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REVIEW

Optimal management of breast cancer in the elderly patient: current perspectives

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Abstract: Breast cancer (BC) is the most common female malignancy in the world and almost one third of cases occur after 70 years of age. Optimal management of BC in the elderly is a real challenge and requires a multidisciplinary approach, mainly because the elderly population is heterogeneous. In this review, we describe the various possibilities of treatment for localized or metastatic BC in an aging population. We provide an overview of the comprehensive geriatric assessment, surgery, radiotherapy, and adjuvant therapy for early localized BC and of chemotherapy and targeted therapies for metastatic BC. Finally, we attempt to put into perspective the necessary balance between the expected benefits and risks, especially in the adjuvant setting.

Keywords: elderly, breast cancer, geriatric assessment, surgery, chemotherapy, radiotherapy

Introduction

Breast cancer (BC) now represents the most common female malignancy in both the Western world and in developing countries, and is the leading cause of cancer death among women worldwide.[1] Approximately one third of BCs occur over the age of 70 years.[2] Aging women over 75 years have poor survival rates.[3] Unlike in younger women, survival for elderly patients with BC has not improved significantly over recent years.[4]

The poor prognosis in older women is largely related to their unfavorable stage distribution,[5] with larger tumor size at presentation, greater lymph node involvement, and more metastatic BC. This is mostly explained by delayed diagnosis in this age group.[6,7] Indeed, older patients have tumors with more favorable biological characteristics when compared with younger postmenopausal patients, ie, a higher degree of estrogen receptor (ER) and progesterone receptor expression (81% of patients ≥70 years of age in the study by Pierga et al[8]), less peritumoral vascular invasion,[9] less HER2/neu expression,[10] lower proliferative rates, diploidy, and normal p53.[11] These factors affect treatment decisions, as they are, as for the youngest patients, predictors of the risk of relapse. Furthermore, indolent tumor types, such as lobular, mucinous, and papillary mammary carcinoma, are encountered more frequently in the elderly.[12]

However, some studies suggest that BC in the elderly is not more indolent. In a single-institution analysis by Sigh et al in a subgroup of elderly patients (>70 years of age) with lymph node-negative disease, BC appeared to be more aggressive, with a greater risk of developing distant metastases compared with younger patients.[13] Similarly, in another single-institution analysis by Wildiers et al smaller tumors seemed to be associated with increased axillary lymph node involvement.[14] The hypothesis made by the authors was that small BCs in older patients have different behavior because of decreased immune defense mechanisms related to aging.

Increasing age is independently associated with decreased compliance with guidelines, decreased likelihood of surgical procedures, less frequent use of adjuvant radiation therapy following breast-conserving surgery (BCS), increased use of primary endocrine therapy,[15] and decreased use of adjuvant chemotherapy even in "fit" patients.[16] As a consequence, we reviewed the clinical evidence concerning BC in the elderly to help practitioners give their patients optimal and individualized treatment.

Pharmacologic issues

Age can have an impact on most pharmacokinetic parameters, ie, absorption, distribution, metabolism, and excretion.[17] Firstly, polypharmacy can alter absorption.[18] Secondly, the volume of distribution is modified by an increase in body fat, and a decline in body water and serum albumin levels. For example, with aging, the volume of distribution of anthracyclines is reduced. Thirdly, in the aging process, drug metabolism is altered by decreased hepatic function (reduced hepatic blood flow and decreased liver mass and metabolic activity, including that of the cytochrome P450 enzyme system). Lastly, after the age of 30 years, glomerular filtration and renal blood flow rates decline in a linear fashion, so that values in octagenarians are only half to two thirds those measured in young adults.[19] Consequently, careful drug prescribing is mandatory in the elderly due to the physiologic changes of aging, comorbidity (such as cardiac disease), and polypharmacy. Clinical and pharmacologic data on the pharmacokinetics of chemotherapy are available.[20]

What does the Comprehensive Geriatric Assessment add to standard oncologic evaluation?

The Comprehensive Geriatric Assessment (CGA) has been evaluated in a systematic review in the oncology setting, including BC.[21,22] Geriatric assessment both adds information to a standard oncologic assessment[23] and impacts treatment decisions, modifying them in 0%–49% of cases.[21,24] Conflicting findings regarding the predictive ability of geriatric assessment for treatment toxicity/complications have been reported. Several domains, including instrumental activities of daily living, poor performance status, and numerous geriatric deficits, are consistently associated with an increased mortality risk.

In the subgroup of BC, a cancer-specific Geriatric Assessment (GA) evaluating six measures (financial resources, comorbidity, obesity, physical function limitations, general mental health, and social support) predicted BC-specific survival.[25] Comorbidity, cognitive function, financial status, functional limitation, and social support were associated with poor treatment tolerance and mortality,[26,27] and geriatric intervention directly influenced oncologic treatment in four of 15 BC patients.[28]

However, CGA lacks standardization, and specific randomized trials focusing on the effectiveness of CGA and its impact on clinical decision-making in the oncology setting and in different tumor types such as BC are still needed.

In geriatric oncology, the Vulnerable Elders Survey (VES-13),[29] the Groningen Frailty Indicator,[30] the G8 instrument,[31] and the abbreviated CGA[32] are screening tools that help identify vulnerable patients who would benefit from a full CGA. The G8 was validated in a French multicenter prospective cohort of 1,668 patients, 53.7% of whom had BC. The sensitivity of G8 was significantly superior to the VES-13 (76.6% versus 68.7%, respectively), although its specificity was inferior (64.4% versus 74.3%). When the G8 and VES-13 were used together, sensitivity increased to 86.6% but specificity decreased to 53.2%.[33,34] Other screening tools have been evaluated, such as the abbreviated CGA.[32] In the specific setting of BC, the VES-13 was compared with the Barber questionnaire and showed better predictive ability for detecting frailty risk.[35]

Early stage and locally advanced breast cancer
Neoadjuvant therapy

Preoperative therapy may be offered to render surgery feasible or allow BCS. It has no impact on overall survival (OS) or disease-free survival (DFS) compared with adjuvant therapy.[36]

