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REVIEW

Aromatase inhibitor strategies in metastatic breast cancer

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Abstract: Despite ongoing therapeutic innovations, metastatic breast cancer (MBC) remains a treatable but incurable disease. In the developed world, a diagnosis of MBC without a preceding diagnosis of early stage disease is a rare event. However, approximately one-third of women with early stage breast cancer ultimately experience a distant recurrence. Because the majority of breast cancers express estrogen and/or progesterone receptors and are accordingly considered hormone-sensitive, therapeutic strategies that interfere with hormone-mediated tumorigenesis have been a cornerstone of the breast cancer management paradigm for decades. Historically, the selective estrogen receptor modulator tamoxifen has been the most extensively studied and widely used hormone maneuver in breast cancer. However, a recent therapeutic innovation, namely the successful development of third-generation aromatase inhibitors (AIs), has had a dramatic impact on the treatment paradigm for women with hormone-sensitive MBC. Because of the demonstrated efficacy in postmenopausal breast cancer patients, the generally favorable side-effect profile, and the convenience of oral administration, AIs are now in widespread clinical use. Currently, there are three clinically available third-generation AIs: two reversible, nonsteroidal AIs, letrozole and anastrozole; and one irreversible, steroidal AI, exemestane. All three agents are at least as efficacious as tamoxifen as monotherapy for postmenopausal women with hormone-sensitive MBC. Current clinical research aims to improve upon existing strategies by evaluating AIs in combination with systemic chemotherapy regimens and/or novel targeted agents. It is hoped that these therapeutic innovations will lead to ongoing improvements in quality of life parameters and ideally survival for women with hormone-sensitive MBC.

Keywords: metastatic, breast cancer, aromatase inhibitors

Introduction

Breast cancer is a global public health burden with more than one million new cases diagnosed annually.[1] Worldwide, the distribution of early versus advanced cases varies widely. In the developed world, for example, a diagnosis of metastatic breast cancer (MBC) without a preceding diagnosis of early stage disease is a rare event.[1,2] However, despite ongoing therapeutic innovations, approximately one-third of women with an early stage diagnosis ultimately develop metastatic disease. Once distant metastases occur, breast cancer is treatable but no longer curable and is associated with a median survival of only two to three years.[2] Consequently, investigators strive, through therapeutic innovation, to improve quality-of-life outcomes by preventing or relieving cancer-related symptoms and, ideally, to optimize disease-specific outcomes including disease free and overall survival. Typically, MBC management strategies are devised after considering a number of patient and tumor characteristics including the

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disease-free interval, the prior adjuvant therapy prescription, the number of metastatic sites, the potential for visceral crisis, patient age, patient preference, co-morbid conditions, performance status, and tumor biomarkers including human epidermal growth factor receptor 2 (HER2) status and hormone receptor status. Treatment strategies are increasingly tailored to the biology of an individual's tumor and information about hormone receptor status, one of the earliest known breast cancer biomarkers, remains critical.

The majority of breast cancers in the developed world are considered "hormone-sensitive." Although significant controversy persists regarding the optimal definition of "hormone-sensitive," hormone receptor status is typically defined by immunohistochemistry (IHC) determined estrogen receptor (ER) and/or progesterone receptor (PR) expression and reported as a percentage of cells staining positive or as the intensity of staining.[3] Although no consensus exists regarding a specific cut-off to define hormone sensitivity, hormone therapies are typically preferred over systemic chemotherapy strategies in the initial treatment of most women with hormone-sensitive MBC who are not at risk for visceral crisis. The typical advantages of hormone-targeted strategies include the demonstrated efficacy, the generally favorable side-effect profile, and the general ease of administration. Additional features of potentially appropriate candidates for endocrine therapy include a long disease-free interval between primary breast cancer diagnosis and the development of metastases, minimal MBC-related symptoms, and modest disease burden.

