, suggesting that receipt of surveillance mammograms reduces the rate of breast cancer mortality in older patients diagnosed with early stage disease.

Surgery

Several treatment guidelines and practice standards have been developed for the surgical management of patients with breast cancer. For the elderly population, breast cancer surgery-related mortality is low, ranging from 0 to 0.3%. Alternatives to conventional surgery include outpatient surgery or surgery under local anaesthesia, which are preferably undertaken when family support is present [reviewed in 5]. Careful pre-surgical evaluation including the use of a comprehensive geriatric assessment can identify patients at risk of unusual morbidity. A major study in 460 consecutively recruited elderly cancer patients has shown that preoperative assessment of cancer in the elderly (PACE) incorporating validated instruments including the CGA, an assessment of fatigue and performance status and an anaesthesiologist's evaluation of operative risk is of value. Poor health in relation to disability (assessed using the instrumental activities of daily living (IADL), fatigue, and performance status (PS) were associated with a 50% increase in the relative risk of postoperative complications. Multivariate analysis identified moderate/severe fatigue, a dependent IADL, and an abnormal PS as the most important independent predictors of post-surgical complications. Disability assessed by activities of daily living (ADL), IADL and PS were associated with an extended hospital stay. Breast conservation treatment, consisting of BCS (lumpectomy or partial mastectomy) and postoperative radiotherapy, is now recommended as the standard of care for patients of all ages with early disease. One should note that studies involving patients aged 70 years or older have documented that breast conservation treatment, in comparison with mastectomy, is associated with better quality of life and is preferred by most elderly patients compared with mastectomy [12, 13]. Sentinel lymph node biopsy is now widely considered as an acceptable treatment option in patients of all ages with tumour size less than 2–3 cm and no clinical evidence of axillary involvement [14]. Elderly patients with breast cancer are ideal candidates for biopsy of sentinel lymph nodes and should be encouraged to undergo this procedure. Surgery should not be denied to patients with breast cancer who are older than 70 years of age, and should not differ from procedures offered to younger patients, unless patient preference dictates.

Radiotherapy

Postoperative radiotherapy after BCS combined with appropriate systemic treatment has been shown to achieve reduction in absolute risk of 5-year local recurrence from 25.9 to 7.3% ($p < 0.0001$), and a reduction in the 15-year absolute breast cancer mortality risk from 35.9 to 30.5% ($p = 0.0002$) [15]. A slight but noticeable increase in non-breast cancer mortality in women who received radiotherapy (mainly heart disease and lung cancer) was probably related to the use of older suboptimum radiotherapy regimens and technique. Despite these benefits, elderly patients continue to receive radiotherapy less frequently after BCS than younger patients. Shorter courses of radiotherapy, such as hypofractionation or intraoperative radiation therapy (which in turn prolongs the time of anaesthesia), are under investigation. A supplementary dose (boost) of radiation to the excision site after BCS with clear margins and 50 Gy of whole breast radiation improved 5-year local recurrence (4.3 vs. 7.3% compared with no boost). Although the absolute benefits decreased with age, the relative effect of reducing the local recurrence by nearly half remains similar in all age groups. The 10-year reduction in risk of local recurrence in patients over the age of 60 years was 3.5% (7.3 vs. 3.8%; $p = 0.008$) in favour of a boost [16]. The International Society of Geriatric Oncology (SIOG) recommendations [5] also include that postmastectomy chest wall irradiation is indicated if patients have 4 or more involved nodes or a T3 or T4 tumour. In older patients with a life expectancy of less than 5 years, the decision of whether to implement adjuvant radiotherapy should be based on considerations of locoregional control alone. The role of adjuvant postmastectomy irradiation is currently being explored by the UK Medical Research Council/EORTC 22052–10051 SUPREMO trial for which there is no upper age limit of eligibility.

Adjuvant Hormone Treatment

A primary issue is whether or not hormone treatment is necessary in all elderly patients with hormone receptor-positive (HR+) early breast cancer. For women with minimum risk disease, treatment decisions should be based on a risk-benefit analysis that takes into account the low relapse rate within the first 10 years, the potential reduction in ipsilateral and contralateral breast cancer relapse, the patient's life expectancy, and treatment-related adverse events. In terms of tolerability, treatment with tamoxifen is associated with an increased risk of endometrial cancer and thromboembolic events such as deep venous thrombosis, pulmonary embolism, and cerebrovascular accidents. However, the small increase in mortality from endometrial cancer and thromboembolic episodes is much smaller than the mortality reduction as a result of deaths avoided from contralateral

breast cancer and cardiovascular events in patients between 50 and 80 years of age. Of note, ageing has been shown to be related to alterations in the metabolism of tamoxifen, resulting in higher levels of tamoxifen and its metabolites in elderly women, but whether this leads to altered efficacy or side effects is unknown [17, 18]. A lower dose of tamoxifen might prove to be as useful and potentially less toxic than standard doses, as suggested by several biological surrogate endpoints studied in a small randomised trial [19]. This area deserves further investigation.