In the neoadjuvant setting, hormone therapy is more often prescribed over chemotherapy. Only two Phase II studies have compared neoadjuvant endocrine therapy with chemotherapy.[37,38] The first study[37] compared anastrozole or exemestane for 3 months with doxorubicin plus paclitaxel for four cycles in older postmenopausal patients with hormone receptor-positive BC. It found no statistically significant difference between the two treatment arms for clinical response rate (64% in both arms), time to response, or pathologic complete response (3% versus 6%, respectively). However, a trend toward a superior rate of BCS was observed in patients receiving endocrine therapy (33% versus 24%, $P=0.58$). In the second study,[38] comparing epirubicin plus cyclophosphamide for four cycles versus exemestane for 24 weeks, a greater clinical response rate with chemotherapy versus hormone therapy was found (66% versus 48%), but this did not reach statistical significance ($P=0.075$). In contrast, patients with a low proliferation rate (Ki67 $\leq$10%) had a similar response rate in both treatment arms (63% versus

58%, P=0.74). Results from a multicenter Phase III study of neoadjuvant chemotherapy (FEC100) compared with hormone therapy (letrozole) are awaited (ClinicalTrials.gov identifier NCT00963729).[39] Currently, neoadjuvant endocrine therapy is used for postmenopausal patients with HR-positive BC when the risk of chemotherapy combined with surgery is greater due to advanced age or comorbidities. Indeed, it is questionable whether chemotherapy should be prescribed for older patients when toxicity is not negligible and effectiveness is not well established, especially in HR-negative BC.[40] Moreover, the toxicities attributed to chemotherapy are not justified in HR-positive/HER2-negative tumors, which have a good prognosis irrespective of pathologic complete response after neoadjuvant therapy.[40]

Concerning endocrine therapy, a meta-analysis[41] showed that aromatase inhibitors are significantly more effective and as safe as tamoxifen, and reported a clinical objective response rate (relative risk 1.29), ultrasound objective response rate (relative risk 1.29), and BCS rate (relative risk 1.36). Anastrozole, letrozole, and exemestane can be used (Table 1). Continuing letrozole in responding patients beyond 3–4 months achieves a further clinical reduction in tumor size for up to 2 years.[42]

Limited data exist concerning neoadjuvant chemotherapy in the geriatric setting. Chemotherapy and trastuzumab seem to be interesting in fit elderly patients with HR-negative and HER2-positive BC.[43] For frail or elderly patients, sequential chemotherapy might also be appropriate in order to avoid the toxicity of combination chemotherapy. Few studies have compared sequential versus combination therapy in the neo-adjuvant setting. One Phase II study compared concomitant versus sequential doxorubicin and docetaxel[44] and reported similar objective clinical responses but more hematologic adverse events in the concomitant arm, with more hand–foot syndrome in the sequential arm (42%).

Is surgery avoidable?

Elderly BC patients are sometimes denied surgery because the risk of postoperative complications and mortality is higher in this population, especially when concomitant diseases and polypharmacy are associated or when mastectomy is chosen over BCS.[45,46]

Historically, primary endocrine therapy alone with tamoxifen was prescribed as an alternative to surgery.[47] Nevertheless, surgery followed by endocrine therapy was shown to do better than endocrine therapy alone in PFS and specific survival[48–50] and, for one study, in overall survival.[51] Primary endocrine therapy should only be offered to women with ER-positive tumors who are unfit for or refuse surgery and have a short estimated life expectancy of less than 2–3 years, since that is the median duration of response to primary endocrine therapy with tamoxifen.[52–55]

However, no randomized trial has compared surgery versus primary endocrine therapy with aromatase inhibitors,

Table 1 Neoadjuvant hormone therapy

Hormone therapy	Reference	Age, median and range (years)	Study design and population	Efficacy	Toxicity
Exemestane 25 mg orally once daily for 4 months	Mlineritsch et al[198]	71 (54–92)	Multicenter, Phase II, 80 patients	ORR 34% BCS 76%	Grade 3 hot flushes 3.8% Grade 2 bone pain 5%
	Tubiana-Hulin et al[199]	67.6 (52.1–92.2)	Multicenter, Phase II, 45 patients	ORR (clinical) 73.3% ORR (ultrasonographic) 45.2% BCS 57.1%	Grade 1–2 toxicity 69.6%
Anastrozole (1 mg once daily for 3 months) versus tamoxifen	Cataliotti et al[200] PROACT trial	67.3 (48.7–91.5)	Randomized, double-blind, multicenter, Phase III, 451 patients	ORR 39.5% (ultrasound measurements) and 50% (caliper measurements) BCS 43%	Nausea 20.6% Hot flushes 8.3%
	Smith et al[201] IMPACT trial	73.2 (51.8–90.2)	Randomized, double-blind, multicenter, Phase III, 330 patients	Clinical ORR 37% Ultrasound ORR 24% BCS 44%	Hot flushes 18%
Letrozole (2 mg once daily for 4 months) versus tamoxifen	Eiermann et al[202]	68	Multinational, randomized, double-blind, Phase IIb–III, 324 patients	Clinical ORR 55% Ultrasound response 35% BCS 45%	Hot flushes 20%

Note: Grading based upon NCI-CTC (National Cancer Institute Common Toxicity Criteria).
Abbreviations: ORR, objective response rate; BCS, breast-conserving surgery; PROACT, Pre-Operative "Arimidex" Compared to Tamoxifen trial; IMPACT, Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen trial.

which are more efficient than tamoxifen in the elderly. The UK ESTEEM (Endocrine ± Surgical Therapy for EldErly women with Mammary cancer) trial comparing primary anastrozole with surgery plus adjuvant anastrozole in women aged 75 years or older with ER-positive tumors was closed because of poor accrual. In a prospective study evaluating neoadjuvant letrozole,[42] 33 of 63 women (mean age 83 years at diagnosis) evaluated remained on letrozole alone, and at 3 years the median time to treatment failure had not been reached. In conclusion, letrozole alone may provide long-term disease control for elderly women with a short life expectancy.