For decades, the hormone treatment strategy was largely dominated by the selective estrogen receptor modulator, tamoxifen. Tamoxifen is a complicated and incompletely understood drug with beneficial anti-estrogen effects in breast tissue and deleterious pro-estrogen effects elsewhere, ultimately accounting for the small but significantly increased risk of venous thromboembolic events and uterine cancers observed with its administration.[4] However, the tamoxifen-based treatment strategies were ultimately revised with the development of a novel class of hormone-targeting agents (AIs). The first generation of AIs demonstrated promising activity in the early clinical studies but had the significant disadvantage of requiring parenteral administration to optimize activity.[5–7] Numerous refinements to the chemical structure ensued, and the currently available, orally-administered, third-generation AIs are highly active and generally well tolerated. The most commonly cited AI-mediated side-effects include myalgias and arthralgias that typically affect the small joints of the hands, and menopausal-like symptoms including hot flashes.[8] Although AI administration is also associated with a significant rate of bone mineral density declines in the adjuvant setting,[8] this potential side-effect is of lesser relevance in the metastatic setting given that hormone-sensitive MBC frequently involves bone and the majority of these patients are treated with bisphosphonates.

Menopausal status is a critical determinant of patient selection for AI therapy. In premenopausal women the primary source of estrogen is the ovaries, while in postmenopausal women estrogen is produced mainly from androgen precursors in adipose tissue. A critical step in the peripheral conversion of androgen precursors to estrogen is catalyzed by aromatase, an enzyme that is reversibly inhibited by the nonsteroidal AIs, letrozole (Femara®; Novartis, Basel, Switzerland) and anastrozole (Arimidex®; AstraZeneca, Wilmington, DE, USA), and irreversibly by the steroidal AI exemestane (Aromasin®; Pfizer, New York, NY, USA). Because peripheral inhibition of aromatase cannot overcome ovary-derived estrogen production, AI monotherapy is not appropriate for premenopausal women with MBC.[9,10] Furthermore, because of the potential for increased gonadotropin secretion and thus, ovarian follicular stimulation, it may even be deleterious in this setting. Some clinicians have adopted a practice of rendering premenopausal patients medically or surgically postmenopausal (with GnRH agonists or bilateral salpingo-oophorectomy) and then introducing AI therapy. However, it is important to note that this approach is an extrapolation of the data from the postmenopausal setting and has not yet been validated in an adequately powered randomized study. Thus, the following discussion is limited to the evidence for AI strategies in postmenopausal women with hormone-sensitive MBC only.

Strategies for postmenopausal women with hormone-sensitive MBC

The three third-generation AIs (letrozole, anastrozole, and exemestane) are at least as efficacious as tamoxifen for the first-line treatment of postmenopausal women with hormone-responsive MBC (Table 1).[11–17] For example, a combined analysis of 1,021 women with advanced breast cancers that were either ER-positive, PR-positive or of unknown receptor status, participating in two large randomized studies of first-line anastrozole versus tamoxifen, was recently reported.[12,17] In this analysis, at a median follow-up of 18.2 months, there was no significant difference in objective response rate (ORR) between the study arms (27.1% for tamoxifen versus 29.0% for anastrozole, $p = 0.1129$) and only a trend in favor of anastrozole for progression-free

Table 1 Selected studies of first-line tamoxifen versus an aromatase inhibitor in metastatic breast cancer

	Tamoxifen versus Anastrozole[12,17,39]	Tamoxifen versus Letrozole[14]	Tamoxifen versus Exemestane[16]
Patients	1021 ER+, PR+ or HR-unknown	916 HR+/unknown	371 HR+/unknown
Median follow-up (months)	43.7	32	29
ORR (%)	27 vs 29 (P = 0.1129)	21 vs 32 (P = 0.0002)	31 vs 46 (P = 0.005)
TTP/PFS (months)	TTP 7.0 vs 8.5 (P = 0.103)	TTP 6.0 vs 9.4 (P < 0.0001)	PFS 5.8 vs 9.9 (P = 0.121)
MS (months)	40.1 vs 39.2 (HR = 0.97, lower 95% CL = 0.84)	30 vs 34 (P = 0.53)	37.2 vs 43.3 (P = 0.821)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; ORR, objective response rate; TTP, time to progression; PFS, progression free survival; MS, median survival; CL, Confidence Limit.

