

REVIEW ARTICLE

Early-Stage Breast Cancer in the Elderly: Confronting an Old Clinical Problem

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Breast cancer generally develops in older women and its incidence is continuing to increase with increasing age of the population. The pathology and biology of breast cancer seem to be different in the elderly, often resulting in the undertreatment of elderly patients and thus in higher rates of recurrence and mortality. The aim of this review is to describe the differences in the biology and treatment of early breast cancer in the elderly as well as the use of geriatric assessment methods that aid decision-making. Provided there are no contraindications, the cornerstone of treatment should be surgery, as the safety and efficacy of surgical resection in elderly women have been well documented.

Because most breast cancers in the elderly are hormone responsive, hormonal therapy remains the mainstay of systemic treatment in the adjuvant setting. The role of chemotherapy is limited to patients who test negative for hormone receptors and demonstrate an aggressive tumor profile. Although the prognosis of breast cancer patients has generally improved during the last few decades, there is still a demand for evidence-based optimization of therapeutic interventions in older patients.

Key Words: Aged, Breast, Disease management, Neoplasms, Therapeutics

INTRODUCTION

Breast cancer (BC) is the prevailing malignancy of women in industrialized countries, which affects women of all ages. However, the majority (almost 60%) of cases are diagnosed at 65 years or older and more than 30% of cases are diagnosed over the age of 70 years [1-4]. The risk of developing BC increases with age. In the United States, the risk of BC in women aged under 40 is one in 202; however, this risk increases to one in 26 for women between 40 and 60 years old, and to one in 15 over the age of 70 years [5]. Overall, BC is responsible for one out of every three cancer-related deaths [1,2]. BC mortality rates increase significantly with age; most BC-related deaths are observed in women over 65 years old [6].

Owing to the aging population and increased life expectancy in the Western world, the incidence of BC is expected to rise, reaching a peak in women between the ages of 70 and 84 years [7]. Despite the magnitude of this clinical problem, the treatment approach for this patient group is not based on evi-

dence and widely accepted knowledge. Consequently, almost 50% of older women with early-stage BC (BC that has not spread beyond the breast or axillary lymph nodes, including ductal carcinoma *in situ*, stages I, IIA, IIB, and IIIA) are not managed with the currently available treatment approaches, leading to poor prognosis and increased mortality [8]. The aim of this review is to synthesize all the available knowledge regarding early-stage BC in elderly women (older than 65 years) and to present a brief reference to molecular markers and a more extensive account of the treatment options.

BREAST CANCER BIOMARKERS IN THE ELDERLY

It is well documented that a favorable molecular profile is observed more frequently in elderly BC patients [9,10]. This profile includes the expression of the estrogen (ER) and progesterone receptors (PR), decreased levels of cell proliferation markers [11], lower expression of human epidermal growth factor receptor 2 (HER2) [12], a higher frequency of diploids, a lower frequency of p53 mutations [13], and the overexpression of the B-cell lymphoma 2 (Bcl-2) protein [9].

In terms of ER/PR positivity, a considerable number of studies using large datasets, such as the San Antonio Breast Cancer Database and the Surveillance, Epidemiology and End Results registry, have shown that elderly women are more

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Received: December 17, 2014 Accepted: July 20, 2015

likely to have ER-positive tumors. Eighty-three percent of women younger than 65 years old, 85% of patients between 65 and 74 years of age and 91% of patients older than 85 years old were found to have ER-positive tumors [14].

This observation can lead to the erroneous conclusion that hormonal therapy is a panacea for BC in the elderly [15]. However, a significant percentage of these tumors lack both ER and PR expression. Thus, they not only possess an aggressive biological phenotype, but also affect relapse-free and overall survival (OS), because hormonal therapy has little or no effect [15-17].

Another interesting finding is that early-stage BC is detected less frequently in elderly women than in younger patients [13]. For example, T1 tumors are observed in 70% of patients between 45 and 64 years old, but in only 47% of women over 75 years [18]. This difference further highlights the fact that elderly women undergo mammography less frequently. Additionally, differences in the tumor biology may not account for this discrepancy [19].