Mastectomy or BCS

Concerning surgery, the randomized European Organisation for Research and Treatment of Cancer (EORTC) 10850 trial found no difference in terms of OS and PFS between tumorectomy and modified radical mastectomy.[48] However, tumorectomy plus tamoxifen is associated with improved time to distant progression[48] and less functional limitation than mastectomy alone.[56] Moreover, mastectomy has a negative psychologic impact for both old and younger women.[57] Minimally invasive techniques such as radiofrequency ablation are under evaluation for frail elderly patients with a short life expectancy and who are not candidates for conventional surgery.[58]

Axillary dissection

Lymph node involvement and lymph node ratio are major prognostic factors in BC, even in the elderly.[59] Axillary lymph node dissection enables lymph node mapping and a decision regarding adjuvant therapy, and has an impact on disease control. However, this technique has major morbidity, including lymphedema, pain, paresthesia, limited arm abduction, and altered quality of life.[60] Axillary clearance can be avoided when nodes are clinically negative[61–63] and when sentinel lymph node biopsy is negative,[64] with no impact on DFS, OS, or locoregional control. Concerning micrometastatic (≤2 mm) sentinel lymph nodes with no extracapsular extension and a primary tumor ≤5 mm, axillary dissection can be avoided, eliminating the complications of axillary surgery and with no adverse effect on survival.[65]

Among patients with limited metastatic sentinel lymph node involvement (1–2 nodes) T1–T2 invasive BC treated with lumpectomy, tangential whole breast irradiation, and systemic therapy, the American College of Surgeons Oncology Group Z0011 Phase III study showed that axillary dissection does not significantly improve OS or DFS.[66]

This conclusion was confirmed in a randomized trial evaluating all BC patients from 30 to 65 years[67] and validated by the American Society of Clinical Oncology Clinical Practice Guideline Update.[68]

An alternative to axillary dissection is axillary radiotherapy for patients with cT1-2N0 BC up to 5 cm and a positive sentinel lymph node biopsy. In the AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery) trial, after 5 years of follow-up, there were no significant differences between axillary dissection and axillary radiotherapy in terms of DFS (86.9% versus 82.7%, *P*=0.1788) or OS (93.3% versus 92.5%, *P*=0.3386). However, 5 years after therapy, the rate of lymphedema in the surgery group was twice as high when compared with the radiotherapy group (28% versus 14%). An issue with this technique is the incomplete axillary staging. Nevertheless, axillary radiotherapy does not significantly modify adjuvant systemic therapy.[69]

Breast reconstruction

The rate of breast reconstruction after mastectomy is lower in elderly women.[70,71] This may be due to patient preference or to the physician's reluctance to address the topic of reconstruction in this population. Age alone should not be an exclusion criterion.[72] Indeed, breast reconstruction in the elderly preserves their quality of life.[73] Breast site complications associated with reconstruction occur more often in older patients but are often minor. Autologous tissue-based reconstruction may provide greater benefits than implant-based reconstruction.[71]

Adjuvant therapy
Radiotherapy
Whole breast radiation therapy following BCS
Omission of radiotherapy after BCS is controversial. Firstly, radiotherapy after BCS results in a decreased risk of ipsilateral recurrence[74,75] and BC mortality, but not in OS.[76–78] Secondly, patients aged 70–79 years with minimal comorbidity are the most likely to benefit from radiotherapy, and older patients with substantial comorbidity are the least likely to benefit from it.[78] Thirdly, the risk of local recurrence declines with age, an effect likely to be enhanced by endocrine therapy.[79]

In this context, PRIME 2 (Post-operative Radiotherapy In Minimum-risk Elderly – Phase II), an international, randomized, controlled Phase III trial, set out to address the question of whether whole breast radiation therapy (WBRT) could be omitted in carefully defined groups of older patients.[80] This trial enrolled 1,326 patients aged 65 years or older with

hormone-positive, low-grade cancer, negative axillary nodes, and free-tissue margins who were receiving hormone therapy. At 5 years, the primary endpoint, ie, ipsilateral breast tumor recurrence, was 1.3% in patients who received radiotherapy and 4.1% in those who did not. DFS was significantly different, but there was no difference in OS. In accordance with this trial, a retrospective study[81] and an exploratory subgroup analysis of a randomized trial[82] identified a subgroup of patients with a low risk of local recurrence (T1–T2, node-negative, grade 1 tumors ≤1 cm, HR-positive) after BCS with a clear excision margin in whom postoperative radiotherapy could be omitted.

Unlike these trials, retrospective analyses showed that the elderly had lower 5-year OS and BC-specific survival and an increased risk of subsequent mastectomy when radiotherapy was omitted.[83,84] Furthermore, breast radiotherapy is well tolerated by most older BC patients without impairment of their overall health-related quality of life.[85]

To conclude, radiotherapy should only be omitted in frail patients with an obviously limited life expectancy and T1N0, ER-positive BC, given that the burden of local recurrence is likely not to appear before the patient dies from another cause.[86] A nomogram including age, race, tumor size, ER status, and receipt of radiotherapy was developed to predict the likelihood of long-term breast preservation after BCS.[87]

Breast boost after BCS
WBRT after BCS, with a boost to the tumor bed, should be considered in all elderly patients since it decreases the risk of local relapse. The randomized EORTC 22881-10882 trial found, after a median follow-up period of 10.8 years, that a boost dose of 16 Gy led to improved local control in all age groups, but with no difference in survival.[88] A total of 5,318 patients with a median age of 54.8 (25.6–78.8) years were evaluated.

Postmastectomy radiotherapy
There is no randomized controlled trial evaluating postmastectomy radiotherapy in elderly patients. In a retrospective analysis, postmastectomy radiotherapy was associated with improved survival in older women with high-risk (T3/4 and/or N2/3) BC.[89] The SUPREMO (Selective Use of Postoperative Radiotherapy aftEr MastectOmy) trial is ongoing, with no upper limit of age in patients at intermediate risk of locoregional recurrence, ie, 1–3 positive nodes (N1), or T2 with additional risk factors, ie, grade 3 histology and/or lymphovascular invasion.[90]

Hypofractionated radiotherapy
Underuse of radiotherapy in the elderly may be related to the cost and inconvenience of a regimen protracted over several weeks. In this regard, hypofractionated radiotherapy is an attractive validated option.[91] The UK START (Standardisation of Breast Radiotherapy) trial[92,93] and a randomized Canadian study[94] prospectively validated two hypofractionated regimens delivering 41.6 Gy in 13 fractions and 42.5 Gy in 16 fractions, respectively. Using these regimens, locoregional relapse at 10 years did not differ significantly between standard and accelerated radiotherapy. Toxicity (breast shrinkage, telangiectasia, and breast edema) was significantly less common in the hypofractionated WBRT group in the START trial. This technique when associated with hormonal therapy is also a good alternative to surgery in nonoperable older patients and in the event of refusal to undergo surgery.[95]

Alternative to WBRT: accelerated partial breast irradiation
Various accelerated partial breast irradiation techniques, including intraoperative or postoperative brachytherapy, targeted intraoperative radiotherapy, and electron intraoperative radiotherapy, are under investigation.

