Treating Elderly Patients With Hormone Receptor–Positive Advanced Breast Cancer

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ABSTRACT: As the overall population ages, the proportion of elderly patients (aged ≥65 years) with breast cancer also increases. Studies have shown that elderly patients with hormone receptor–positive breast cancer can derive as much benefit from treatment as do younger patients, yet they remain underrepresented in clinical trials and are often undertreated in clinical practice. Treatment decisions for older patients should not be based solely on chronologic age; a patient’s physiologic functioning and comorbidities must also be taken into consideration. For recurrent or metastatic disease, systemic treatment with endocrine therapies or chemotherapy may prolong a patient’s life and alleviate troublesome symptoms. Resistance to therapy remains a problem in the advanced breast cancer setting, with most patients eventually becoming resistant to additional treatment. New combination regimens that target multiple pathways, such as everolimus plus exemestane, have shown efficacy in elderly patients previously resistant to endocrine therapies, and future research may need to focus on such combinations in order to improve outcomes in this patient group. A number of investigational agents are in clinical development, although few studies identify their effects in the elderly patient population. Optimizing effective yet tolerable therapeutic regimens for elderly patients could improve their outcomes while ensuring that the goals of improved survival and quality of life are considered.

KEYWORDS: hormone receptor positive, advanced breast cancer, targeted therapy

Introduction

The incidence of breast cancer increases with age, and as the overall mean population ages, the proportion of elderly (aged >65 years) breast cancer patients will increase. The median age for breast cancer diagnosis is 61 years (Surveillance, Epidemiology, and End Results [SEER] program data, 2007–2011)1,5; more than 40% of patients are aged at least 65 years at the time of diagnosis, and approximately 10% are older than 80 years. Breast cancer can be classified into the following subtypes based on receptor status and cellular proliferation (assessed by the proportion of cells staining for the nuclear antigen Ki67): luminal A–like: low Ki67 expression, estrogen receptor–positive (ER+), progesterone receptor–positive (PR+), and human epidermal growth factor receptor 2–negative (HER2–); luminal B–like: either high Ki67 expression or low/no expression of PR, ER+, and HER2– (HER2+ luminal B–like subtype consists of ER+, any Ki67 expression, and any PR expression); nonluminal: HER2+ and both ER– and PR–; ductal (triple negative): ER–, PR–, and HER2–. Compared with younger patients, a larger proportion of elderly breast cancer patients have hormone receptor–positive (HR+) disease, which is defined as being ER+, PR+, or both. Disease characteristics may vary based on patient age; with younger women typically having more aggressive tumors and older women more commonly having less aggressive disease, although the basis for this disparity remains unclear. However, despite improvements in overall survival (OS) rates over the past 20 years, disease-related deaths have not declined as much in elderly breast cancer patients compared with younger patients.

Elderly patients are generally underrepresented in many breast cancer trials compared with the general cancer population, and this may contribute to the relative lack of progress seen in reducing mortality in older breast cancer patients compared with younger patients. A post hoc analysis of older postmenopausal patients with HR+ breast cancer showed that older age was associated with higher disease-specific mortality, with undertreatment the most likely explanation. Such data emphasize the need for age–specific studies to be undertaken to improve outcomes for all ages and the necessity of ensuring that elderly women are offered participation in current clinical studies. The relatively low enrollment numbers of elderly women in breast cancer clinical trials may reflect toxicity issues (physician perceived or actual) and the impact of comorbidities on eligibility for entering trials, despite the fact that there is usually no cutoff age specified for clinical trials. Compared with younger patients, many older patients may opt for less aggressive treatment of their cancer. In addition, physicians may be less likely to encourage
elderly women to participate in clinical trials, compared with younger women. To improve the survival chances for older women, it is necessary to optimize their therapeutic regimens while accounting for their comorbid illnesses, functional status, social requirements, and life expectancy. Although many older cancer survivors can function well, they are more likely to be challenged by their comorbid illnesses, which can lead to decreased quality of life. It is especially important to include quality-of-life measures in studies of elderly patients with cancer. Targeted therapies may lead to an improved therapeutic ratio, if treatment-related toxicities are lower.