Aromatase inhibitors are more likely to cause muscle and osteoarticular pain, osteoporosis and bone fractures than tamoxifen, a consideration in elderly patients who have lower bone mineral density than younger patients. The optimum use of bisphosphonates to prevent bone loss in patients receiving aromatase inhibitors is currently under investigation, and present data show that the strongest evidence is for the use of 4 mg zoledronic acid given intravenously every 6 months [20, 21]. Cognitive impairment has also been described in association with adjuvant hormonal treatment, but the data are controversial [22] and insufficient to confirm this association or to compare the relative effect of aromatase inhibitors versus tamoxifen on cognitive function.

Recent data have indicated that elderly patients seem to have the same benefit from letrozole as younger patients, and have identified some important considerations. Older women with early stage breast cancer experience higher rates of non-breast cancer-related death. Using data from the MA.17 trial, authors have recently examined factors associated with cause-specific death in a large cohort of breast cancer patients treated with extended adjuvant endocrine therapy [23]. During follow-up, 256 deaths were reported (102 from breast cancer, 50 from other malignancies, 100 from other causes, and 4 from an unknown cause). Non-breast cancer deaths accounted for 60% of the 252 known deaths (72% for those ≥ 70 years, and 48% for those < 70 years). Two baseline factors were differentially associated with type of death: cardiovascular disease was associated with a statistically significant increased risk of death from other causes ($p = 0.002$), and osteoporosis was associated with a statistically significant increased risk of death from other malignancies ($p = 0.05$). An increased risk of breast cancer-specific death was associated with lymph node involvement ($p < 0.001$). Increased risk of death from all 3 causes was associated with older age ($p < 0.001$). The clinical results subanalyses about the advantage of letrozole over tamoxifen in the elderly have been published in 2008. The potential differences in efficacy, treatment completion, and adverse events in elderly women receiving adjuvant tamoxifen or letrozole for 5 years in the Breast International Group (BIG) 1–98 trial were explored in 4,922 patients allocated to 5 years of letrozole or tamoxifen [24]. Letrozole significantly improved disease-free survival (DFS), the primary end point, compared with tamoxifen. Elderly patients were less likely to complete trial treat-

ment, but at rates that were similar in the 2 treatment groups. The incidence of bone fractures, observed more often in the letrozole group, did not differ by age. In elderly patients, letrozole had a significantly higher incidence of any grade 3 to 5 protocol-specified non-fracture adverse events compared with tamoxifen ($p = 0.002$), but differences were not significant for thromboembolic or cardiac adverse events. The National Cancer Institute of Canada Clinical Trials Group trial MA.17 had 5,169 randomly assigned patients who were for the purposes of the 'age-related analysis' divided into 3 age groups: younger than 60 years ($n = 2,152$), 60–69 years ($n = 1,694$), and ≥ 70 years ($n = 1,323$). At 4 years, DFS demonstrated statistically significant differences favouring letrozole only in patients aged younger than 60 years (hazard ratio = 0.46; $p = 0.0004$); however, there was no interaction between age and treatment, indicating a similar effect of letrozole among all age groups. There was no difference in toxicity or quality of life at 24 months among letrozole- and placebo-treated patients aged ≥ 70 years [25].

Adjuvant Chemotherapy

An EBCTCG meta-analysis of randomised trials done before 1995 showed substantial benefits of adjuvant chemotherapy in postmenopausal women of all age groups, compared with no chemotherapy [26]. The gain was larger in those aged under 50 years of age compared with those over 50 years. The gain for patients above age 70 was in the same range as for those between 50 and 70 years, but was not significant due to smaller numbers. Only two phase III trial specifically designed for elderly patients (≥ 65 years of age) have been presented [27, 28]. In the first study, weekly flat doses of epirubicin plus tamoxifen improved DFS compared with tamoxifen alone, but did not improve OS. The benefit of adjuvant chemotherapy in addition to hormone treatment in hormone-sensitive breast cancer is likely to be higher in tumours that are not clearly hormone sensitive (e.g., low levels of HR, absence of oestrogen or progesterone receptors, high grade), although no conclusive data are available. The second study has been presented at the American Society for Clinical Oncology meeting in 2008. The CALGB/CTSU 49907 was designed to compare the efficacy of capecitabine (X) with standard treatment (S) (cyclophosphamide, methotrexate, 5-fluorouracil (CMF) or cyclophosphamide, doxorubicin (AC) per physician choice) in breast cancer patients older than age 65. Endocrine therapy was recommended after completion of chemotherapy for HR+ patients. The primary endpoint was relapse-free survival (RFS) defined as locoregional or distant relapse or death. Per protocol, accrual stopped with 633 patients (326 on S, 307 on X) based on predictive probability that with longer follow-up X was unlikely to be equivalent to S. Median follow-up is 2 years. Patients above age 70 represented 61%, and tumours larger than