UNDERTREATMENT OF BREAST CANCER IN THE ELDERLY

The limited number of elderly patients in clinical studies not only prevents clinicians from concertedly drawing sound conclusions regarding disease management [20], but also leads to suboptimal treatment. The undertreatment of early-stage disease is more common than overtreatment, as these patients are more likely to have less axillary surgery as well as less adjuvant radiation therapy and more frequently hormonal monotherapy [21].

The fact that the impact of BC on survival decreases with age is a major factor in the undertreatment of the elderly [22]. Besides, the widely accepted notion that BC in older women is biologically less aggressive than in younger patients is a principal cause of undertreatment and clearly affects the survival outcome [23]. Moreover, the uncertainty of whether elderly women can tolerate the optimal treatment makes physicians opt for less aggressive therapeutic approaches [24].

This approach may be justified in light of the frequency of comorbidities, which is a frequent clinical problem in the elderly [25]. For instance, 14% of newly diagnosed patients aged 70 to 79 years and 22% of patients older than 80 years suffer from two or more coexistent conditions/illnesses [25]. A recent study, in which more than 64,000 BC patients with a median age of 75 years were enrolled, also showed that comorbid conditions are associated with decreased OS and increased mortality [26]. However, recent data show that the differential management of elderly BC patients does not influence the loco-

regional or metastatic recurrence rate, or disease-free survival (DFS) [22,27]. On the other hand, treatment according to existing recommendations may improve the therapeutic results and survival [28,29]. It is clear that effective treatment requires the achievement of a balance between over- and undertreatment.

COMPREHENSIVE GERIATRIC ASSESSMENT

The selection of the optimal therapy, particularly for the elderly, requires consideration of not only the estimated survival, but also other clinical parameters such as comorbidity, age, organ function, and physical status, as mentioned above [30]. Comprehensive geriatric assessment (CGA) is an objective, scientific method, which enables clinicians to assess these characteristics and to predict the outcome after treatment interventions [31]. In particular, CGA incorporates validated tools to assess physical performance, comorbidity, medications, cognition, psychological status, nutrition, and social support [30]. Notably, an initial geriatric assessment in combination with a comprehensive oncological evaluation has been proposed as the gold standard for the management of elderly BC patients [32]. Despite concerns about its time-consuming character, the CGA is undeniably a useful tool providing oncologists with valuable information about the past, present, and future of the patients and makes treatment more personalized.

THERAPY

Local therapy

Surgery

The most prevalent therapeutic approach for early BC in elderly patients is surgical resection of the tumor, unless there are clear contraindications. The surgical management can include either a breast-conserving operation (lumpectomy or quadrantectomy), usually followed by postoperative radiation therapy, or a more radical operation (mastectomy), with or without resection of the sentinel lymph node, followed by postoperative radiotherapy in selected cases [33,34].

Most elderly women can tolerate breast-conserving operations and mastectomies; the mortality during surgery ranges from 1% to 2% according to previous studies that applied old anesthesia techniques [35]. However, after advances in anesthesiology, the rate of surgical mortality in elderly patients without other health problems has decreased [35]. In addition, the American College of Cardiology and the American Heart Association have reported that breast operations are low-risk and that the co-existence of other medical conditions is the main factor affecting surgical morbidity and mortality

rather than the age of the patient *per se* [35,36]. Despite the documented safety and efficacy of breast operations in the elderly, common clinical practice is substantially different. For example, in some countries, up to 50% of elderly patients do not undergo surgery [37]. Moreover, according to a multinational study, the vast majority of patients (92%) over 80 receive hormonal therapy without any surgery [38]. Furthermore, elderly patients generally undergo less aggressive local operations, without any postoperative radiation therapy or chemotherapy [34].

