Challenges in treating older cancer patients: breast cancer

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Introduction

The International Society of Geriatric Oncology (SIOG) has recently published guidelines on the management of breast cancer in the elderly [1]. This overview summarizes the most important aspects and recommendations. Breast cancer is the most commonly diagnosed cancer and leading cause of cancer mortality in women worldwide. Nearly one-third of the global total of breast cancer cases occurs in patients >65 years of age and in more developed countries it accounts for >40% of cases [2].

Advanced age at the diagnosis of breast cancer is associated with more favourable tumour biology, as indicated by increased hormone sensitivity, attenuated HER-2/neu overexpression, and lower grades and proliferative indices [3]. Elderly patients, however, are more likely to present with larger and more advanced tumours, and recent reports suggest that lymph node involvement increases with age [4]. Elderly patients are less likely to be treated according to accepted treatment guidelines [5] and undertreatment can, as a consequence, have a strong negative impact on survival [6]. Despite the fact that breast cancer occurs mainly in elderly patients, this population is significantly underrepresented in clinical trials.

Collaboration with geriatricians and comprehensive geriatric assessment are of paramount importance in detecting unaddressed problems, improving functional status and, possibly, survival in elderly patients with cancer [7]. Because comorbidities and functional status significantly impact on prognosis and treatment choice [8], thorough consideration must be given to the overall health of elderly patients. A significant proportion of patients older than 70 years with operable breast cancer die of noncancer-related causes [9]. Age alone, however, should not be a barrier to treatment.

Early-stage breast cancer treatment

Surgery

For the elderly population, breast cancer surgery-related mortality is low, ranging from 0% to 0.3% [10]. Alternatives to conventional surgery include outpatient surgery [11] or surgery under local anaesthesia [12], which are preferably undertaken when family support is present.

Hormone therapy instead of surgery. Past assumptions that elderly patients should receive less aggressive forms of breast cancer treatment and about reduced life expectancy have meant that hormonal therapy alone without surgery has been considered a reasonable treatment option for elderly women with breast cancer with limited life expectancy, mainly in frail patients or the very old, e.g. ≥80 years [13]. The impact of omitting surgery on overall survival (OS) is not clear and differs in different studies (Table 1) [14–19]. A Cochrane meta-analysis on this topic has confirmed that primary hormonal therapy with tamoxifen is inferior to surgery (with or without hormonal therapy) for the local control and progression-free survival of breast cancer in medically fit older women [20]. Surgery, however, does not result in significantly better OS.

Breast conservation therapy. Elderly patients are less likely to receive breast conservation therapy (BCT) [21]. The conclusions of the large randomised trials of BCT versus mastectomy are not easily applied to elderly patients given that women over the age of 70 years were excluded from these trials. However, smaller studies involving patients ≥70 years of age have documented that BCT in comparison with mastectomy is associated with better quality of life [22] and is preferred by the majority of elderly patients [23] compared with mastectomy.

Axillary surgery. Axillary lymph node dissection (ALND) should be performed in patients with clinical evidence of axillary lymph node involvement. For those without clinical lymph node involvement, however, the indication for upfront ALND has been less clear for the elderly population. Before the sentinel lymph node (SLN) procedure, older patients with breast cancer were less likely to undergo ALND than younger patients. Several studies have shown no difference in outcome in older patients with small tumours without palpable lymph nodes when ALND was omitted [24–28]. In elderly patients in whom the results of an ALND will not influence adjuvant chemotherapy decisions, including those with small tumours and low risk of nodal involvement, it may be appropriate to omit ALND. In recent years, however, SLN biopsy has been introduced as an alternative to ALND also in patients aged ≥70 years [4, 29] and is a generally accepted standard in patients of all ages with tumour size <(2)–3 cm and no clinical evidence of axillary involvement [30].