Additional Considerations for Treating Elderly Patients

Treating elderly patients requires consideration of a number of potentially confounding factors that may not be as relevant to treating younger cancer patients, such as poorer overall physiologic functioning and, in particular, the presence of comorbidities that can lead to potential adverse drug reactions. Increased age is associated with declining organ function, including heart, lungs, kidneys, bone marrow, and liver, which may result in decreased physiologic reserve in older patients. However, this needs to be assessed on a case-by-case basis because chronologic age does not always equate with physiologic age. Adequate assessment of physiologic functioning should be undertaken before deciding on an appropriate breast cancer treatment regimen, using a comprehensive geriatric assessment tool that assesses physical, psychological, and social aspects of function.

Comorbidities are generally more common in older patients and may adversely affect survival. When deciding how to treat elderly breast cancer patients, oncologists need to balance the risk posed by the cancer versus the risk from other major comorbidities, such as cardiovascular disease, that could be worsened by cancer therapy. The role of chemotherapy needs to be questioned if there are several significant comorbid conditions. In addition to the direct effects of the comorbidities on a patient’s ability to tolerate cancer-related therapy, the treatments associated with those comorbidities might potentially result in unintended drug–drug interactions. The number of drugs taken by a patient is an important predictor of risk for adverse events and treatment outcome because AEs may limit treatment duration and benefits. Evidence suggests, however, that severe treatment-related symptoms are actually less commonly reported by women aged ≥75 years. This implies that oncologists, nurses, and other medical professionals must be vigilant in asking about toxicities before treatment is continued.

Older patients may be at greater risk of not complying with their cancer therapy regimen due to increased prevalence of chronic illnesses and concomitant medications. In patients with HR+ breast cancer, the likelihood of discontinuing hormone therapy has been shown to increase with age in breast cancer trials, particularly in patients experiencing AEs from their medication. Good patient-centered care and advance warning of expected AEs can improve adherence.

Current Treatment Options for Advanced/ Metastatic Breast Cancer

Current treatment options for elderly patients with HR+ breast cancer are similar to those for younger patients. The International Society of Geriatric Oncology and the European Society of Breast Cancer Specialists have issued recommendations for the management of older individuals with breast cancer. These recommendations state that the management of elderly breast cancer patients should not be driven by chronologic age alone; instead, a multidisciplinary oncologic and geriatric approach should be used. Patients should be closely monitored for treatment response and AEs. There is evidence that elderly patients may be undertreated, and oncologists should keep this in mind when making treatment decisions. In the absence of empirical data from large, randomized, controlled trials about outcomes for elderly breast cancer patients, prospectively defined subgroup analyses and observational studies may provide an alternative source of data to guide management decisions. Table 1 summarizes the current recommendations for the use of individual pharmacologic breast cancer therapies in elderly patients.

First-line therapy. In contrast to early breast cancer, wherein the goal for treatment is cure, for patients with advanced or metastatic breast cancer, the emphasis of treatment is to palliate symptoms and extend life. Current first-line treatment for postmenopausal patients diagnosed with HR+ advanced breast cancer depends on previous treatment. For women who are naive to treatment, or who have been off treatment for at least 1 year, aromatase inhibitors (AIs) would be considered first-line therapy. The same treatment is recommended for elderly patients diagnosed with HR+ breast cancer, including those with diminished functional status. The AIs currently approved for use in advanced HR+ disease include anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin). There are no clear differences in efficacy among these three agents. As a treatment class, AIs have demonstrated improved outcomes relative to tamoxifen or other first-generation hormone agents.