survival (PFS; 7.0 versus 8.5 months, p = 0.103). However, in a retrospective subgroup analysis of the 60% of trial participants with ER-positive and/or PR-positive tumors, anastrozole proved superior to tamoxifen for time to progression (TTP) (median values of 10.7 months for anastrozole and 6.4 months for tamoxifen, p = 0.022). Notably, because of the low event rate at the time of the data cut-off, survival analyses were not initially performed. However, in an updated analysis at a median follow-up of 43.7 months, no significant difference in survival was observed (median time to death: 40.8 and 41.3 months for anastrozole versus tamoxifen, respectively; hazard ratio [HR] 0.97, lower 95% confidence limit 0.84). Similar results have been observed in first-line MBC studies of letrozole or exemestane versus tamoxifen. In a multicenter study of 916 patients with hormone receptor-positive or unknown advanced breast cancer randomized to letrozole or tamoxifen, with optional cross-over permitted and 32 months of follow-up, letrozole proved superior to tamoxifen for TTP (9.4 versus 6.0 months, respectively; p < 0.0001) and ORR (32% versus 21%, p = 0.0002).[14] A nonsignificant trend toward a survival benefit was observed in favor of letrozole (34 versus 30 months, p = 0.53), however, the absence of a clear survival benefit may reflect the approximately 50% cross-over rate. A comparable study of 371 women with hormone receptor-positive or hormone receptor-unknown advanced breast cancer randomized to first-line exemestane or tamoxifen was recently updated.[16] After a median follow-up period of 29 months, the ORR proved superior for exemestane compared with tamoxifen (46% versus 31%, respectively; p = 0.005). In addition a trend toward a PFS benefit in favor of exemestane was observed (9.9 versus 5.8 months; p = 0.121). However, no survival benefits were observed in favor of either strategy (37.2 versus 43.3 months; p = 0.821). Although no statistically significant survival benefits have been observed in individual studies of AIs versus tamoxifen, a recent meta-analysis demonstrated a significant survival advantage with 3rd generation AIs compared with tamoxifen or progestin therapy.[18] Thus, overall, the AIs appeared to be at least as efficacious as tamoxifen in the first-line MBC setting, although ultimately, no definitive survival advantage has been demonstrated with this approach. AIs are commonly favored over tamoxifen in the first-line setting for postmenopausal women who are AI-naïve or who have relapsed more than one year after adjuvant AI administration because of the lower incidence of thromboembolic events and incident uterine cancers. To date, there has been no large, head-to-head comparison of all three currently available AIs in this setting, and cross-trial comparisons should be discouraged. Thus, there is no compelling evidence to date indicating superiority of one AI over another. Furthermore, it is anticipated that the first-line AI MBC strategy will become less relevant as more women receive immediate or delayed AIs in the adjuvant setting, and thus, might no longer be candidates for upfront AI therapy.

AIs as second-line therapy for the treatment of hormone-sensitive MBC

Although there is currently no evidence to suggest superiority of one AI over another in the first-line MBC setting, clinical strategies have recently been shaped by the reporting of a large study evaluating second-line hormone strategies in this setting. In the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) study, 693 postmenopausal women with hormone receptor-positive advanced breast cancer with disease progression or recurrence on a nonsteroidal AI were randomly assigned to receive either intramuscular fulvestrant, a pure antiestrogen, or oral exemestane.[19] The study was both double-blinded and placebo controlled. In the analysis, no significant difference was observed between the two study arms for the primary endpoint of TTP (3.7 months in each

