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Aromatase inhibitors in the treatment of elderly women with metastatic breast cancer

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ABSTRACT

The proportion of elderly women in the population is rising, and in tandem, the incidence of breast cancer rises with age. Because of health and tolerability concerns, as well as life expectancy, physicians may be reluctant to advise a standard treatment regimen for elderly patients with metastatic breast cancer. To elucidate this issue, we performed a literature review of clinical studies that included women with metastatic breast cancer who were over the age of 65. Our results show that although little clinical evidence exists, what is available suggests that standard treatment is tolerated and beneficial for patients meeting certain criteria. A geriatric assessment may identify specific patient groups (independent, dependent, or frail) and thereby guide treatment. Treatment recommendations for elderly patients with metastatic breast cancer are sparse, although first-line endocrine treatment, usually aromatase inhibitors or tamoxifen, is recommended for hormone-sensitive disease. In general, the evidence from clinical studies suggests that aromatase inhibitors are more effective than either tamoxifen or megestrol acetate as first- or second-line treatment in postmenopausal women with metastatic breast cancer. Ultimately, quality of life, treatment effects, and comorbidities are important aspects in this population and may guide treatment choice. To provide evidence-based treatment guidance, future clinical trials should include more patients over the age of 65 years.

Introduction

The incidence of breast cancer (BC) increases with age until menopause; thereafter, incidence remains stable. In the United States and Europe, overall incidence of BC has declined since 2002, and BC-specific deaths have been declining for the past decade; however, the proportion of elderly women with BC is rising.[1–6] Median age at diagnosis is 61 years in the United States and 63 years in Europe.[7,8] Moreover, diagnosis of metastatic BC (mBC) is more frequent among women >75 years than among women 65–75 years.[9]

For cancer patients, "elderly" is generally considered ≥65 or ≥70 years of age, but definitions used in clinical trials vary from ≥60 to ≥70 years.[4,10] However, regardless of definition, approximately half of BC patients are considered elderly based on median age at diagnosis and are underrepresented in clinical trials. For example, in Southwest Oncology Group (SWOG) BC trials, it was estimated that <10% of patients were ≥65 years.[10] Patients ≥65 years are often excluded from BC clinical trials either because of eligibility criteria or physician perceptions that older patients are less able to tolerate standard therapies.[11] However, a case-comparison study of chemotherapy for mBC showed that patients ≥70 years had similar outcomes and side effects as younger patients.[12] Few trials have specifically enrolled elderly patients. Therefore, data to support evidence-based guidelines for management of mBC in elderly women are limited, resulting in different patterns of care and/or suboptimal treatment.[6,10]

This review of published clinical studies including women aged ≥65 with mBC focuses on factors influencing treatment decisions in elderly patients and available evidence supporting use of aromatase inhibitors (AIs) in this setting.

Factors affecting treatment of metastatic breast cancer in elderly women

Although age is not an independent prognostic factor, BC in elderly women is frequently less aggressive than in younger

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women, and the tumors often display more favorable biologic characteristics. Elderly patients more often have estrogen and progesterone receptor-positive tumors (~80%) versus younger women (range, 42%–77%).[13] Although bone metastasis is more common in elderly patients, incidence of visceral metastasis is similar to that of younger patients.[9] Various factors should be considered during treatment decisions for elderly BC patients (Table 1). Improved tumor evaluation and risk assessment are also needed to determine appropriate therapy for elderly patients. Indeed, receptor status of a recurrent metastatic tumor may be different from the primary tumor and require separate biopsy for treatment guidance.[14–19]

Age-related physiologic factors

Older patients may have cognitive impairment, compromised gastrointestinal function, first-pass metabolism, or renal function affecting pharmacokinetics/pharmacodynamics (PK/PD) of drugs. Decreased bone marrow reserve increases hematologic toxicity risk.[4] Although there are small or no chemotherapy PK differences between patients aged ≥65 years and younger patients,[20] differences in PD are common, with increased risk for toxicities in elderly patients. However, older patients can benefit from standard, dose-intense chemotherapy,[21,22] and chemotherapy doses can be modified without compromising efficacy.[23,24] Dehydration related to decreased thirst reflex may become life-threatening in the presence of diarrhea or prolonged vomiting,[10] and the resulting electrolyte imbalance may have more serious consequences in elderly patients with cardiovascular conditions. Therefore, antiemetics may be even more important in elderly patients, although current antiemetic guidelines do not offer specific recommendations for this population.[25–27]