For patients with both HR+ and HER2+ metastatic breast cancer, lapatinib (a dual HER2 and epidermal growth factor receptor inhibitor) is approved as a first-line treatment in combination with letrozole. A phase III trial of letrozole plus lapatinib versus letrozole alone as first-line therapy showed that the combination significantly improved the clinical benefit rate (CBR) and progression-free survival (PFS) in postmenopausal women with HR+/HER2+ metastatic breast cancer, but not in patients with HR+/human epidermal growth factor receptor 2–negative (HER2−) disease. Although the proportion of elderly patients included in the study was not reported, it was found that younger age was a significant stratification factor in the observed efficacy benefit.
in the HR+/HER2+ population.63 Several other combinations of a HER2 inhibitor plus an endocrine inhibitor are currently under investigation. Trastuzumab in combination with anastrozole was studied in a phase III trial in postmenopausal patients with HR+/HER2+ metastatic breast cancer, some of whom had previous exposure to endocrine therapy. Although anastrozole alone improved time to progression (TTP) by 2.4 months, the TTP for patients receiving the combination was significantly improved, at 4.8 months (P = 0.0007).64 A phase III trial comparing letrozole combined with trastuzumab to letrozole alone in patients with HR+/HER2+ metastatic breast cancer, in which approximately 40% of patients had received previous tamoxifen therapy, showed that the median TTP with combination therapy was 14.1 months compared with 3.3 months with letrozole alone.65 However, the therapeutic ratio for these combinations in elderly patients remains to be established.

Unfortunately, patients with advanced and metastatic HR+ disease will ultimately become refractory to endocrine treatment,66 and resistance is a major treatment problem because of the complex and intersecting growth factor signaling pathways present in breast tissue.67 For many women with HR+ advanced breast cancer, sequential use of endocrine therapies at each disease progression will provide continued benefit, and current guidelines state that women who respond to an endocrine treatment with tumor shrinkage or disease stabilization should receive additional endocrine therapy at disease progression.41

### Second and subsequent lines of therapy

Many patients have endocrine-resistant HR+ disease, so there is a significant unmet need for therapies to overcome resistance to endocrine therapy.53,68,69 Some patients are resistant to therapy at the initial exposure (ie, due to primary or innate resistance), whereas others who initially respond will subsequently have disease progression while on treatment (ie, acquired resistance).70,71 Most initial responders to endocrine therapy will eventually become resistant.54,72 Trying sequential endocrine therapies usually results in less benefit with each successive therapy, with shorter duration of response in those patients who do still respond.66,67

Second-line therapy options after progression on an AI include switching to another endocrine therapy (including fulvestrant), or everolimus plus exemestane (after anastrozole or letrozole only).44,58,73,74 Evidence from clinical trials indicates that following progression with a nonsteroidal AI (anastrozole or letrozole), it is possible to obtain clinical benefit with a steroidal AI (exemestane) and vice versa.75–77 Other endocrine options after progression on an AI include fulvestrant or tamoxifen.78

Fulvestrant is a 17β-estradiol analog that inhibits the ER with no agonist effect.47,79 Fulvestrant is currently approved for treating HR+ breast cancer in postmenopausal women only after progression;47 however, in the first-line setting, it has also demonstrated efficacy similar to that of tamoxifen and anastrozole.80,81 A combined analysis of two phase III trials82,83 in the second-line setting in postmenopausal women with locally advanced or metastatic breast cancer and disease progression during previous endocrine therapy found fulvestrant 250 mg to be noninferior to anastrozole.84 When tumor response was considered by age in these studies, objective responses to fulvestrant were seen in 22%–24% of patients aged <65 years and in 11%–16% of patients aged ≥65 years.85 Additionally, fulvestrant (45% of patients in the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) were aged ≥65 years) has shown comparable efficacy and tolerability versus exemestane in patients with advanced breast cancer after nonsteroidal AI failure.85 In a phase III study assessing fulvestrant 500 mg versus 250 mg in postmenopausal patients with advanced breast cancer who had disease recurrence on or after endocrine therapy or progression following endocrine therapy for advanced disease, a significant PFS benefit for fulvestrant 500 mg versus 250 mg was shown.86 Of note, the last endocrine therapy prior to fulvestrant was either an AI or anastrozole, and a subgroup analysis of the PFS benefit of fulvestrant 500 mg versus 250 mg based on this pretreatment covariate did not differ. At a final OS analysis of this study, fulvestrant 500 mg was associated with a 19% reduction in the risk of death compared to the 250 mg dose, corresponding to a 4.1-month difference in median OS between the two treatments.87 The US Food and Drug Administration (FDA) subsequently approved the high-dose fulvestrant schedule as second-line therapy for postmenopausal women with HR+ metastatic disease.87
It has been hypothesized that coadministration of fulvestrant with an AI may improve efficacy and delay the onset of resistance by simultaneously blocking both the aromatase enzyme and the ER. However, results from clinical trials have been mixed, with one study indicating that the combination of fulvestrant plus anastrozole was superior to anastrozole alone, while others reported no advantage with the combination versus either of the agents as monotherapy. Women with newly diagnosed stage 4 disease who have not had previous adjuvant endocrine therapy seem to derive the most benefit from this combination. However, more studies are needed to confirm the efficacy of this treatment approach.