arm; p = 0.6531). Furthermore, no significant difference was observed between the study arms for ORR (7.4% versus 6.7% for fulvestrant versus exemestane, respectively; p = 0.736). Although the reported ORR was modest, it should be noted that a significant group of patients had stable disease such that the clinical benefit rate (CBR, the combined rate of objective responses and stable disease) was 32.2% and 31.5% in the fulvestrant and exemestane groups, respectively. Thus, CBR may be a more relevant end-point than TTP for patients with hormone-sensitive MBC, given that many have bone-dominant disease which can be difficult to measure by standard response evaluation criteria. In summary, the EFECT study not only confirmed that a subset of patients with hormone-sensitive MBC can derive durable benefits from serial endocrine manipulation but also indicated that some patients with tumor progression on a nonsteroidal AI can derive benefit from a switch to a steroidal AI and that the benefits are equivalent to those observed with a different class of intramuscularly-administered hormone therapies. As a result, the arsenal of orally available, active agents with favorable toxicity profiles was broadened for women with hormone-sensitive MBC.

Other studies of AIs for the treatment of hormone-sensitive MBC

AIs have been evaluated against other conventional hormone maneuvers for postmenopausal women with hormone-sensitive MBC. For example, equivalent efficacy was demonstrated in two phase III trials of anastrozole versus fulvestrant in women with primarily tamoxifen-resistant MBC.[20,21] Furthermore, all three AIs have been evaluated against megestrol acetate (Megace) in women with tamoxifen-resistant MBC with consistent survival benefits in favor of the AI.[22–24] Given the number of efficacious hormone maneuvers for hormone-sensitive MBC, no single treatment paradigm exists. However for appropriately selected postmenopausal women, many clinicians now opt for a nonsteroidal AI in the first-line MBC setting followed by a steroidal AI with disease progression as per the EFECT study design. Depending on a number of patient and tumor characteristics including the pace of an individual's disease and the prior therapy history, other hormone maneuvers including tamoxifen, fulvestrant, or megestrol acetate may subsequently be considered and cytotoxic therapy delayed if possible.

AI-based combination strategies

Given the efficacy demonstrated with AI monotherapy in MBC, clinical investigators have endeavored to derive further improvements by combining AIs with various conventional chemotherapy and novel targeted strategies. In a retrospective systematic review of various chemotherapy, hormone therapy and combination strategies among 31,510 patients with MBC participating in 189 clinical trials, no survival benefit was observed with chemotherapy combined with hormone therapy versus chemotherapy alone in the relevant subset of 3,606 patients.[25] Consequently, combination chemotherapy-AI strategies are not typically recommended in clinical practice off-study. However, combination strategies with other targeted agents, including HER2-directed and antiangiogenesis molecules are ongoing.

In both the adjuvant and metastatic setting, significant benefits have been observed with HER2-targeted therapies among the 20%–30% of patients with HER2-"positive" breast cancer, where HER2 status is determined by assessment of gene amplification and/or protein overexpression.[26–30] Approximately 50% of HER2-positive breast cancers are hormone-sensitive and preclinical models implicate cross-talk between ER and HER2 as a putative mechanism of endocrine-resistance.[31] Consequently, there has been considerable interest in studies evaluating hormone- and HER2-targeted combination therapies. In a phase II study of first or second-line letrozole in combination with a HER2-directed humanized monoclonal antibody, trastuzumab (Herceptin®; Genentech, San Francisco, CA, USA), in 33 women with hormone-sensitive, HER2-positive advanced breast cancer, an ORR of 26% and a CBR of 52% were observed.[32] In the phase III TAnDEM study, 207 patients with hormone-sensitive, HER2-positive MBC were randomized to first-line anastrozole alone or in combination with trastuzumab.[33] The combination was associated with a significant improvement in PFS (4.8 versus 2.4 months; p = 0.0016) and a trend toward an overall survival benefit that was not statistically significant (28.5 versus 23.9 months; p = 0.325). Preliminary results from another phase III study of combination endocrine- and HER2-targeted therapy were also recently reported. In EGF30008, 1286 postmenopausal women with hormone receptor-positive MBC were randomized to letrozole with or without lapatinib, an oral tyrosine kinase inhibitor of both HER1 and HER2.[34] Notably, only 219 (17%) of enrolled patients had HER2-positive breast cancer. Among the patients with HER2-positive MBC, combination therapy was associated with significant improvements in PFS (3.0 versus 8.2 months; p = 0.019) and ORR (15% versus 28%; p = 0021) but no significant survival benefit (32.3 versus 33.3 months for letrozole alone or the combination, respectively; p = 0.113). Not surprisingly, there were no PFS (13.4 versus 13.7 months; p = 0.188) or ORR (32 versus 33%; p = 0.726) benefits observed