Concerning postoperative accelerated partial breast irradiation, a meta-analysis[96] of three randomized trials[97–99] evaluating 1,140 patients compared whole versus partial breast irradiation and found comparable OS for both treatment modalities. However, the studies included had relatively short follow-up, and partial breast irradiation was associated with a statistically significant increase in the risk of local and axillary recurrences.

However, this technique is promising in the elderly, since a single fraction therapy delivered concomitantly with surgery may avoid the inconvenience of several weeks of daily therapy. The targeted intraoperative radiotherapy technique consists of a single dose delivered concurrently with lumpectomy. It showed noninferiority to fractionated external beam radiotherapy with regard to local recurrence in the conserved breast. Wound-related complications were much the same between the groups, but grade 3 or 4 skin complications were significantly reduced with targeted intraoperative radiotherapy.[100,101] This is an option for low-risk patients (ER-positive, no nodal involvement, no lymphovascular invasion, grade 1–2, clear excision margins). Another technique, ie, electron intraoperative radiotherapy, was evaluated in an equivalence randomized trial.[102] In women with early small BC, electron intraoperative radiotherapy resulted

in significantly more local recurrence than did conventional postoperative external radiotherapy after 5 years of follow-up, but OS did not differ between the groups.[102]

Adjuvant systemic therapy
Adjuvant endocrine therapy
Omission of endocrine therapy is an option for patients with very low-risk tumors (≤10 mm, grade 1 ductal carcinoma, grade 1 or 2 lobular carcinoma).[103] In other cases, for HR-positive tumors, adjuvant endocrine therapy is indicated. Aromatase inhibitors are preferred to tamoxifen for their safety and efficacy. In a subgroup analysis of the Breast International Group (BIG) 1-98 Collaborative Group, adjuvant treatment with letrozole, compared with tamoxifen, significantly improved DFS, OS (hazard ratio 0.82), and time to distant recurrence.[104,105] Elderly healthy patients completing 5 years of tamoxifen should be considered for extended adjuvant therapy with letrozole.[106]

Concerning toxicity, aromatase inhibitors are associated with fewer thromboembolic events, endometrial cancers,[107] and cognitive impairment[108] when compared with tamoxifen. On the other hand, aromatase inhibitors are associated with more bone fractures[107] and musculoskeletal adverse events. In the exploratory analysis of ATAC (Arimidex Tamoxifen Alone or in Combination), 35.2% of women treated with anastrozole developed joint symptoms.[109] These symptoms are a frequent reason for discontinuing therapy (20%).[110] In routine clinical practice, only 69% of women on anastrozole remained adherent to this therapy.[111] In this regard, the PROACTIVE (RECF2252) trial evaluating the impact of geriatric intervention on endocrine therapy observance is ongoing.[112] Furthermore, aromatase inhibitors are associated with a 1.5 times higher risk of bone fractures than tamoxifen (from 0.9% to 11%).[113] All patients initiating aromatase inhibitors should be encouraged to undertake physical activity and to receive bone mineral densitometry, calcium/vitamin D supplements, and antiresorptive therapy if their T-score for bone mineral density is less than –2.0 or if they have two or more risk factors for fracture. Unsatisfactory compliance/decreasing bone mineral density after 12–24 months on oral bisphosphonates should trigger a switch to intravenous bisphosphonate therapy.[114] Finally, specific adverse events predict a survival benefit in patients treated with aromatase inhibitors.[115]

Adjuvant chemotherapy
The challenge in geriatric oncology is to balance the potential benefits and risks of adjuvant therapy. The majority of BCs in women aged 70 years and older are HR-positive and HER2-negative. The major issue in these patients, most of whom are candidates for endocrine therapy, is the potential added value of chemotherapy. The decision regarding adjuvant therapy should be taken considering life expectancy[116] (for example, with the 4-year mortality prognostic index developed by Lee et al),[116] cancer prognosis,[117] and the estimated reduction in risk of recurrence and specific mortality.[118]

The risk of relapse can be estimated using the Adjuvant! computer program developed by Ravdin et al[119] or the 70-gene signature.[120] Adjuvant! was developed to estimate 10-year DFS and OS incorporating all of the prognostic factors except for HER2 tumor status. This tool helps the clinician to estimate the outcome with local treatment only and the potential benefit of systemic therapy. It should be noted that Adjuvant! was developed using data from patients up to 69 years of age and that the effectiveness of second-generation and third-generation chemotherapy regimens in older patients, as estimated by Adjuvant!, has not been validated in clinical trials, and it is possible that the value of such regimens is overestimated in this patient group. Adjuvant! also integrates patient age into its survival calculations and can be adjusted to account for comorbidity, which is extremely helpful information when discussing the risks and benefits of treatment with older patients.