SIOG recommendations concerning surgery. Surgery should not be denied to breast cancer patients ≥70 years of age and should not differ from procedures offered to younger patients, unless patient preference dictates. ALND should be used when there is clinical suspicion of axillary lymph node involvement.
or high-risk tumours, as adjuvant treatment may depend on the pathological results of the ALND. SLN biopsy is a safe alternative to ALND in patients with clinically node-negative tumours. Elderly patients with tumour size <2–3 cm and no clinical evidence of axillary involvement should be offered an SLN biopsy. Controversy exists regarding the need for ALND after a positive SLN.

radiotherapy
after breast-conserving surgery

Elderly patients continue to receive radiotherapy less frequently after breast-conserving surgery (BCS) than younger patients [31]. Several studies have specifically evaluated the benefits of radiotherapy in the elderly. The absolute incidence of relapse as well as the absolute benefit from radiotherapy tended to be low and data on OS was generally absent with the exception of one trial [32]. Some have concluded that radiotherapy may be avoided in low-risk older patients [33, 34] while others have suggested it may offer benefits in terms of slight reductions in local relapse rates [32, 35] and improvements in OS. The Early Breast Cancer Trialists’ Group Overview, involving ~42 000 women with breast cancer, found that the 5-year risk of local recurrence after BCS was higher in women aged <50 years (33%) compared with those aged >70 years (13% of 3459 in this age group) [36]. The absolute effects of post-BCS radiotherapy on local recurrence (mainly in the conserved breast) were also greater for women aged <50 years than in older women (5-year risk reductions of 22% versus 11%, respectively), although the risk reduction was still statistically significant in older women. A supplementary dose (boost) of radiation to the excision site after BCT with clear margins seems to reduce the risk of local recurrence also in patients over the age of 60 years [37].

postmastectomy radiotherapy

In contrast to radiotherapy following BCS, the absolute effects of postmastectomy radiotherapy on the 5-year risk of local recurrence (mainly in the chest wall or lymph nodes) have been shown to be independent of age [36]. In this meta-analysis of women who had a mastectomy, axillary clearance and node-positive disease, reductions in recurrence averaged about 18% in all age groups; however, few women aged >70 years were included in the trials assessed.

SIOG recommendations on radiotherapy

Radiotherapy after BCS and adjuvant systemic therapy decreases the risk of local relapse and should be considered in all elderly breast cancer patients. The absolute benefit on local relapse might be small in elderly patients with low risk tumours, but the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis shows no differences in proportional reductions in local recurrence risk by age. The influence of radiotherapy on breast cancer and non-breast cancer mortality is less clear and further stratification is not available. It is unlikely that radiotherapy will improve OS, which is much more influenced by comorbidity/aging or the occurrence of distant metastases. A decision to offer radiotherapy will need to take into account patient health and functional status, risks of mortality from comorbidities (particularly cardiac and vascular), and the risks of local recurrence.

In principle, postmastectomy chest wall radiation is indicated if patients have four or more involved nodes or a T3 or T4 tumour. In older patients with a life expectancy <5 years, a decision of whether to implement adjuvant radiation should be based on considerations of locoregional control alone. There are limited data available to support the use of systematic postmastectomy chest wall radiation therapy in patients with one to three positive nodes or in node-negative patients with other risk factors.

Additional doses of radiation to the tumour bed should be considered in older patients after BCT and systemic therapy in order to decrease risk of local relapse.

adjuvant hormone therapy

The meta-analysis by the EBCTCG demonstrated that for hormone receptor-positive breast cancer, treatment with 5 years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31%, independently from age [38] (Figure 1). Aromatase inhibitors were superior to tamoxifen in terms of disease-free survival (DFS), although there was little difference in OS rates and no age-related differences have been observed.

SIOG recommendations on adjuvant hormonal therapy

Elderly patients with hormone-sensitive breast tumours benefit from adjuvant hormone therapy. There is no evidence for age-related differences in the efficacy of tamoxifen and aromatase inhibitors. Aromatase inhibitors are slightly more effective than tamoxifen, but elderly patients are more vulnerable to some adverse events, and safety should be an important factor in choosing between tamoxifen and aromatase inhibitors. Older patients who are candidates for endocrine therapy should be offered initial treatment with aromatase inhibitors or tamoxifen. For those initially treated with

Figure 1. Relative recurrence and mortality reduction per age group with adjuvant tamoxifen according to the 2005 overview of the Early Breast Cancer Trialists’ Collaborative Group [38]. With permission from Lancet Oncology.
tamoxifen, consideration should be given to changing to an aromatase inhibitor after 2–3 years of tamoxifen therapy.