Comorbid conditions

Compared with younger patients, elderly (≥65 years) BC patients have more comorbid conditions and a wider range of comorbidities that can affect life expectancy, physiologic reserves, and ability to tolerate treatment.[4,10] Among women >67 years diagnosed with BC (any stage), the most common comorbidities are diabetes, chronic obstructive pulmonary disease, cardiovascular diseases, and cerebrovascular disease.[28] Cardiovascular disease, in particular, is an important competing cause of death in elderly patients with mBC.[29] Therefore, drugs with significant cardiovascular toxicity, such as anthracyclines, are of concern in elderly patients.[4] Combining anthracyclines with trastuzumab or paclitaxel may also increase risk of cardiotoxicity in patients with mBC, although a liposomal anthracycline might provide lower cardiotoxicity risk.[30,31] Obesity is another factor associated with all-cause and BC-specific mortality among postmenopausal women.[32]

Table 1
Factors to consider in disease management of metastatic breast cancer in elderly patients.

Physiologic age
Physiologic reserves
Renal and hepatic function
Thirst reflex
Cognitive decline
Comorbid conditions
Cardiovascular diseases
Diabetes/insulin resistance
Pulmonary diseases
Dementia
Bone health
Life expectancy
Number and extent of comorbid conditions

Breast cancer may increase risk of osteoporosis and fractures in elderly women,[33,34] and many BC treatments, except tamoxifen, reduce bone mineral density.[35] In general, therapy with bone-modifying agents is recommended.[35–40] Hypertension and thromboembolism are other concerns, especially with tamoxifen or bevacizumab treatment. However, none of the studies that include tamoxifen in advanced BC have subanalyses by age; therefore, risk of thromboembolism from tamoxifen treatment cannot be determined.[41] A recently validated algorithm that includes specific factors for women, such as tamoxifen and hormone replacement therapy, can estimate risk of venous thromboembolism at 1 and 5 years.[42]

Life expectancy

Generally, in BC patients with distant metastases, the 5-year survival rate is <25% (for patients ≥50 years).[3,43] However, comorbid conditions in women aged 65–70 years have a very pronounced effect on survival (Fig. 1).[4] Therefore, elderly patients should have a geriatric assessment for likelihood of death from BC. Although overall likelihood of death from BC decreases with advancing age, this is not the case with distant disease.[44] Among patients aged ≥70 years with distant mBC, BC-specific death accounted for 75% of the 5-year death rate following diagnosis. Even among patients ≥70 years with regional disease (estrogen receptor-positive), BC-specific death accounted for 39% of the 5-year death rate following diagnosis (63% among patients with estrogen-negative tumors). Furthermore, metastasis site is an independent prognostic factor for survival in elderly patients, similar to younger patients.

Assessments for elderly patients with metastatic breast cancer to guide disease management

Advanced age and declining physical performance in elderly patients may lead physicians to decrease their use of diagnostic tests, which may result in suboptimal treatment for mBC.[45–47] A comprehensive geriatric assessment provides the best estimate of functional age; this should include a number of evaluations before deciding on a treatment course[4,19,43,45,48–50] (Table 2).[50]

The assessment of functional independence provides information on survival and tolerance of adverse effects from cancer treatment.[50] The need for assistance in certain activities of daily living (ADL) is associated with decreased tolerance for chemotherapy. Determining socioeconomic conditions and cognition evaluates the patient's ability to comprehend and adhere to treatment.[50] This assessment can also reveal frailty (dependence in ≥1 ADL) and exhaustion of functional reserves.

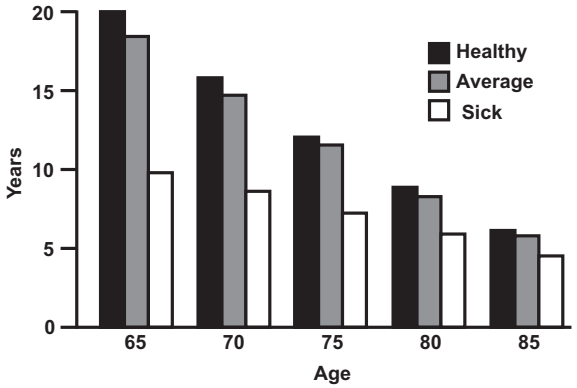

Fig. 1. Life expectancy by general health status in older patients with breast cancer. Reprinted with permission from *JNCCN–Journal of the National Comprehensive Cancer Network*.