However, the benefits of adjuvant therapy in the elderly must be weighted by some elements. First, in older patients, comorbidities and competing causes of deaths[121] are more frequent. Second, the gain in reduction of recurrence or mortality as a result of adjuvant therapy is less important in older patients.[118,122,123] Third, the toxicity of adjuvant chemotherapy is higher. Indeed, adjuvant polychemotherapy has substantial toxic effects (around 60%–70% grade 3 or 4 adverse events),[124] more grade 4 hematologic toxicity, more treatment discontinuation for toxicity, and more acute myeloid leukemia/myelodysplastic syndrome (1.8%).[125] Age is a risk factor for the development of myelodysplasia and acute myelogenous leukemia after anthracycline-based adjuvant chemotherapy for BC.[126] In a retrospective review of four randomized Cancer and Leukemia Group B (CALGB) trials,[124] older patients had higher chemotherapy-related mortality (1.5% of patients aged ≥65 years), and the incidence of treatment-related mortality increased linearly with age. Recently, the phenomenon of "chemobrain" (long-term chemotherapy-induced cognitive impairment) has been described and has been associated with altered quality of life and functionality.[127] Moreover, adjuvant chemotherapy was shown to have a progerontogenic effect, estimated as 10.4 years of chronologic aging.[128]

The other barrier to adjuvant therapy is the feasibility of chemotherapy in the elderly. Indeed, as outlined above, standard chemotherapy regimens prescribed for younger patients, such as cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), result in higher grade 3 toxicities (hematologic events, mucosal toxicity) and more dose reductions.[129,130]

The subgroup of patients in whom chemotherapy is associated with a significant reduction in mortality is HR-negative BC irrespective of pN status.[131,132] Its role in HR-positive BC remains controversial. In this regard, GERICO (the French Group of Geriatric Oncology) has developed a trial to evaluate the benefit of adjuvant chemotherapy with regard to OS in patients aged over 70 years, with pN0 or pN-positive, HR-positive HER2-negative disease, and with a high genomic grade index assessed by reverse transcriptase polymerase chain reaction (ClinicalTrials.gov identifier NCT01564056).[133]

Elderly patients should be given clear information regarding the benefits and risks of therapy, given the fact that the toxicity is not negligible and the benefit is sometimes modest. They should become active participants in the decision to adhere to such treatment.[134]

As for younger patients, polychemotherapies are more efficient than monotherapy.[135] In the CALGB 49907 trial, standard adjuvant chemotherapy with CMF or doxorubicin plus cyclophosphamide was superior to capecitabine alone in fit patients over 65 years.[124] Only one Phase III trial compared adjuvant epirubicin plus tamoxifen versus tamoxifen alone, but the difference in DFS did not reach statistical significance.[136]

Anthracyclines are another option. However, the risk of being diagnosed with congestive heart failure is increased in elderly women.[137] In this regard, the International Society of Geriatric Oncology recommends the use of liposomal anthracycline formulations.[138]

In fit elderly women aged 70–85 years with HR-negative early BC and a significant risk of recurrence, four cycles of non-pegylated liposomal doxorubicin plus cyclophosphamide was feasible but had a certain impact on social and role functioning; however, autonomy was preserved and toxicity was acceptable.[139]

The other feasible regimen is four cycles of adjuvant docetaxel plus cyclophosphamide.[140,141] Docetaxel plus cyclophosphamide was compared with doxorubicin plus cyclophosphamide in one study.[142] In patients aged 65–74 years, docetaxel plus cyclophosphamide was superior to standard doxorubicin plus cyclophosphamide in terms of DFS and OS. However, older women experienced higher

rates of febrile neutropenia.[143] The last feasible regimen in patients aged 65–77 years is 5-fluorouracil, epirubicin, and cyclophosphamide with pegfilgrastim support.[144]

In conclusion, the chemoregimens possible are CMF (with precautions), anthracyclines plus cyclophosphamide with a preference for liposomal anthracyclines, and docetaxel plus cyclophosphamide. Capecitabine alone is not recommended. Primary prophylaxis with granulocyte colony-stimulating factor should be discussed before initiating adjuvant chemotherapy.[145]

Adjuvant HER2-targeted therapy
Age itself should not be a contraindication, but cardiac function should be carefully monitored.[146] RESPECT (N-SAS BC07; ClinicalTrials.gov identifier NCT01104935), a randomized controlled trial evaluating trastuzumab without chemotherapy as postoperative adjuvant therapy in women aged 70–80 years, is ongoing.[147]

Metastatic breast cancer
Endocrine therapy
Elderly women with HR-positive metastatic BC should be treated like postmenopausal women, regardless of age. Aromatase inhibitors are superior to tamoxifen and better tolerated. In first-line, anastrozole,[148,149] letrozole,[150,151] and exemestane[152] have shown their superiority. In second-line, fulvestrant and anastrozole have been shown to be similar in terms of OS.[153] In the BOLERO (Breast cancer trials of OraL EveROlimus)-2 trial,[154] addition of everolimus to exemestane after progression on nonsteroidal aromatase inhibitors improved PFS. Elderly everolimus-treated patients had incidences of adverse events (stomatitis, infections, rash, pneumonitis, and hyperglycemia) that were similar to those in younger patients, but had more on-treatment deaths.[154]

One Phase II study compared letrozole plus cyclophosphamide versus letrozole alone[155] and found an overall response rate of 71.9% in 57 patients randomly assigned to receive primary letrozole and 87.7% in 57 patients randomly assigned to receive letrozole plus cyclophosphamide.

Chemotherapy
Chemotherapy is recommended in elderly women with HR-negative or rapidly progressing metastatic BC, with a preference for monotherapy and oral and weekly chemotherapies. The chemotherapy regimens that can be prescribed are summarized in Tables 2–4. Considering monotherapies (Table 2), anthracyclines are important drugs in BC. However, congestive heart failure is more frequent in patients