**adjuvant chemotherapy**

The EBCTCG analysis of randomized trials conducted before 1995 showed substantial benefits of adjuvant chemotherapy in postmenopausal women in all age groups [38]. The gain was larger in those aged <50 years compared with those >50 years (Figure 2). The gain for patients above age 70 years was in the same range as for those between 50 and 70 years, but was not significant due to smaller numbers. Elderly patients with hormone receptor-negative tumours have been shown to have significant benefit from adjuvant chemotherapy [39, 40]. For hormone-sensitive tumours, the benefits of chemotherapy are reduced and less obvious in the elderly. Only one phase III trial designed specifically for elderly patients (>65 years of age) has been published [41]. In this study, weekly flat doses of epirubicin plus tamoxifen improved DFS compared with tamoxifen alone, but did not improve OS. Considerable uncertainty remains regarding the subgroups of older women most likely to benefit.

With regard to choice of chemotherapy, healthy older patients can basically receive the same regimens as their younger counterparts, but care is warranted since elderly patients experience greater toxicity [42], with up to 1.5% of treated patients dying from the treatment-related deaths in the CALGB retrospective analysis [43]. Special considerations might apply to elderly women. Anthracycline-containing regimens have been shown to have superior efficacy to combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF), and this effect was not age-dependent [44]. Although not specifically aimed for elderly patients, a recent study showed that docetaxel in combination with cyclophosphamide (TC) was superior compared with four cycles of doxorubicin–cyclophosphamide [45], and the effect was also seen in patients above age 65 years.

Treatment with adjuvant trastuzumab improves outcome significantly in HER-2/neu-positive patients [46, 47]. Few patients aged ≥70 years, however, have been included in these large trials and age >50 years was an independent predictor of trastuzumab-associated congestive heart failure [48]. Cardiac adverse events are more a concern in older patients who are at higher risk of cardiovascular disease.

**SIOG recommendations concerning adjuvant chemotherapy**

Treatment with adjuvant chemotherapy should not be an age-based decision, but instead take into account an individual patient’s estimated absolute benefit, life expectancy, treatment tolerance and preference. Older patients with node-positive, hormone-negative breast tumours potentially derive the largest benefit in survival gain. Although not specifically validated in the elderly population (>270 years), decision aids such as adjuvant online (www.adjuvantonline.com) can be used to help weigh the risks and benefits of adjuvant therapy together with the patient.

In the absence of cardiac contraindications, four courses of an anthracycline-containing regime are usually preferred over CMF in elderly patients with breast cancer. Taxanes could be added to anthracyclines in high-risk fit elderly women. TC or CMF can replace anthracyclines in patients at cardiac risk.

In the absence of cardiac contraindications, adjuvant trastuzumab should be offered to older patients with HER-2-positive breast cancer when chemotherapy is indicated, but cardiac monitoring is essential.

**metastatic breast cancer**

Metastatic breast cancer is treatable but not curable. Therefore, the main aims in treating elderly patients, like younger patients, with metastatic breast cancer are to maintain quality of life, minimize symptoms from disease and prolong survival without causing excessive toxicity.

Several hormonal treatments are available and should be the treatment of choice for women with ER-positive and/or PR-positive tumours without life-threatening disease. The use of chemotherapy should be considered in hormone receptor-negative or hormone-refractory patients. Preference should be given to chemotherapeutic agents with ‘safer’ profiles, such as weekly taxane regimens, newer less cardiotoxic anthracycline formulations, capecitabine, gemcitabine and vinorelbine. Particular attention should be paid to supportive care, as older patients are more likely to develop neutropenia than younger patients [49] and generally have less functional reserve than their younger counterparts. In HER-2/neu-positive patients, trastuzumab can be used in conjunction with chemotherapy.

**SIOG recommendations on metastatic breast cancer**

The goals of treating metastatic breast cancer in older patients are not different from those in younger patients. For the majority of patients with hormone receptor-positive breast cancer, hormonal therapy should be the first choice. The use of chemotherapy should be considered in patients with hormone receptor-negative, hormone-refractory or life-threatening disease. Choice of chemotherapy regimens and agents is

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Figure 2. Relative recurrence and mortality reduction per age group with adjuvant polychemotherapy according to the 2005 overview of the Early Breast Cancer Trials’ Collaborative Group [38]. With permission from Lancet Oncology.
dependent on individual patient characteristics, preferences and drug availability.

**disclosures**

No significant relationships.

**references**