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway has been shown to be another mechanism by which breast cancer cells bypass estrogen blockade, resulting in endocrine resistance, and many agents targeting this pathway are currently under clinical development (Fig. 1). For patients with advanced HR+ breast cancer who have progressed after treatment with endocrine therapy, one option is to combine an mTOR inhibitor with an endocrine therapy; this combination has demonstrated efficacy with reasonable tolerability. Recently, the mTOR inhibitor everolimus in combination with exemestane was approved for the treatment of postmenopausal women with advanced HR+/HER2– breast cancer after failure of anastrozole or letrozole therapy, based on the findings of clinically meaningful benefit in the pivotal phase III Breast cancer trials of OrAl EveROlimus-2 (BOLERO-2) trial. A post hoc analysis of the elderly patients in the BOLERO-2 trial (more than one-third of patients [275/724] were aged ≥65 years, and 164/724 were aged ≥70 years) showed that everolimus and exemestane significantly improved median PFS (primary end point of the study) versus exemestane alone in patients aged ≥70 years (median PFS: 6.77 versus 1.51 months; hazard ratio: 0.45; 95% confidence interval [CI]: 0.30–0.68); this was similar to the primary efficacy results for the overall population (median PFS at the final analysis: 7.8 versus 3.2 months; hazard ratio: 0.45; 95% CI: 0.38–0.54; P < 0.0001). Disease and pretreatment characteristics were generally comparable between patients aged ≥70 years and those aged <70 years in the post hoc analysis. Similarly, the CBR in patients aged ≥70 years in the everolimus plus exemestane group was greater compared with the exemestane-alone group (36% vs 23%). The safety profile of combination everolimus plus exemestane in patients aged ≥70 years was consistent with the known overall profiles of each agent. Similar to the results in the overall population in the BOLERO-2 study, the most common AEs were stomatitis (49%), fatigue (38%), decreased appetite (36%), and diarrhea (36%). The incidence of special-interest AEs was similar between patients aged ≥70 years and those aged <70 years, including pneumonitis (14% vs 17%, respectively).

Figure 1. Key targeted agents against breast cancer under clinical development. Adapted from: Munagala R et al. Promising molecular targeted therapies in breast cancer. Indian J Pharmacol. 2011;43(3):236–245. 

Abbreviations: EGFR, epidermal growth factor; EGFR, EGFR receptor; IGFR-1, insulin-like growth factor-I; IGFR-1R, IGFR-1 receptor; PI3K, phosphatidylinositol 3-kinase; Ras, rat sarcoma subfamily of genes; Akt, protein kinase B; PDK1, pyruvate dehydrogenase kinase isozyme 1; mTOR, mammalian target of rapamycin; MEK, mitogen-activated protein kinase kinase; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; BRAF, B-type RAF kinase; src, v-src (Rous sarcoma virus) tyrosine kinase; BCR-ABL, Philadelphia chromosome; JAK/STAT, Janus kinases/signal transducers and activators of transcription; PTEN, phosphatase and tensin homolog; HDAC, histone deacetylase.
hyperglycemia (12% vs 15%), and hypercholesterolemia (7% vs 11%).45 However, the incidence of grade 3/4 AEs was somewhat higher in patients aged ≥70 years than in those aged <70 years, and adverse reactions leading to treatment discontinuation occurred in more patients aged ≥70 years than in those aged <70 years.45,95 The results from this post hoc analysis of older patients showed that no dosage adjustment in initial dosing is required in older patients who have no other health concerns, although close monitoring is recommended. Dose should be adjusted as appropriate if AEs occur (per the prescribing information).45