Table 1. Recent randomized trials of chemotherapy as adjuvant treatment of breast cancer in elderly women

Trial	Patient population	Control arm	Experimental arm
ICE (ibandronate with or without capecitabine in elderly patients with early breast cancer); active	> 65 years; all ER; N positive and high risk N negative	ibandronate; anastrozole in ER positive	capecitabine × 6 + ibandronate; anastrozole in ER positive
CALGB/CTSU 49907 presented at ASCO 2008; see text	> 65 years; all ER; stage IIA or IIIA	AC × 4 or CMF × 6; tamoxifen or anastrozole in ER positive	capecitabine × 6; tamoxifen or anastrozole in ER positive
ACTION (adjuvant cytotoxic chemotherapy in older women); active	> 70 years; poor risk ER negative or weak ER positive	no drugs if ER negative; tamoxifen if ER positive	AC or EC × 4 every 2 weeks (+ GCSF) vs. every 3 weeks; if ER positive, tamoxifen added after chemotherapy
CASA (chemotherapy adjuvant studies for women at advanced age); IBCSG 32–05/ BIG 1–05; closed for lack of recruitment	66 years or older; ER negative only; N positive and N negative	none or metronomic (× 16 weeks)	pegylated liposomal doxorubicin × 4

^aHER2-positive patients will compare chemotherapy/anti-HER2 vs. anti-HER2 without chemotherapy.
ER = Oestrogen receptor; N = lymph node; AC = doxorubicin, cyclophosphamide; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; EC = epirubicin, cyclophosphamide; GCSF = granulocyte colony-stimulating factor.

2 cm were seen in 54%, 69% were node-positive, and 66% HR+. Patients randomized to X were 2.4 times (95% CI: 1.5–3.8) more likely to experience an RFS event (adjusted $p = 0.0003$), and 2.1 times (95% CI: 1.2–3.7) more likely to die ($p = 0.02$). An unplanned subset analysis showed a highly significant interaction between HR and chemotherapy arm ($p = 0.0032$ for RFS; $p = 0.0067$ for OS). The authors conclude that X is inferior to S in older patients, particularly in those with HR-negative tumours. Docetaxel and cyclophosphamide might be an alternative, certainly in patients at cardiac risk and when CMF is felt to be inadequate [29, 30]. Further closed or ongoing trials are mentioned in table 1. Using chemotherapy in elderly patients requires even more attention than in younger patients for dose adaptation to the physiological reserves, and paying attention to co-medications and decreases in renal and other functions. Extensive recommendations have been published [31, 32].

Metastatic Breast Cancer

Metastatic breast cancer is treatable but very rarely curable. Therefore, the main aims in treating elderly patients, like younger patients, with metastatic breast cancer are to maintain quality of life, minimise symptoms from disease, and prolong survival without causing excessive toxicity. Hormone treatment is the treatment of choice for women with oestrogen receptor-positive or progesterone receptor-positive tumours without life-threatening disease. The superiority of aromatase inhibitors as first-line treatment over tamoxifen has been shown in the postmenopausal population, but

whether the same is true beyond the age of 70 years, is suggested only in a single trial with letrozole [33]. Since the benefit of aromatase inhibitors over tamoxifen is mainly in terms of DFS and not OS, tamoxifen can be a valuable alternative to aromatase inhibitors if adverse events or cost are a concern. Women older than 70 years of age who are treated with chemotherapy for metastatic disease derive similar benefits to their younger counterparts [34]. The SIOG paper [5] comments that preference should be given to chemotherapeutic drugs with safer profiles, such as weekly taxane regimens, newer less cardiotoxic anthracycline formulations, capecitabine, gemcitabine, and vinorelbine. These drugs are often used in elderly patients with adapted doses compared with younger patients, based on pharmacokinetic or pharmacodynamic (toxicity) alterations in this population, but level I evidence on these specific dosing schedules is generally lacking. Monotherapy is generally favoured over combination chemotherapy since the latter is generally associated with increased toxicity and little, if any, survival gain compared with the sequential use of single drugs.

Conclusions

Elderly patients actually represent the majority of the breast cancer population, and there are important specific considerations for this population. Recommendations for the treatment of breast cancer in this population remains mainly based on little evidence and lots of consensus. The main consensus of course had to be that of the patient who needs to be appropriately informed, respecting her wishes [35].

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