Table 2
Elements of a comprehensive geriatric assessment.

Parameter	Screening questions	Confirmatory testing
Function	Ask about help needed for daily living such as • "Can you eat without help?" • "Can you dress yourself?" • "Do you have trouble with stairs?" • "Do you drive?"	Performance status Katz activities of daily living scale Instrumental activities of daily living scale
Comorbidity	Evaluate systems for number and severity	Confirm presence and grade
Socioeconomic conditions	Ask about help during an emergency	Adequacy of caregiver
Cognition	Serial 3 (name 3 objects and have patient repeat later)	Folstein mini-mental state examination (work up for dementia if <24)
Emotional condition	Ask about often feeling sad or depressed	Geriatric depression scale (work up for depression if >10)
Pharmacy	Review number and type of medications	If >3 medications, assess for duplications, interactions, and compliance
Nutrition	Inquire about weight loss Weigh patient and measure height	Mini nutritional assessment

Adapted with permission from Balducci and Extermann.[50]

The results of comprehensive geriatric assessment can identify 3 groups of elderly cancer patients.[50] Group 1 is independent and without serious comorbidities, and may be eligible for standard cancer treatments (adjusted for renal or hepatic function when appropriate). Group 2 is dependent in ≥1 instrumental ADL and/or may have 1–2 comorbid conditions. Patients in this group may receive standard cancer treatments if their overall life expectancy is longer than that expected from cancer and they can tolerate treatment; otherwise, palliation may be the best possible management. Overall, functional dependence in ≥1 ADL is associated with average life expectancy of <3 years. Group 3 patients are considered frail, and palliation (with possible addition of endocrine or anti-HER2 treatment) may be most appropriate.

Management of metastatic breast cancer in elderly patients

In general, mBC treatment goal is to prolong survival and palliate symptoms while maintaining or improving quality of life.[43,45,51,52] Surgery for primary tumor in primary stage IV BC may improve survival in elderly patients with low tumor burden.[52–55] Radiation therapy following surgery does not have an established role in elderly patients with mBC, and there are no data on the use of stereotactic whole body radiation treatment in elderly patients for management of oligometastatic disease.

First-line treatment

Although evidence is sparse for treatment of elderly patients with metastatic disease, guidelines recommend systemic first-line therapy.[4,19,40,51,52] Age-related and comorbidity factors should be considered in deciding among the numerous agents available (Table 3).[43] Because toxicity is more likely to have serious consequences with combination treatment in the elderly, sequential single chemotherapeutic agents are preferred. Endocrine treatment must be considered first, even when results suggest receptor-poor status. In 1 study involving 271 patients with mBC, 24 patients with receptor-poor results received tamoxifen because of suspected false-negative histochemical results, and 6 of these patients responded with durations from 11 to 51 months.[56] In cases of human epidermal growth factor receptor 2 (HER2)-positive disease, endocrine therapy has been evaluated in combination with trastuzumab/lapatinib. Clinical evidence from 2 studies has shown improved progression-free survival with anastrozole ($N = 207$) or letrozole ($n = 219$) plus trastuzumab/lapatinib, although the patients had a wide age range (27–95 years), and no analyses were performed by age.[57,58] Moreover, there was an increased incidence of grade 3/4 adverse events or serious adverse events (anastrozole + trastuzumab) with combination therapy. In contrast, although no direct comparative studies have been conducted, the clinical activity observed in trials using chemotherapy in combination with anti-HER2 therapies may be more favorable than that in trials with AIs and anti-HER2 therapies.[59] However, in a recent observational study ($N = 1001$), elderly patients with HER2-positive mBC ($n = 50$; aged ≥75 years) were less likely to receive chemotherapy plus trastuzumab and more likely to receive endocrine therapy plus trastuzumab compared with patients aged 65–74 years ($n = 117$) or patients <65 years ($n = 674$).[60] Safety data were not reported by treatment group and BC-related deaths were similar across age groups, so no definitive conclusions regarding the optimal trastuzumab-based therapy in elderly patients with HER2-positive BC can be drawn. Therefore, improved risk assessment is

Table 3
Chemotherapeutic agents available for breast cancer treatment and special considerations in elderly patients.