with the addition of lapatinib in the HER2-normal population. However, overall, the addition of lapatinib to letrozole was associated with an increased incidence of clinically relevant adverse events, including a 10% increase in the rate of grade 3/4 diarrhea. Therefore, both studies demonstrated improved outcomes with combined AI and HER2-targeted strategies in appropriately selected populations. However, because neither study design included an anti-HER2 monotherapy arm, it is unknown whether a combined approach is superior to HER2-targeted therapy alone. Thus, because first-line AI monotherapy has the convenience of oral administration and a generally well tolerated side-effect profile, clinicians frequently delay introducing HER2-targeted strategies until hormone strategies have been exhausted or are no longer appropriate.

Angiogenesis plays a critical role in physiologic growth as well as tumor growth and metastasis. Bevacizumab is a humanized monoclonal antibody against an angiogenic factor, vascular endothelial growth factor (VEGF), and has been shown to improve PFS when combined with taxane-containing regimens in MBC.[35] Because estrogen modulates VEGF-induced angiogenesis in hormone-sensitive MBC, AI and bevacizumab combination strategies are being investigated. For example, in a phase II study of letrozole with bevacizumab, the combination was well-tolerated with preliminary evidence of activity.[36] Phase III studies examining this approach are ongoing.

Another putative mechanism of endocrine-resistance in MBC is increased expression of the epidermal growth factor receptor (EGFR). Preclinical models indicated that endocrine resistance could be overcome with EGFR targeted agents such as gefitinib, an oral tyrosine kinase inhibitor of EGFR. However, in clinical breast cancer models, gefitinib in combination with endocrine therapy has demonstrated variable activity. For example, in a recently reported randomized phase II study, the addition of gefitinib to anastrozole was associated with marked improvements in PFS (8.2 versus 14.5 months; HR 0.55, 95% confidence interval [CI]: 0.32–0.94) in women with hormone-sensitive MBC.[37] However, in a randomized, phase II study of 216 postmenopausal women, the addition of neoadjuvant gefitinib to anastrozole failed to improve response rate or to decrease cell proliferation index.[38] Further studies are needed to determine whether this is indeed a valid approach.

Conclusion

Hormone therapies remain a therapeutic cornerstone for patients with hormone receptor-positive MBC, modest disease burden and low risk of visceral crisis. Aromatase inhibitors represent an important therapeutic innovation in the management of hormone receptor-positive MBC, demonstrating superior benefits compared with conventional hormone maneuvers such as megestrol acetate and efficacy profiles at least equivalent and potentially superior to tamoxifen in the first-line MBC setting. The oral route of administration and generally tolerable side-effect profile add to their clinical appeal. It is anticipated, however, that as more women receive an adjuvant AI prescription, that the MBC treatment algorithm will need to be revised accordingly. It is also hoped that novel strategies whereby AIs are administered in combination with other treatments including novel cytotoxics and biologic agents, will confer additional survival benefits in this population.

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