The surgical management of the axilla in older women should be similar to that in younger women. Axillary lymph node dissection has historically been used for axillary evaluation in early BC patients. However, sentinel lymph node biopsy is increasingly preferred and is surpassing the use of axillary dissection [39]. Axillary dissection prolongs the operation time and the time under anesthesia and it is also accompanied by a higher percentage of complications [15]. Notably, 16% of patients develop edema, 17% have shoulder mobility restriction, and 75% present with disordered intercostal nerves [40].

In older women with no palpable lymph nodes, forgoing lymph node dissection in early BC has almost no effect on OS, as shown by the low frequency of recurrence in the axillary lymph nodes [41-44]. Contrastingly, axillary lymph node dissection is recommended for patients with clinically positive nodes. In patients with positive sentinel lymph nodes, surgical clearance of the axilla is usually recommended. However, in an American College of Surgeons Oncology Group trial (Z0011), patients with positive sentinel lymph nodes who did not undergo axillary dissection did not have worse 5-year survival [45]. In a recent study, Yi et al. [46] suggested that almost 75% of sentinel lymph node-positive patients could avoid axillary clearance. However, when axillary lymph node dissection is chosen, it should ideally be performed at the same time to avoid the complications of a delayed surgery [8]. In the European Organisation for Research and Treatment of Cancer (EORTC) AMAROS trial (310 of 1,425 sentinel lymph node-positive patients were over 65 years old), axillary irradiation was evaluated as an alternative to axillary dissection. The results indicated that the axillary node status did not influence the administration of adjuvant radiotherapy, suggesting that axillary radiotherapy is an acceptable option [8,47-49].

Should adjuvant radiation therapy be performed?

Usually, the second step in the management of patients with early-stage disease is adjuvant radiation therapy. It is well documented that adjuvant radiation therapy significantly reduces the risk of local recurrence after conservative surgical resection [14,50]. In an Italian study that randomized 579 patients

with tumors less than 2.5 cm in size, quadrantectomy and axillary lymph node dissection with and without radiation therapy were compared; the rates of local recurrence were 5.8% and 23.5%, respectively. In the same study, local recurrence was inversely associated with patients' age. For example, local recurrence was more frequent in women up to 45 years of age and almost absent in patients over 65 [15]. Smith et al. [51] reported that 70- to 79-year-old women without comorbidity were more likely to benefit from radiotherapy, and that the benefit was less significant in patients over 80 years old. Furthermore, according to a meta-analysis of 17 trials of breast-conserving therapy, radiotherapy after surgery not only halves the risk of local or distant 10-year recurrence, but also reduces BC annual death rate in early BC patients (T1-T2) by a sixth (rate ratio, 0.82) [52]. Although postsurgery radiation does not seem to improve OS in early-stage disease, postmastectomy chest wall irradiation improves the survival of elderly patients (70 years or older) with advanced disease (T3-T4, N2-N3) [53].

A further reduction in local recurrence was also observed when adjuvant radiotherapy was combined with hormonal therapy. The Cancer and Leukemia Group B (CALGB) 9343 trial compared the outcomes of 636 low-risk patients who were over 70 years of age (ER-positive, tumor size less than 2 cm, stage I, and no lymph node infiltration) and received adjuvant tamoxifen treatment with or without radiation. A reduction in local recurrence (from 4% to 1%) was observed in patients who had received radiation therapy, but there was no difference in OS [54]. In a previous study, Fyles et al. [55] studied 769 women aged 50 years or older who had node-negative breast tumors (5 cm or less in size, T1/T2), had undergone breast-conserving surgery, and received adjuvant tamoxifen with or without radiotherapy. The local recurrence rate at 5 years was 0.6% for the radiotherapy and tamoxifen group and 7.7% for the tamoxifen monotherapy group. Fisher et al. [56] compared radiotherapy, tamoxifen therapy, and their combination in BC patients of all age groups with small tumors (<1 cm) and found no difference in the total first event rate among the three treatment arms.