**Recurrent Disease**

Once metastatic disease becomes insensitive to further endocrine therapies, cytotoxic chemotherapy becomes the next stage of treatment for many patients.46 For recurrent disease, sequential single-agent chemotherapy regimens are preferred, including taxanes (paclitaxel, docetaxel), anthracyclines (doxorubicin, pegylated liposomal doxorubicin [PLD]), capcitabine, gemcitabine, vinorelbine, or eribulin.41 In a study of taxanes administered to patients aged ≥70 years and/or frail patients with metastatic breast cancer, weekly dosing was shown to be well tolerated, retaining the same efficacy observed in nonfrail/nonelderly patient cohorts.97 Furthermore, weekly paclitaxel is as effective as the newer chemotherapeutic agents ixabepilone and nab-paclitaxel, while demonstrating less toxicity.98 PLD has been specifically assessed in patients aged ≥70 years with metastatic breast cancer at a dose of 40 mg/m² every 28 days, producing an overall response rate of 21% and a CBR of 84% with manageable hematologic toxicities, although only 48% of patients were able to complete six treatment cycles due to overall toxicity.99 A second trial of PLD (the Chemotherapy Adjuvant Study for Women at Advanced Age [CASA] trial), which included women aged ≥66 years with endocrine-nonresponsive tumors and who were not suitable for “standard chemotherapy regimens” because of comorbidities, age, or frailty, demonstrated that PLD may be a suitable treatment for such patients, with 81% of subjects free of disease after 42 months of follow-up.100 The efficacy and tolerability of other chemotherapeutic agents in an elderly population remain to be elucidated.16

**Investigational Strategies in the Setting of Endocrine Resistance**

Several strategies are being assessed for overcoming resistance to therapy in patients with HR+ breast cancer. On the basis of the success observed with the everolimus plus exemestane combination, the use of mTOR inhibitors in combination with other endocrine therapies to overcome endocrine resistance in advanced breast cancer continues to be explored in several ongoing phase II trials: everolimus in combination with letrozole (NCT01698918),101 with letrozole and lapatinib (NCT01499160),102 and with fulvestrant (NCT01797120103, NCT00570921104). Other mTOR combinations have also demonstrated some efficacy. In postmenopausal women with HR+ advanced breast cancer in whom previous tamoxifen and/or AI therapy was ineffective, sirolimus plus tamoxifen significantly improved TTP and response rates compared with tamoxifen alone in a phase II trial.105 On the other hand, no benefit was observed when temsirolimus was combined with letrozole versus letrozole alone in a phase III trial in postmenopausal women with AI-naïve locally advanced or metastatic breast cancer in the first-line setting.106 In this study, 41% of patients were aged >65 years, and an exploratory subset analysis showed an interaction between age and treatment outcome.106 Patients aged ≥65 years had longer PFS with letrozole plus temsirolimus than with letrozole alone (median PFS: 9.0 vs 5.6 months; hazard ratio: 0.75; 95% CI: 0.60–0.93; P = 0.009), whereas PFS was comparable for patients aged >65 years (median PFS: 8.5 vs 10.1 months; hazard ratio: 1.21; 95% CI: 0.92–1.59; P = 0.17).106

Additional strategies for targeting the PI3K pathway are also being investigated in ER+ relapsed breast cancer that is resistant to AIs.107 In early studies, PI3K inhibitors produced partial responses and disease stabilization108, BKM120, a pan-PI3K inhibitor, in combination with fulvestrant, is now undergoing two phase III trials, with several other PI3K inhibitors in earlier stages of development. The efficacy and safety of BKM120 are being studied in patients with HR+/HER2– mTOR inhibitor–naïve locally advanced or metastatic breast cancer refractory to AIs in the Buparlisib brEast cancer ClinicaL Evaluation-2 (BELLE-2) (NCT01610284) trial.109 The BELLE-3 trial (NCT01633060) is evaluating the efficacy of BKM120 with or without fulvestrant in postmenopausal women with HR+ HER2– locally advanced or metastatic breast cancer that were treated with an AI and are refractory to endocrine/mTOR inhibitor combination therapy.110 An early-stage clinical trial (phase Ib) is assessing BKM120 or BEZ235 (a novel pan-PI3K/mTOR inhibitor) in combination with letrozole in HR+ metastatic breast cancer (NCT01248494).111