Table 2 Monochemotherapy regimens

Chemotherapy regimens	Dosage	Reference	Age, median and range (years)	Study design and population	Line	Efficacy	Toxicity
Pegylated liposomal doxorubicin	40 mg/m² every 28 days	Falandry et al[158]	77 (71–89)	Multicenter, Phase II, 60 patients	First line	ORR 20% PFS 6.1 months OS 15.7 months	Febrile neutropenia 1.7% Congestive heart failure 3.4%
	40 mg/m² every 28 days	Green et al[203]	72.3 (65–81)	Multicenter, Phase IV, 25 patients	First line	TTP 5.7 months OS 20.6 months	Cardiac events 12%
	20 mg/m² every 2 weeks	Basso et al[159]	78 (70–93)	Multicenter, Phase II, 32 patients	First line (78.1%)	ORR 33.3% TTP 10.3 months	No cardiac event 9.4% treatment interruption for toxicity
Oral Idarubicin	5 mg/day for 21 consecutive days, every 4 weeks	Crivellari et al[204]	75 (65–81)	Phase II, 33 patients	First or second line	PR 22% SD 33% TTP 3 months OS 17 months	Grade 4 neutropenia 6% No cardiotoxicity reported Two toxic deaths with 7.5 mg/day
Capecitabine	1,000 mg/m² twice daily	Bajetta et al[161]	73 (65–89)	Phase II, 73 patients	First line (93%)	ORR 34.9% TTP 4 months	2 toxic deaths with 1,250 mg/m² Low grade 3/4 AEs with 1,000 mg/m²
	1,000 mg/m² twice daily for 14 days every 3 weeks	De Sanctis et al[162]	76 (65–88)	Phase II, 75 patients	First line	Disease control rate 81.3%	Grade 3 events: diarrhea (12%), hand–foot syndrome (8%), mucositis (8%)
Vinorelbine	30 mg/m²/week for 13 weeks and then every 2 weeks	Vogel et al[205]	72 (60–84)	Multicenter, Phase II, 56 patients	First line	ORR 38% TTP 6 months	Febrile neutropenia 11%
	70 mg/m² orally on days 1, 3, and 5, for 3 weeks every 4 weeks (maximum 12 cycles)	Addeo et al[164]	74 (70–84)	Phase II, 34 patients	First line	ORR 38% PFS 7.7 months OS 15.9 months	Febrile neutropenia 6%
Paclitaxel	80 mg/m² weekly for 3 weeks every 28 days	Del Mastro et al[165]	74 (70–87)	Phase II, 46 patients	First line	ORR 53.7% PFS 9.7 months OS 35.8 months	Unacceptable toxicity: 15.2% (febrile neutropenia, severe allergic reaction, and cardiotoxicity)
	80 mg/m² on days 1, 8, and 15 of a 28-day cycle (dose increase 90 mg/m² in absence of toxicity)	Ten Tije et al[166]	77 (71–84)	Multicenter, Phase II, 26 patients	First line	ORR 38% TTP 6.5 months	Fatigue 67% Neuropathy 39%
Docetaxel	36 mg/m² weekly for 6 consecutive weeks, followed by 2 weeks without treatment	Hainsworth et al[168]	74 (50–88)	Phase II, 41 patients	First line 75% Second line 25%	ORR 36% TTP 7 months OS 13 months	Severe neutropenia 0.4% Grade 3/4 fatigue 20%

(*Continued*)

Table 2 (*Continued*)

Chemotherapy regimens	Dosage	Reference	Age, median and range (years)	Study design and population	Line	Efficacy	Toxicity
	36 mg/m² per week	D'hondt et al[169]	Frail and elderly patients (≥70 years)	Phase II, 47 patients	Median: 2 prior chemotherapy regimens	ORR 37%	Febrile neutropenia 8.5% Grade 3 neurotoxicity 2%
	36 mg/m² per week (starting dose of 26 mg/m² and dose escalating if no toxicity is advised)	Hurria et al[170]	75 (66–84)	Phase I, 20 patients	Prostate, lung, and breast (50%) cancer		≥ Grade 3 58% ≥ Hematologic grade 3 16% ≥ Non-hematologic grade 3 53%
Eribulin	1.4 mg/m² on days 1 and 8 of a 21-day cycle	Muss et al[171]	≥70 years, 79 patients	Exploratory analysis from two Phase II studies and one Phase III randomized study, 827 patients	Heavily pretreated MBC	OS 12.5 months PFS 4.0 months ORR 10.1% CBR 21.5%	No overall effect of age on AEs

Abbreviations: AEs, adverse events; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; TTP, time to progression; PR, partial response; SD, stable disease; CBR, clinical benefit rate; MBC, metastatic breast cancer.

aged 65 years and over.[156] In this context, pegylated liposomal doxorubicin was proposed as an interesting alternative[138,157] but appears poorly tolerated in the very old and in vulnerable patients.[158–160] Capecitabine at a reduced dose of 2,000 mg/m² [161,162] and intravenous or oral vinorelbine[163,164] appear to be acceptable monochemotherapies with good benefit/risk ratios, provided follow-up is sufficient. The 1,000 mg/m² twice daily capecitabine dose is the standard since two toxic deaths occurred in the trial by Bajetta et al (in advanced BC)[161] and another two toxic deaths in the CALGB 49907 trial (adjuvant chemotherapy)[124] at the dose of 1,250 mg/m² twice daily. Several studies have shown the efficacy and safety of paclitaxel[165–167] and docetaxel[168–170] in elderly patients. Cardiovascular complications must be monitored with paclitaxel,[165] and docetaxel was proposed to be initiated at 26 mg/m² with dose escalation in the event of no toxicity.[170] Finally, eribulin appears to be a good alternative in heavily pretreated metastatic BC, without any major impact of age on treatment tolerance.[171]

Considering polychemotherapies (Table 4), a combination of gemcitabine and vinorelbine in elderly patients with anthracycline-pretreated and taxane-pretreated metastatic BC showed activity and safety (response rate 33.3%, PFS 6.2 months, OS 17.0 months).[172] A multicenter pilot study by GERICO assessed the effect of an oral combination of capecitabine and vinorelbine in patients with advanced breast, prostate, or lung cancer.[173] After three cycles, 42.9% had stabilized disease. Compliance was excellent (68.8%). The most common grade 3–4 toxicities were hematologic (17.9%) and gastrointestinal (7.7%).

The treatment of cancer patients near death is becoming increasingly aggressive over time,[174] whereas the benefit decreases with the line of chemotherapy.[175] Consequently, the decision to begin another line of chemotherapy should be taken with the patient after information regarding the potential benefits and risks.