Although there is scant evidence about radiation therapy management in older, early-stage BC patients, radiation therapy is an accepted treatment modality for women who undergo conservative operations or mastectomy and have a high risk of local recurrence. This includes women with locally advanced tumors with surgical margins near the tumor, tumor size greater than 5 cm, and more than four infiltrated axillary lymph nodes [1,14,39]. In addition, adjuvant radiation therapy should be considered for all patients with a life expectancy over 10 years [21,29,57]. However, the usefulness of adjuvant

radiation therapy after mastectomy of BC patients with one to three axillary infiltrated lymph nodes remains debatable [14]. Furthermore, in the absence of a survival benefit, radiation therapy should be selected for elderly patients with small tumors and no positive lymph nodes based on an individual's risk of local recurrence [54].

Importantly, the omission of radiotherapy in the adjuvant setting remains controversial [8]. According to the meta-analysis by Early Breast Cancer Trialists' Collaborative Group et al. [52], the omission of whole-breast radiotherapy does not influence OS, even though it reduces the local control rate. The results of the CALGB 9343 trial also support this finding; the OS showed no difference with or without radiotherapy after 10 years of follow-up (63% and 61%, respectively) [39,54,58]. Furthermore, data from the Post-operative Radiotherapy In Minimum-risk Elderly II trial (early-stage patients treated with breast-conserving surgery/endocrine therapy \pm adjuvant radiotherapy) corroborate the CALGB 9343 trial results and show that postoperative radiotherapy does not influence OS and can be safely omitted in ER-positive but not in ER-negative patients [59]. Despite the fact that the omission of radiotherapy is not undertaken widely and should be studied more, we believe that this approach is only acceptable in the personalized medicine context, after the consent of the hospital oncology group, and in light of the patient's wishes.

Hypofractionation and accelerated partial breast irradiation

In the last 5 years, shorter schedules of radiotherapy, which offer the advantage of reduced overall treatment times and possible breast preservation, have been investigated [39]. A trial from the Royal Marsden Hospital and the Gloucestershire Oncology Centre compared different whole-breast fractionation approaches and found that they had similar effectiveness and comparable adverse effects in patients younger than 75 years old at the time of presentation [60]. Two other trials including elderly BC patients (16% and 11.5% of the whole study cohort, respectively) showed that 15- and 16- fraction schedules had the same local recurrence rates and adverse effects as the standard 25-fraction scheme [61,62]. Similar results were published by Ortholan et al. [63] and Kirova et al. [64], who evaluated hypofractionated schedules of 32.5 Gy (five fractions weekly) in elderly groups (367 women aged \geq 70 years and 150 patients with a median age of 78 years, respectively). Consequently, hypofractionated regimens of 40 Gy in 15 or 42.5 Gy in 16 fractions have been endorsed in the recommendations of the St. Gallen 2013 and 2015 panels, which are accepted as the standard of care [61,65-67]. Besides radiotherapy hypofractionation, partial breast irradiation (PBI) has also been investigated intensively during this period

[58]. In PBI, only the tumor region (surgical cavity with a 1 to 2 cm margin) is irradiated with higher single doses, thereby reducing the dose to the normal tumor-adjacent structures (up to a 50% decrease in the irradiated breast volume) and organs (e.g., heart and lungs), while simultaneously shortening the conventional 6 week daily radiotherapy course [68,69].