Agent	Special considerations
Anthracyclines (epirubicin and doxorubicin)	• Limited cardiotoxicity in older patients • Avoid use of doxorubicin in patients with an ejection fraction <50% • New liposomal doxorubicin preparation demonstrates improved side effect profile • Epirubicin in metastatic breast cancer associated with less cardiotoxicity, nausea, and myelosuppression than doxorubicin
Cyclophosphamide	• Elimination decreased in patient with impaired renal function
Methotrexate	• Excretion dependent on renal function • Dose adjustments based on renal function in older women showed reduced toxicity
Fluorouracil	• No increased gastrointestinal toxicity in patients with breast cancer (compared with colorectal cancer) • Cardiotoxicity does not appear to increase with age
Capecitabine	• Minimal myelosuppression • Hand-foot syndrome is frequently dose-limiting • Diarrhea is possible • Age does not significantly affect pharmacology • Dose reductions for renal impairment
Vinca alkaloids (vincristine/vinblastine)	• Monitor carefully for neuropathy
Vinorelbine	• Pharmacokinetics comparable in older and younger women • Favorable toxicity profile in elderly patients
Taxanes (paclitaxel/docetaxel)	• Limited data in older patients • Hepatic impairment increases toxicity • Sensory, motor neuropathy, and fluid retention (docetaxel) side effects • May cause mild to moderate myalgias and arthralgias
Gemcitabine[a]	• Age-related differences in pharmacokinetics • Favorable toxicity profile with mild myelosuppression as a single agent
Trastuzumab	• Early reports of cardiotoxicity may limit use in older women

[a] Not a Food and Drug Administration approved agent for use in breast cancer.
Reprinted with permission from Holmes and Muss.[43]

needed to better define the indication for endocrine treatment versus chemotherapy.

In hormone-sensitive tumors, endocrine treatment is treatment of choice and may continue until disease progression, unless an aggressive tumor with large visceral metastases is diagnosed. Typically, initial endocrine treatment response duration is 1 year.[43] Among available endocrine agents, AIs and tamoxifen are recommended first-line mBC therapy options.[4,40,51,52,61] Among 2 guidelines and an expert panel, AIs are preferred based on clinical evidence in postmenopausal/elderly women.[19,51,52,61,62]

Second-line treatment

At progression of metastatic disease after first-line treatment, patients may receive subsequent noncross-resistant endocrine treatment or, in certain circumstances, chemotherapy. However, tolerability of chemotherapy tends to decrease with age. In contrast, benefits and tolerability of endocrine treatment do not appear to be age-dependent.[4] German Arbeitsgemeinschaft Gynaekologische Onkologie guidelines recommend fulvestrant for patients with early progression on tamoxifen or an AI.[19] If patients develop endocrine-refractory disease, these guidelines recommend mono-chemotherapy for elderly patients with life expectancy >5 years and acceptable comorbidities (eg, taxane after progression on anthracycline treatment).[19] Only the International Society of Geriatric Oncology guidelines contain specific recommendations for endocrine treatments following disease progression in elderly patients,[52] recommending tamoxifen after an AI and vice versa, or exemestane after anastrozole or letrozole and vice versa. For hormone-responsive disease in elderly patients, second-line endocrine treatment may be appropriate.

Emerging data may influence the disease management of patients with hormone-sensitive disease who progress during adjuvant AI therapy. Evidence suggests that interactions between the mammalian target of rapamycin (mTOR) and estrogen receptor pathways may exist,[63] and resistance to AI therapy may occur through the mTOR signaling pathway.[64,65] A recent study involved the addition of everolimus (mTOR inhibitor) to exemestane after disease progression during nonsteroidal AI monotherapy.[66] Although the patient population was not entirely elderly, the median age was 62 years and included patients up to 93 years of age ($N = 724$). Median progression-free survival was significantly increased in the combination treatment group compared with exemestane alone ($P < 0.001$). However, the clinical benefits need to be assessed versus the adverse event profile of everolimus (stomatitis, fatigue, asthenia, diarrhea, cough, pyrexia, and hyperglycemia). Treatment decisions must be driven by disease aggressiveness, metastasis sites, tumor biology, health, patient age, previous treatments, and expectations.