HER2-targeted therapy

The prevalence of HER2-overexpressing tumors in elderly women ranges between 7% and 20%. The major concern about trastuzumab is its safety, given its nearly doubled risk of cardiac events,[176] especially in patients with cardiovascular risk factors, such as a history of cardiac disease and diabetes.[177] Trastuzumab can be given to fit patients with continuous cardiac monitoring and acceptable tolerance.[178,179]

A multicenter, retrospective, observational Italian study reported that use of trastuzumab with taxanes or vinorelbine

Table 3 Comparison of chemotherapy regimens

Chemotherapy regimen	Dosage	Reference	Age, median and range (years)	Study design and population	Line	Efficacy	Toxicity
PLD versus capecitabine	6 cycles of PLD (45 mg/m² every 4 weeks) or 8 cycles of capecitabine (1,000 mg/m² twice daily, days 1–14 every 3 weeks)	Smorenburg et al[160]	75 (65–86)	Multicenter, randomized, Phase III, 78 patients	First line	PFS 5.6 versus 7.7 months, P=0.11 OS 13.8 versus 16.8 months, P=0.59	Comparable grade 3 AEs, no grade 4 AEs
Epirubicin versus gemcitabine	Epirubicin 35 mg/m² or gemcitabine 1,200 mg/m² on days 1, 8, and 15 of a 28-day cycle	Feher et al[206]	68 (59–91)	Multicenter, randomized, Phase III, 397 patients	First line	Superiority of epirubicin TTP 6.1 versus 3.4 months, P=0.0001; OS 19.1 versus 11.8, P=0.0004; Independently assessed RR 40.3% versus 16.4%, P<0.001, 186 and 183 evaluable patients)	Both well tolerated
Ixabepilone plus capecitabine versus capecitabine	Ixabepilone 40 mg/m² every 3 weeks + oral capecitabine (1,000 mg/m² twice each day), or capecitabine alone (1,250 mg/m² twice each day)	Vahdat et al[207]	≥65	Retrospective analysis, 251 patients	Anthracycline and taxane pretreated	PFS 5.5 versus 3.9 months ORR 37% versus 19% OS 13.9 versus 12.2 months	Febrile neutropenia 10% (ixabepilone + capecitabine)
Paclitaxel versus docetaxel	Weekly paclitaxel 80 mg/m² or weekly docetaxel 36 mg/m²	Beuselinck et al[208]	Elderly or frail patients 63.7 (31–84)	Randomized, multicentric, Phase II, 70 patients	First line 17% Second line 49% Third line or more 34%	PR 48% versus 38%, TTP 21.1 weeks versus 12.7 weeks OS 55.7 weeks versus 32 weeks	More anemia and neurotoxicity for paclitaxel and more edema and fatigue for docetaxel

Abbreviations: ORR, objective response rate; PFS, progression-free survival; OS, overall survival; TTP, time to progression; PR, partial response; SD, stable disease; PLD, pegylated liposomal doxorubicin.

was associated with a 67% response rate and a median time to progression of 8.7 months.[180] Subgroup analyses from the randomized, double-blind, placebo-controlled Phase III CLEOPATRA trial (ClinicalTrials.gov identifier NCT00567190) in older patients (median age 69 years) showed improved PFS with pertuzumab plus trastuzumab plus docetaxel. This chemotherapy regimen was safe, with a higher incidence of grade 3 diarrhea in the pertuzumab arm and more fatigue, asthenia, decreased appetite, vomiting, and dysgeusia.[181] Trastuzumab and lapatinib were also evaluated in combination with endocrine therapy, and were found to have a clinical benefit.[182,183]

Vascular endothelial growth factor-targeted therapy

Regarding antiangiogenic agents, a meta-analysis[184] of the three randomized trials evaluating bevacizumab as first-line treatment in HER2-negative, metastatic BC, ie, E2100 (ClinicalTrials.gov identifier NCT00028990), AVastin And DOcetaxel (AVADO) (ClinicalTrials.gov identifier

Table 4 Polychemotherapy regimens

Chemotherapy regimens	Dosage	References	Age, median and range (years)	Study design and population	Line	Efficacy	Toxicity
Gemcitabine and vinorelbine	Vinorelbine 25 mg/m² IV and gemcitabine 1,000 mg/m² IV on days 1 and 8 every 3 weeks	Dinota et al[209]	69 (65–87)	Phase II, 34 patients	First line	ORR 53%	Grade 3/4 neutropenia 20%
	Vinorelbine 25 mg/m² plus gemcitabine 1,000 mg/m² on days 1 and 8, every 3 weeks	Basso et al[210]	74 (70–82)	Phase II prematurely terminated for poor RR, 12 patients	First line	ORR 11.1% TTP 3 months	Grade 3 neutropenia 25% Grade 3 anemia and grade 3 GI toxicity 25%
	Gemcitabine 1,000 mg/m² and vinorelbine 25 mg/m² on days 1 and 8 every 3 weeks for a maximum of 6 cycles	Dong et al[172]	73 (65–84)	Phase II, 51 patients	First line (54.9%)	RR 33.3% PFS 6.2 months OS 17 months	Febrile neutropenia 4% One toxic death because of GI hemorrhage
PLD plus vinorelbine	PLD 40 mg/m² plus vinorelbine 25 mg/m² IV on day 1 and oral vinorelbine 60 mg/m² on day 15	Addeo et al[211]	71 (65–82)	Phase II, 34 patients	First line	ORR 50% OS 13 months TTP 8 months	Neutropenia grade 3/4 26% Febrile neutropenia 8.8%
	PLD 40 mg/m² IV on day 1 and vinorelbine 30 mg/m² IV on days 1 and 15 every 4 weeks	Mlineritsch et al[212]	68 (60–82)	Multicenter, Phase II, 42 patients	First line	ORR 36% TTP 4 months OS 24 months	
Oral capecitabine and vinorelbine	6 cycles: capecitabine 750 mg/m² bid, days 1–14 every 21 days Vinorelbine 45 mg/m², days 1 and 8 Dose escalation after 3 cycles depending on tolerance (capecitabine 1,000 mg/m² bid, days 1–14 and vinorelbine 60 mg/m², days 1 and 8)	Rousseau et al[173]	75.5 (69–86)	Multicenter, Phase II trial, 80 patients	First line	ORR 8.6% 1-year PFS 9.8% 1-year OS 54.9%	Febrile neutropenia 1.3% grade 3/4 hematological toxicity: 17.9% Grade 3/4 GI toxicity 7.7%

Abbreviations: ORR, objective response rate; PFS, progression-free survival; OS, overall survival; TTP, time to progression; PLD, pegylated liposomal doxorubicin; RR, response rate; GI, gastrointestinal; IV, intravenous; bid, twice daily.