The most commonly used techniques are intra- or postoperative brachytherapy (interstitial implants, MammoSite balloon catheter), targeted intraoperative radiotherapy (TARGIT), and electron intraoperative radiotherapy (ELIOT) [8]. Till date, TARGIT A is the only randomized trial that compared whole-breast irradiation postconservative surgery with the TARGIT technique (20 Gy dose intraoperatively). The 4-years survival rate without locoregional recurrence in this trial, wherein 41% of the cohort participants were more than 65 years old, was 1.20% in the TARGIT group versus 0.95% in the whole-breast radiotherapy group. Thus, the TARGIT group did not have inferior survival rates ($p=0.41$) [70,71]. Moreover, in a nonrandomized trial, Veronesi et al. [72] studied the usefulness of the ELIOT technique after conservative surgery in 1,822 patients, 789 of whom were over 60 years old and had the lowest annual local recurrence and the lowest second ipsilateral cancer rates (0.58 and 0.22, respectively). Additionally, in a large registry trial, Shaitelman et al. [73] reported that the failure rate for 5-year local control in women over 60 in the American Society of Breast Surgeons registry, who were "suitable" for breast brachytherapy (MammoSite radiation therapy system) was 2.59%. Despite these promising results, PBI is not recommended as a definitive treatment because of the lack of longitudinal data. However, the St. Gallen 2013 guidelines, the European Society of Medical Oncology (ESMO) clinical guidelines, and the European Society of Breast Cancer Specialists have endorsed PBI as a reasonable and accepted treatment option for well-selected patients with a low risk of recurrence [8,65,74]. However, this issue created a controversy at the last St. Gallen Consensus Conference 2015 [75].

Systemic therapy

Primary endocrine therapy

In the 1980s and 1990s, nonrandomized studies showed that tamoxifen itself was as effective as mastectomy in patients with early BC. As a result, this drug was introduced as a first-line therapy for elderly patients [15]. However, over a 10 years follow-up period, the local recurrence frequency was 9% in patients who had undergone mastectomy, but 57% in patients who had been treated with tamoxifen alone [34,76,77]. The Cochrane review, which included patients over 70 years old with operable BC, also concluded that hormonal therapy was

inferior to surgery in terms of local disease control but not OS [78]. On the contrary, in a more recent, albeit small study, OS, regional recurrence, and the frequency of distant metastases were similar after 20 years of follow-up in women aged over 70 with early operable primary BCs (<5 cm) for both the mastectomy-alone and tamoxifen monotherapy groups [79]. Johnston et al. [80] also reported that combining surgery with tamoxifen in fit elderly people (≥ 70 years) conferred no advantage with regard to the regional recurrence and rate of metastasis or survival, even though local control was better. Thus, various studies have shown an advantage of using surgery or surgery plus tamoxifen compared to tamoxifen alone for better local control. Contradictory findings have also been reported, mainly no difference between surgery and tamoxifen for local control. However, most studies agree that there is no difference in OS between surgery and tamoxifen.

For optimal therapeutic management, and according to the recommendations of the European Society of Breast Cancer Specialists, surgery should be preferred as first-line therapy, as long as it prevents local recurrence, prolongs DFS, and improves patients' quality of life [8,34]. Moreover, if improved local control is achieved, longer OS may be possible [81]. However, endocrine therapy is an acceptable alternative primary choice for women with hormone receptor-positive tumors, when comorbidities and age limit life expectancy or when the patient refuses or is unfit to undergo surgery [82].

Adjuvant hormonal therapy

Adjuvant hormonal therapy is the cornerstone of early BC treatment schedules [58]. The benefits of hormonal therapy, including improved survival, for elderly women with early, ER-positive tumors, have been confirmed in large randomized clinical trials.

According to the Early Breast Cancer Trialists' Collaborative Group overview, 5-year adjuvant therapy with tamoxifen in women of all ages with positive ER and PR status reduces the frequency of yearly BC relapse by more than 39% and mortality by more than 31% regardless of age [83]. In addition, the pivotal role of tamoxifen in the hormonal management of elderly BC patients was documented in the International Breast Cancer Study Group Trial IV, wherein 1 year tamoxifen delivery prolonged DFS and OS during a 21-years follow-up [84]. On the other hand, Christiansen et al. [85] found that in BC patients older than 60 years of age with hormone-responsive histological subtypes, tumors up to 10 mm in size, and grade 1 ductal carcinoma or grade 1 or 2 lobular carcinomas, OS did not seem to improve with adjuvant hormonal therapy.