Clinical studies of aromatase inhibitors in elderly women with metastatic breast cancer

Although many studies have evaluated AIs in postmenopausal women with mBC, few have reported the number of elderly participants or enrolled a substantial number of elderly patients.

Anastrozole

In first-line mBC, 3 studies evaluated anastrozole versus tamoxifen in postmenopausal women but did not identify the proportion of elderly patients (Table 4).[67–70] However, mean or median age was ≥65 years and included patients ≤92 years. The TARGET (Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability) study showed equivalent objective response and time to progression (TTP) between anastrozole and tamoxifen,[67,68] while in North American and European studies, anastrozole had superior clinical benefit and TTP compared with tamoxifen.[69,70] In all 3 studies, both treatments were well tolerated, with decreased incidence of thromboembolism and vaginal bleeding during anastrozole treatment compared with tamoxifen treatment. Although in combined TARGET and North American results anastrozole was equal to tamoxifen in all measures of overall efficacy,[71–73] a subgroup analysis indicated that anastrozole was superior to tamoxifen for median TTP in patients who were estrogen and/or progesterone receptor-positive (11 vs 6 months, respectively; $P = 0.022$). Safety profiles did not change; however, anastrozole resulted in significantly fewer thromboembolisms compared with tamoxifen ($P = 0.043$). At median 44-month follow-up, overall survival remained similar.[73]

In the second-line mBC setting, 2 identical studies compared anastrozole with megestrol acetate in postmenopausal women who had progressed after tamoxifen[74] (Table 4).[75,76] Neither study had significantly different overall efficacy between treatments. However, weight gain and edema occurred more often with megestrol acetate treatment and gastrointestinal disturbance with anastrozole treatment. In combined analysis of the 2 studies, anastrozole (1 and 10 mg) demonstrated longer survival compared with megestrol acetate (HR = 0.78; $P < 0.025$, and HR = 0.83; $P = 0.09$, respectively).[74] There was no difference in 2-year survival estimates for patients with long-duration stable disease (85% and 86%, respectively).

Exemestane

First-line exemestane in postmenopausal women with recurrent or mBC was recently reviewed.[77] The European Organisation for Research and Treatment of Cancer—Breast Cancer Cooperative Group demonstrated that exemestane had an improved overall response rate compared with tamoxifen (Table 4).[78] Progression-free survival was similar between treatment groups at 46 months ($P = 0.121$); however, a Wilcoxon test indicated a significant difference among early events favoring exemestane ($P = 0.028$). An exploratory prognostic model showed that progression-free survival in women aged >65 years was significantly longer regardless of treatment ($P = 0.014$).[77,78] Both treatments were well tolerated, with a decreased incidence of hot flashes, edema, and vaginal discharge/bleeding during exemestane versus tamoxifen treatment, and increased incidence of arthralgia/myalgia, diarrhea, and cardiac dysrhythmia/dysfunction during exemestane versus tamoxifen treatment. In another study, objective response rate (ORR) was similar between exemestane and tamoxifen; however, duration of response and median TTP were longer with exemestane (Table 4).[79]

In the second- or third-line mBC setting, 2 studies compared exemestane with megestrol acetate or fulvestrant in postmenopausal women with advanced BC progressing after tamoxifen or another AI (Table 4).[80,81] In 1 study, ORR and clinical benefit rate were similar between exemestane and fulvestrant.[80] Both treatments were well tolerated, with decreased incidence of asthenia during exemestane versus fulvestrant treatment, and increased incidence of hot flashes, fatigue, arthralgia, and dyspepsia during exemestane versus fulvestrant treatment. In contrast, exemestane significantly improved ORR, duration of response, TTP, and time to treatment failure (TTF) ($P = 0.042$) versus megestrol acetate in the second study.[81] Additionally, median survival was significantly longer in the exemestane group versus the megestrol acetate group (not reached vs 123 weeks; $P = 0.039$). There was significantly less weight gain in the exemestane group versus megestrol acetate group ($P = 0.001$), lower incidence of dyspnea, and increased hot flashes, nausea, and vomiting in the exemestane group versus the

Table 4
Clinical studies evaluating Aromatase inhibitors in patients with metastatic breast cancer.

