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REVIEW

Anastrozole Versus Exemestane in Patients with Postmenopausal Breast Cancer and Visceral Metastases

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Abstract

Background: For patients with hormone receptor positive metastatic breast cancer (MBC), both steroidal and non-steroidal aromatase inhibitors (AIs) have demonstrated efficacy as initial and subsequent lines of treatment in trials comparing them with other hormonal agents like tamoxifen and megestrol acetate. Patients with MBC and predominant visceral involvement have a shortened survival compared to those with non-visceral disease. These patients are usually treated with chemotherapy, with under-utilization of endocrine strategies due to fear of rapid progression. In this review, we present the available data for both classes of AIs in patients with visceral predominant MBC and examine efficacy and safety differences between them.

Methods: An exhaustive Medline search to retrieve published articles based on pre-defined inclusion criteria was conducted. Data from 13 published studies of randomized comparisons of the two classes of AIs with other hormonal therapies or each other form the basis of the efficacy analyses in this report.

Conclusion: Based on our review of the available data, we argue that their manageable toxicity profile with demonstrable clinical benefit supports the use of both classes of AIs, with no significant efficacy differences between the agents, in appropriately selected patients with visceral predominant MBC. Due to the lack of randomized trial data comparing the two classes of AIs in this setting with the exception of one study, the comparisons in this review are mostly indirect and need confirmation in future prospective trials. This is likely to come from comparative trials in the adjuvant setting like the FACE and the MA-27 trials.

Keywords: metastatic breast cancer, hormone positive, visceral disease, aromatase inhibitors, clinical benefit, Type I and II

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Introduction

Manipulation of the hormonal milieu via medical or surgical means is an integral part of the treatment of hormone receptor positive (HR+) breast cancer. Notably, the regression of inoperable breast cancer by means of oophorectomy was demonstrated over a century ago by Sir George Beatson in 1896. Estrogen blockade via pharmacologic means subsequently evolved as an effective treatment strategy for HR+ metastatic breast cancer (MBC) in both premenopausal and postmenopausal patients, with the development of the selective estrogen modulator tamoxifen.[1,2] Other classes of drugs such as the progestins and aromatase inhibitors (AIs) were later introduced to the clinic. The success of these drugs in advanced disease prompted the conduct of large adjuvant trials, the results of which have significantly contributed to reducing mortality for women with HR+ breast cancer.[3,4]

Despite the advances made in treatment, metastatic breast cancer remains incurable and interventions for patients with metastatic disease are palliative in intent. Even when a complete remission is obtained with chemotherapy, only a small proportion of patients remain free from progression for an extended period of time.[5] The goal of treatment in the majority of patients is palliating symptoms, delaying tumor progression, and prolonging survival while maintaining a reasonable quality of life for as long as possible. Thus, hormonal therapies like aromatase inhibitors with their favorable toxicity profile and demonstrable efficacy in this setting are an attractive alternative to chemotherapy for suitable patients.

In clinical practice, several factors help determine suitable therapy in the first-line and subsequent settings for a patient with metastatic disease. Patients' age, tumor burden, pace of progression, disease free interval from the completion of adjuvant therapy, sites of disease, presence of tumor related symptoms, and residual toxicities from prior therapies all factor into decision making. In contrast to patients with non-visceral metastases, visceral metastases often predict a grave prognosis.[6] Visceral metastases, hormone receptor negative status, and a disease free interval of less than 24 months have been shown to be predictors of a shorter survival time post-relapse.[7] Patients with symptomatic visceral disease are usually treated with chemotherapy as initial treatment due to the desired urgency of response. In contrast, patients with HR+ disease, with a limited tumor burden, non-visceral disease and a slowly progressive course are often treated with sequential lines of hormonal manipulation.

While chemotherapy is the default intervention in the setting of visceral metastases, hormonal therapy for selected patients with visceral disease may still be an appropriate first line therapy. There is a need to identify this subset of visceral disease patients for whom chemotherapy can be delayed or avoided without compromising efficacy.

In this review, we critically examine the efficacy data for AIs in the treatment of HR+ MBC, particularly in the setting of visceral disease. We also evaluate efficacy differences, if any, between the two classes of AIs (described in a subsequent section) with exemestane as the prototype for class I and anastrozole for class II respectively.

Methods

We performed a Medline search for all English language articles published between 1970–2009 with the terms "breast neoplasms", "metastasis", "aromatase inhibitors", "anastrozole", "exemestane" and "visceral metastasis". Only final peer reviewed publications of randomized controlled trials of the two classes of AIs represented by exemestane and anastrozole in first and subsequent lines of therapy for metastatic breast cancer were included in the main outcome of efficacy comparisons. We excluded case reports, review articles, and re-publications of the same study except when efficacy data for patient subsets were reported in a subsequent publication. Of the 90 publications retrieved, 13 publications met our inclusion criteria and are included in this review for the main outcome. Two reviewers assessed the study data, quality and applicability to allow unbiased abstraction.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

In the late 1970's, after a discovery that aminoglutethimide, an anticonvulsant, leads to adrenal insufficiency and suppresses estrogen synthesis via aromatase inhibition,[8] it was developed for the treatment of metastatic breast cancer.[9] Aromatase inhibitors suppress

plasma estradiol levels in post menopausal women by inhibiting the enzyme aromatase responsible for the conversion of androstenedione to estrone and testosterone to estradiol (Fig. 1). Efforts to improve the efficacy and therapeutic index of this class of drugs led to the development of the current significantly more specific third generation aromatase inhibitors: anastrozole, letrozole, and exemestane. The third generation aromatase inhibitors are divided into two major types, namely type I and type II inhibitors. The type I inhibitors e.g. exemestane, are steroidal analogues of androstenedione and bind irreversibly to the same site on the aromatase molecule resulting in enzyme inactivation. Conversely, the type II inhibitors e.g. anastrozole and letrozole are nonsteroidal in nature and bind reversibly to the heme group of the enzyme.[10]