Several large-scale randomized trials have demonstrated

that adjuvant treatment with aromatase inhibitors (AIs) provides additional benefits compared to tamoxifen treatment, but only a small proportion of the participants in these studies were elderly [1,8,86,87]. The Breast International Group 1-98 study, which compared letrozole treatment to tamoxifen therapy in a cohort of 8,010 patients (36% aged 65 or over) with a median follow-up time of 5 years, demonstrated that letrozole was superior in terms of local and distant metastasis reduction, decreased contralateral BC development, and improvement of DFS irrespective of age [88,89]. In addition, grade 3 and 4 nonfracture adverse effects were observed in older patients in the letrozole treatment arm, but no differences in thromboembolic or cardiac events were documented between the two treatment arms. Besides, the discontinuation of treatment was observed more often in the elderly (both arms) and higher rates of hypertension (51.4%), cardiac events (19.6%), and fractures (15.5%) were detected [90].

The Arimidex Tamoxifen Alone or in Combination trial confirmed the above findings by showing that anastrozole treatment improved DFS compared to tamoxifen therapy (hazard ratio, 0.75; $p=0.01$) and prolonged the time to recurrence, with fewer thromboembolic events and endometrial carcinomas, even after a median follow-up of 100 months [91,92]. The median age of patients in this trial was 64 years with 27% of the cohort aged over 70, but no data were available regarding tolerance and efficacy in the elderly subgroup [93]. Besides, the superiority of AIs was recently confirmed in two separate meta-analyses. First, upfront tamoxifen monotherapy was compared with AIs, which resulted in a 3.9% decrease in recurrence after 8 years observation. The ratio of annual event rates was similar between the two arms in women over 60. On the other hand, switching strategies (2–3 years of tamoxifen then continuing with AIs) reduced BC recurrence rates in a statistically significant manner (absolute decrease of 3.1%, 5 years after diagnosis), but there were no statistically significant differences between the recurrence rates in women over 60 [94]. In addition, the MA.17 trial showed that letrozole therapy after 5 years of tamoxifen treatment was superior to placebo in terms of DFS, distant DFS, and OS in all age groups [95,96].

The protective role of tamoxifen against fractures has also been well documented in the older population. Five-year tamoxifen administration in the adjuvant setting prevented 23 and 90 spine fractures per 10,000 women aged 50–59 and 70–79 years, respectively [97,98]. On the contrary, AI users over the age of 65 are more likely to have hip (adjusted hazard ratio, 3.24) and nonvertebral (adjusted hazard ratio, 1.34) fractures than patients treated with tamoxifen [99]. Patients aged over 75 with low bone mineral density who have one or more

risk factors for fracture, may benefit from bisphosphonate treatment [39,100]. Eidtmann et al. [101] recently confirmed the effectiveness of zoledronic acid in preventing bone mineral loss in patients treated with letrozole.

Furthermore, treatment with tamoxifen could result in a range of adverse effects, and their co-evaluation is significant, particularly for the elderly. More specifically, tamoxifen treatment in women aged 70–79 years increases the absolute risk of endometrial carcinoma (2.2%), strokes (2%), thromboembolic episodes (0.5%), and cataracts (3.8%) [1]. On the other hand, the administration of AIs poses a lower risk of developing endometrial cancer, thromboembolism, vaginal hemorrhage and hot flushes than that of tamoxifen in any age group. However, arthralgia, myalgia, bone loss, and synovial pain occur more frequently with AIs [102,103].

According to the St. Gallen 2015 consensus, some postmenopausal patients could be treated with tamoxifen. However, it was strongly suggested that women at high risk (involvement of four or more nodes, grade 3, high Ki-67, or HER2 positivity) should be treated with AIs upfront and then switched to tamoxifen treatment. AIs can also be administered, beyond the first 5 years, in node-positive patients treated initially with tamoxifen or for less than 5 years with AIs. No consensus has been reached on AI administration after the first 5 years of AI treatment [66,67]. ESMO guidelines recommend AI (nonsteroidal AI and exemestane) management in an upfront schedule or sequentially after 2 to 3 years of tamoxifen. As extended adjuvant treatment, letrozole and anastrozole could be used after 5 years of tamoxifen [104]. The American Society of Clinical Oncology guidelines also recommend the incorporation of AIs as up-front therapy or as sequential treatment after tamoxifen in postmenopausal women with hormone-responsive early BC, although the ideal initiation time and duration of treatment have not been defined [105]. It is obvious that more data are needed to determine the most effective sequence of drug administration, especially in elders, but in the interim, the inclusion of AIs in the adjuvant hormonal therapy of elderly patients is well justified.