Study [follow-up]	Patients, *N* (median age, years)	Treatment	Clinical benefit, %			Median time to progression, months		
			Aromatase inhibitor	Competitor	*P*	Aromatase inhibitor	Competitor	*P*
First-line Treatment								
TARGET[67,68] [19 months]	668 (NR)	Anastrozole 1 mg/day Tamoxifen 20 mg/day	33[a]	33[a]	NS	8	8	NS
North American[69] [17.7 months]	353 (67)	Anastrozole 1 mg/day Tamoxifen 20 mg/day	59	46	0.0098	11	6	0.005
European[70] [13.3 months]	238 (NR)	Anastrozole 1 mg/day Tamoxifen 40 mg/day	83	56	< 0.001	18	7	<0.01[b]
EORTC-BCCG[78] [29 months]	371 (63)	Exemestane 25 mg/day Tamoxifen 20 mg/day	46[a]	31[a]	0.005	–	–	–
Chernozemsky et al.[79] [NR]	167 (NR)	Exemestane 25 mg/day Tamoxifen 20 mg/day	79	79	NS	~13[c]	~9[c]	NR
Mouridsen et al.[88,89] [32 months]	916 (65)	Letrozole 2.5 mg/day Tamoxifen 20 mg/day	50	38	0.0004	9	6	<0.0001
Second-line treatment								
Buzdar et al.[75] [6 months]	386 (NR)	Anastrozole 1 or 10 mg/day MA 160 mg/day	30[d]	36	NS	~5[c,d]	~5[c]	NR
Jonat et al.[76] [6.4 months[c]]	378 (NR)	Anastrozole 1 or 10 mg/day MA 160 mg/day	34[d]	33	NS	~5[c,d]	~4[c]	NS
EFECT[80] [13 months]	693 (63)	Exemestane 25 mg/day Fulvestrant IM 500 mg day 1, 250 mg days 14 & 28, 250 q28 days	32	32	0.853	4	4	0.6531
Kaufman et al.[81] [12.2 months[c]]	769 (65)	Exemestane 25 mg/day MA 160 mg/day	37	35	NS	~5[c]	~4[c]	0.037
Buzdar et al.[91] [NR]	602 (66)	Letrozole 0.5 or 2.5 mg/day MA 160 mg/day	16[a]	15[a]	NS	3[e]	3	NS
Dombernowsky et al.[92] [NR]	551 (NR)	Letrozole 0.5 or 2.5 mg/day MA 160 mg/day	35[e]	32	NS	6[e]	6	0.07
Gershanovich et al.[93] [20 months]	555 (65)	Letrozole 0.5 or 2.5 mg/day Aminoglutethimide 500 mg/day	20[a,e]	12	0.06	3[a,e]	3	0.008

Abbreviations: TARGET, Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability; NR, not reported; NS, not significant; MA, megestrol acetate; EORTC-BCCG, European Organization for Research and Treatment of Cancer-Breast Cancer Cooperative Group; EFECT, Evaluation of Faslodex versus Exemestane Clinical Trial; IM, intramuscularly.

[a] Objective response rate.
[b] In patients who achieved a clinical benefit.
[c] Calculated months from reported days (÷30) or weeks (÷4).
[d] Results for 10 mg dose.
[e] Results for 2.5 mg dose.

megestrol acetate group. Several studies evaluated exemestane as second- or third-line treatment after disease progression with a nonsteroidal AI or aminoglutethimide in postmenopausal patients with advanced or mBC.[82–87] Overall, exemestane demonstrated 24%–47% clinical benefit rate in these studies (*N* range, 30–241).

Letrozole

In first-line mBC, 1 study evaluated letrozole, wherein TTP, ORR, clinical benefit, and TTF were significantly improved compared with tamoxifen ($P \leq 0.0004$ each) (Table 4).[88,89] Both treatments were well tolerated, with increased incidence of hot flashes and bone fractures during letrozole versus tamoxifen treatment. This study also had a prospective subgroup analysis for TTP and ORR by age (<70 vs ≥70 years).[90] Among patients ≥70 years, TTP was 6 months longer in the letrozole group versus the tamoxifen group ($P = 0.0001$; Fig. 2).[90] Furthermore, overall response rate was >2-fold higher following letrozole compared with tamoxifen (38% vs 18%, respectively; $P = 0.0001$).