NCT00333775), and Regimens in Bevacizumab for Breast Oncology (RIBBON-1) (ClinicalTrials.gov identifier NCT00262067), showed a benefit in PFS but not in OS. The benefit in PFS in the elderly (≥65 years) was less important than in younger patients (hazards ratio 0.67 for PFS in patients aged <65 years and 0.75 in patients aged ≥65 years). Concerns exist regarding safety, especially about cardiovascular events. In exploratory subanalyses of the AVADO trial,[185] the MO19391 study (ClinicalTrials. gov identifier NCT00448591),[186] and a large, multicenter, noninterventional German study,[187] bevacizumab was well tolerated with no increase in the incidence of bevacizumab-related adverse events in patients aged over 65 years. In the

subgroup analysis from the MO19391 study,[186] the incidence of grade ≥3 hypertension was the only side effect reported more frequently in the elderly.

The ATHENA trial (MO19391, ClinicalTrials.gov identifier NCT00448591)[188] is a large (2,251 patients), international, open-label study assessing first-line bevacizumab in combination with standard chemotherapy in HER2-negative metastatic BC. Data from the ATHENA trial were analyzed in the subgroup of elderly patients aged ≥70 years.[189] Bevacizumab was combined with single-agent paclitaxel in 46% of older patients. Only hypertension and proteinuria were more common in older patients when compared with younger patients (6.9% versus 4.2%, respectively, for grade

≥3 hypertension; 4.0% versus 1.5%, respectively, for grade ≥3 proteinuria); and grade ≥3 arterial/venous thromboembolism events occurred in 2.9% versus 3.3%, respectively. Median time to progression was 10.4 months.

Ongoing clinical trials

In the adjuvant setting, a randomized multicenter trial (ClinicalTrials.gov identifier NCT0019301) comparing weekly docetaxel and CMF in the treatment of women with high-risk BC who are aged >65 years or are not candidates for anthracycline-based therapy has been completed.[190] A randomized controlled trial is currently recruiting participants to evaluate trastuzumab without chemotherapy as a postoperative adjuvant therapy in HER2-positive elderly BC patients (ClinicalTrials.gov identifier NCT01104935).[191] GERICO has developed a trial to evaluate the benefit of adjuvant chemotherapy on OS in patients aged 70+ years with pN0 or pN-positive, HR-positive/HER2-negative disease and a high genomic grade index assessed by reverse transcriptase polymerase chain reaction (ClinicalTrials.gov identifier NCT01564056).[133]

In the metastatic setting, a randomized Phase II trial by the EORTC Elderly Task Force and Breast Cancer Group is currently recruiting participants (ClinicalTrials.gov identifier NCT01597414).[192] This trial will compare pertuzumab plus trastuzumab versus pertuzumab plus trastuzumab plus metronomic chemotherapy in the elderly with HER2-positive metastatic BC. After progression, patients will be given the option of receiving trastuzumab emtansine.

Concerning radiotherapy, a randomized Phase II trial is currently recruiting participants to compare partial versus WBRT in women aged ≥60 years operated with BCS (ClinicalTrials.gov identifier NCT00892814).[193] A multicenter, controlled, randomized, nonblinded, Phase III noninferiority study (ClinicalTrials.gov identifier NCT01803958) is ongoing. This study was designed to evaluate whether partial hypofractionated and accelerated irradiation of the sole surgical cavity in patients suffering from BC with a low risk of local recurrence and who undergo conservative surgery is not inferior to postoperative irradiation with conventional fractionation of the entire breast as regards local control (incidence of ipsilateral recurrences as the prime event).[194]

Conclusion

To conclude, management of BC in the elderly is complex, firstly because this population is heterogeneous. Secondly, limited data are available, mainly because the aging population is poorly represented, especially in randomized controlled trials. Level 1 evidence data from randomized controlled trials in specific older populations (medically fit and medically frail patients) are urgently needed. We recommend a geriatric assessment when available to help the practitioner decide the best treatment for their patient. In this regard, the collaboration between oncology and geriatrics teams has resulted in the creation of oncogeriatric coordination units to facilitate access to treatment and coordinate the care of elderly patients suffering from cancer. Lastly, it is appropriate to have patient participation in decision-making, since elderly preferences often favor quality of life and independence.[195] Yet, practitioners should inform their patients that undertreatment strongly decreases the prognosis of BC.[196,197]

In the local setting, fit elderly and young women should be treated similarly. Frail patients should undergo surgery if possible. Primary endocrine therapy should only be offered to women with ER-positive tumors who are unfit for or refuse surgery and have a short estimated life expectancy less than 2–3 years. Minimally invasive techniques such as radiofrequency ablation are under evaluation. Management of the axilla in fit elderly women is the same as in younger women. Concerning radiotherapy, WBRT following BCS can only be omitted in frail patients with an obvious limited life expectancy and T1N0, ER-positive BC, as the burden of local recurrence is likely not to appear before the patient dies from another cause. Hypofractionated radiotherapy is an attractive validated option given that underuse of radiotherapy in the elderly may be related to the cost and inconvenience of a regimen protracted over several weeks. Accelerated partial breast irradiation is a promising alternative to WBRT, but the evidence is not sufficiently robust to recommend it as standard therapy. Regarding adjuvant medical therapy, omission of endocrine therapy is an option for patients with very low-risk tumors. For adjuvant chemotherapy, elderly patients should be given clear information on the benefit and risks of the therapy, given the fact that the toxicity is not negligible and the benefit is sometimes modest. Polychemotherapies are superior to capecitabine alone. The chemoregimens possible are CMF (with precautions), anthracyclines plus cyclophosphamide with a preference for liposomal anthracyclines, and docetaxel plus cyclophosphamide. Trastuzumab should be prescribed in combination with chemotherapy in HER2-positive BC in the absence of cardiac disease. In the metastatic setting, endocrine therapy is the preferred treatment in the absence of life-threatening or rapidly progressing disease. When chemotherapy is indicated, monochemotherapy, oral, and weekly regimens are preferred.

Disclosure

The authors report no conflicts of interest in this work.

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