Adjuvant chemotherapy

Ten percent to 20% of elderly BC patients have aggressive tumors with negative ER or PR status [106]. Thus, hormonal therapy is not recommended for these patients, and chemotherapy is the only realistic therapeutic approach. Moreover, patients with hormone-sensitive tumors and negative prognostic markers, such as HER2 overexpression, infiltrated lymph nodes and a high proliferation rate, are also potential candidates for chemotherapy [107,108]. However, the importance of adjuvant chemotherapy in elderly patients is difficult

to evaluate, as data from relevant studies are limited [109]. Thus, conclusions cannot be safely drawn to provide conclusive guidelines [107].

The Early Breast Cancer Trial Group demonstrated that adjuvant chemotherapy was beneficial for patients up to 70 years of age, although the efficacy decreased with age [109,110]. In addition, the CALGB and United States Breast Cancer Intergroup have shown that chemotherapy mostly benefits patients with negative hormone receptor status; thus, chemotherapy remains the most prevalent systemic therapy for this group [111]. In contrast, with the exception of high-risk patients who receive clear benefits, the efficacy of adjuvant chemotherapy in elderly BC patients with positive hormone receptor status is debated. A retrospective study compared tamoxifen adjuvant monotherapy against a combination of tamoxifen and anthracycline-based chemotherapy in BC patients (29.4% of patients over 65 years) with positive ER status and infiltrated lymph nodes, and found that survival was not improved as long as the recurrence score was low [1,19,112]. Similarly, Fargeot et al. [47] documented that although low doses of epirubicin and tamoxifen therapy versus tamoxifen alone improved DFS, but not OS in node-positive BC patients ≥ 65 years.

Adjuvant chemotherapy has historically included four cycles of doxorubicin (adriamycin) and cyclophosphamide (AC) or six cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). These regimens have been shown to notably improve survival from BC [113]. In addition, regimens such as cyclophosphamide/doxorubicin/5-fluorouracil, cyclophosphamide/epirubicin/5-fluorouracil, or AC plus four cycles of taxanes have recently been shown to be somewhat more effective than standard CMF or 4AC therapies [114]. In a recent trial with women aged 65 years or older, both AC and CMF were found to be superior to capecitabine monotherapy in terms of both the relapse-free survival (85% vs. 68%, respectively) and OS (91% vs. 86%, respectively) after 3 years of follow-up [110]. On the other hand, four cycles of docetaxel/cyclophosphamide were found to be superior with regard to DFS and OS compared to standard 4AC, not only in younger patients but also in older women [115]. Third-generation regimens such as dose-dense AC and paclitaxel, AC followed by docetaxel, or the combination of docetaxel/doxorubicin/cyclophosphamide are recommended for patients without major health problems, but with a very high risk of recurrence [113].

In any case, as differences in survival between various chemotherapeutic agents are slight, contraindications, comorbidities, and potential toxicities should be co-evaluated when selecting the ideal therapy [29,47,116]. Although the type of

toxicity in elderly patients without other health problems, does not differ from that in younger patients, adjuvant chemotherapy causes toxicity more frequently in older patients [117]. Thus, the administration of adjuvant chemotherapeutic regimens seems feasible in older patients, but has higher rates of treatment breaks, hospitalization, and dose reductions [8].