In second-line mBC, 3 studies evaluated letrozole versus megestrol acetate or aminoglutethimide (Table 4).[91–93] In 2 studies, patient age was reported in groups: 40% and ~30%, respectively, were ≥70 years.[91,92] In the first study, only letrozole 0.5 mg improved TTP and TTF versus megestrol acetate ($P = 0.044$ and $P = 0.018$, respectively), with a trend toward improved survival ($P = 0.053$); however, results were not stratified by age. Both treatments were well tolerated, with less weight gain, dyspnea, and vaginal bleeding during letrozole versus megestrol acetate

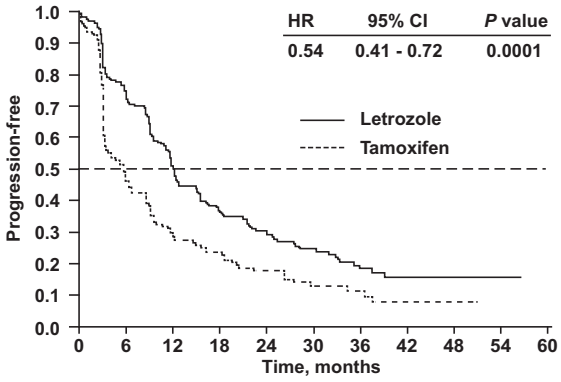

Fig. 2. Time to disease progression in elderly patients (≥70 years of age) with metastatic breast cancer during first-line treatment with letrozole or tamoxifen. HR, hazard ratio; CI, confidence interval. Adapted with permission from Mouridsen et al.[90]

treatment, and increased incidence of headache, diarrhea, and hair thinning during letrozole versus megestrol acetate treatment. In contrast, the second study demonstrated that letrozole 2.5 mg produced significantly improved ORR and TTF versus both letrozole 0.5 mg and megestrol acetate, including a survival benefit versus letrozole 0.5 mg ($P = 0.03$).[92] However, overall survival was similar between the letrozole 2.5 mg group and the megestrol acetate group ($P = 0.15$). The last study compared letrozole with aminoglutethimide, with similar primary results.[93] Additionally, letrozole 2.5 mg significantly improved TTF versus aminoglutethimide ($P = 0.003$). Both treatments were well tolerated, with decreased incidence of rash during letrozole versus megestrol acetate treatment, and increased incidence of nausea during letrozole versus megestrol acetate treatment.

Taken together, the evidence from anastrozole, letrozole, and exemestane studies tends toward a benefit over tamoxifen for first-line mBC. For second-line mBC, there was a survival benefit for anastrozole and exemestane versus megestrol acetate. Evidence in second line was also positive for letrozole; however, optimal dose seems uncertain. Although survival benefit is the best possible outcome, in elderly population subgroups, prolonged TTP may also provide a benefit. In addition, survival data can be confounded by subsequent therapies that may differ per arm. Moreover, adverse event manageability and/or tolerability (eg, edema versus gastrointestinal) influence the treatment of choice for an individual patient. Evidence from clinical trials suggests that elderly patients with mBC can be effectively treated with endocrine therapy, especially AIs.

Conclusions

Despite the fact that most women with mBC are aged ≥65 years, this population is underrepresented in clinical trials, and limited evidence exists to guide treatment decisions in elderly patients. Available clinical evidence suggests that elderly patients benefit from standard chemotherapy and/or hormonal treatment strategies, and that age alone should not limit treatment options offered. However, many factors, particularly comorbidities, must be considered when determining the best management strategy for the elderly patient. Quality of life and effects of treatment on comorbidities are important endpoints in this population and may guide treatment choice. Comparison of AIs with tamoxifen or progestins in first- and second-line mBC indicated AIs had equal efficacy but different safety profiles. Future clinical trials in mBC should include more elderly patients and stratify results based on age to establish effective treatment guidelines for this important patient population.

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