Also in development for HR+ breast cancer are agents targeting histone deacetylase (HDAC) and cyclin-dependent kinase (CDK) 4/6 inhibitors (Fig. 1),92,112,113 although few trials specifically evaluate the investigational agents in elderly patients. One that did include a relatively high proportion of elderly patients is a phase II trial [ENtino Stat Combinations Overcoming REsistance (ENCORE) 301] of entinostat (an HDAC inhibitor) in combination with exemestane in patients with HR metastatic breast cancer in the first-line setting.114 In this trial, 42% of the patients were aged ≥65 years, and the results suggested a trend for prolonged PFS in the combination arm compared with exemestane alone.114

Palbociclib (PD-0332991) is an orally bioavailable CDK inhibitor that blocks progression of the cell cycle and has shown good efficacy in early studies in women with HR+ endocrine-refractory breast cancer.115 In the PALBociclib: Ongoing trials in the Management of breast cancer (PALOMA-1)
randomized phase II study, PFS improved from 10 to 20 months in women receiving letrozole plus palbociclib versus letrozole alone for first-line metastatic disease. The confirmatory larger phase III PALOMA-3 trial has not been reported. Based on the data from the phase II study, palbociclib was recently approved by the FDA for first-line use in combination with letrozole in women with postmenopausal HR+ breast cancer who have metastatic disease. Several other studies with palbociclib are ongoing, including those that evaluate its use as monotherapy in women who experienced progression on first- or second-line endocrine therapy, a phase II study in combination with anastrozole (NCT01723774), a phase III study in combination with exemestane (NCT02028507), and three studies as first-line treatment in combination with letrozole for HR+ advanced breast cancer (phases I/II, NCT00721409; phase II, NCT01709370; phase III, NCT01740427). A second CDK4/6 inhibitor, LEE011, is also in development for the treatment of HER2-advanced breast cancer, in combination with letrozole (phases I/II, NCT01872260; phase III, NCT01958021) or added to everolimus plus exemestane (phases I/II; NCT01857193).

Initial accelerated approval for the antiangiogenic anti-body bevacizumab, in combination with paclitaxel, in metastatic breast cancer was revoked by the FDA because of additional clinical trial results that failed to demonstrate a significant improvement in OS or a clinically relevant therapeutic benefit. Overall, however, analysis of bevacizumab in elderly patients included in clinical trials indicates that PFS benefits are comparable in older and younger patients.

In the recently reported Avastin THErapy for advaNced breAst cancer (ATHENA) trial, bevacizumab plus chemotherapy for first-line clinical use produced a median TTP of 10.4 months in a subanalysis of patients aged ≥70 years, thus mirroring the overall results of the ATHENA study.

Conclusions
Elderly women are an increasingly large proportion of the HR+ breast cancer population, yet they are often underrepresented in clinical trials. Current treatment options for older patients are similar to those for younger patients, although consideration needs to be given to the higher number of comorbidities that may be present in this population. These comorbidities may hinder older patients’ use of more aggressive therapies and limit their involvement in clinical trials. Therefore, a patient’s biological rather than chronological age must be considered because of the heterogeneity of characteristics present in older patients. This variability may significantly affect treatment choices and patient outcomes and thus represents a limitation in clinical trials in which patient populations are defined by chronological age. The potential for resistance to endocrine treatment and chemotherapy is the same for older patients. Although elderly patients may be less able to tolerate some of the more toxic combination regimens, a few novel combination therapies entering the treatment market, such as everolimus plus exemestane, have shown good tolerability in elderly patients. It is important that elderly patients receive optimized therapeutic regimens that will improve their PFS, while also taking into account the challenges induced by their comorbid illnesses and functional status.

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