Targeted therapies

The urgent need for more efficient and less toxic therapies has led to the development of selective targeting molecules, among which monoclonal antibodies play a crucial role. The main monoclonal antibody used in early-stage BC is trastuzumab, which targets the extracellular domain of HER2 [118]. Ten percent to 16% of breast tumors in women aged over 65 years are positive for HER2; this frequency is similar or slightly lower than that observed in younger patients [119]. Moreover, HER2 overexpression, even in small lesions (less 1 cm), seems to be associated with a worse natural history and poorer prognosis. Hence, the use of trastuzumab in women with small breast tumors is an accepted therapeutic option with the exception of T1a disease, which does not require anti-HER2 therapy according to the St. Gallen 2015 consensus [74].

It is well documented that trastuzumab adjuvant treatment for HER2+ BC patients, measured either by immunohistochemistry or gene amplification (fluorescent *in situ* hybridization or chromogenic *in situ* hybridization), improves survival and reduces the risk of local recurrence and death [74]. Furthermore, when trastuzumab was combined with chemotherapy, it was shown to reduce the relapse frequency to 50% compared to chemotherapy alone [29,120]. Therefore, combined chemotherapy and trastuzumab administration should be used as adjuvant treatment in the absence of cardiac contraindications, as recommended by the International Society of Geriatric Oncology guidelines [8]. Consequently, the St. Gallen 2015 consensus unanimously recognized the concurrent administration of trastuzumab with paclitaxel over a 1-year period as a reasonable option for stage I HER2-positive patients with a maximum tumor diameter of 1 cm. For stage I patients with tumors larger than 1 cm, a slim majority of the panel favored anthracycline treatment followed by a taxane and trastuzumab regimen [67]. The same panel accepted that the concurrent combination of HER2 treatment with taxane should precede the administration of an anthracycline in stage 2 and HER2 BC patients [67]. However, because data for elderly patients are limited, conclusions cannot be safely drawn for this subpopulation [15].

The major limiting factor and adverse effect of trastuzumab is cardiotoxicity [118], resulting in a decreased left ventricular ejection fraction and possibly congestive cardiac failure, which

is usually reversible [39]. The patient's age is a risk factor for cardiotoxicity; in particular, older patients run a higher risk and should be monitored for a reduced left ventricular ejection fraction [121]. However, the HERA trial did not demonstrate a significant difference in cardiac adverse events between patients older or younger than 60 years of age [70]. Although the incidence of cardiotoxicity in trastuzumab monotherapy is only 5%, combination treatment with trastuzumab and anthracyclines dramatically increases this frequency to 25% [118]. To minimize the risk of cardiac toxicity, ESMO guidelines suggest the concurrent administration of trastuzumab with a non-anthracycline-containing regimen and the avoidance of delivery after an anthracycline-based treatment scheme [74,104].

Lapatinib is another targeted drug, which interrupts the HER2 and epidermal growth factor receptor pathways. A multicenter, randomized phase III trial, recently documented lapatinib as an accepted treatment option for trastuzumab-naïve HER2-positive early-stage BC women who do not or cannot receive adjuvant trastuzumab [122]. However, more data are needed to elucidate the role of lapatinib in early-stage BC in elderly patients.

CONCLUSION

The management of BC in the elderly constitutes a persistent clinical problem because of the aging population in Western countries. The current therapeutic approach for elderly patients with early-stage BC is based mostly on clinical studies performed in women of different ages. Thus, the optimization of therapeutic interventions for these patients can be achieved not only by the co-evaluation of the life expectancy, possible comorbidities, and the treatment benefit/risk ratio, but also by incorporating the results of large-scale and adjusted-for-age clinical trials. At present, the management of early-stage BC patients is based on common clinical tools such as tumor stage, differentiation grade, ER or PR status, and HER2 expression. In the years to come, we hope that medics will be armed with highly efficient molecular markers that allow better stratification of patient groups with increased probability of benefiting from adjuvant therapy, and highly sophisticated targeted drugs that alter the prognosis and physical history of the disease.

During the last few decades, screening programs and new treatment options have considerably improved the prognosis of BC patients. However, more research and education of health providers in certain geriatric issues is required for elderly patients.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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