Anastrozole and letrozole have a half-life (t½) of nearly 48 hours.[11,12] Exemestane, in contrast, has a t½ of approximately 27 hours.[13] Regardless of these differences, the long half-lives of all the third generation aromatase inhibitors permit a once-daily oral dosing schedule. The time to obtain maximal estradiol (E2) suppression is 2–4 days for anastrozole and 7 days for exemestane,[14,15] but both anastrozole and exemestane achieve a steady state drug level by day seven.[16] A comparable inhibition in excess of 90%, of in vivo aromatase activity has been observed with both classes of aromatase inhibitors.[17,18]

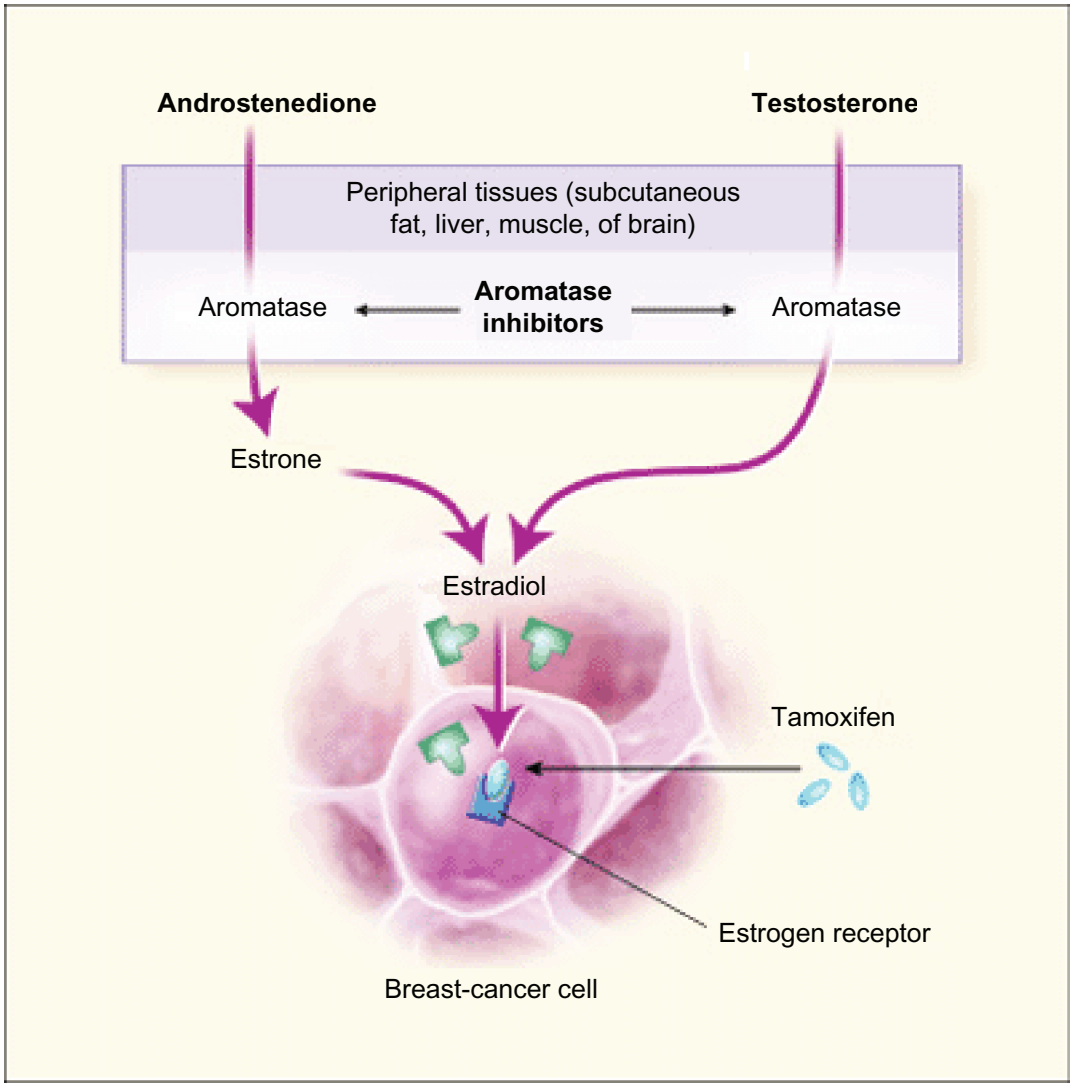

Figure 1. Mechanism of action of Aromatase Inhibitors. Reprinted by permission from Smith IE, Dowsett M. *Aromatase inhibitors in breast cancer. N Engl J Med*. 2003;348(24):2431–42. Copyright © *[2003] Massachusetts Medical Society. All rights reserved.*

While both anastrozole and exemestane are hepatically metabolized unlike anastrozole, exemestane is a major substrate of the CYP3A4 enzyme system in the liver. Pharmacokinetic inhibition of the cytochrome P450 system has been noted with both anastrozole and exemestane at concentrations of ≤500 μm in human and rat microsomal preparations,[19] but no formal drug-drug interactions with other substrates have been reported for either class of aromatase inhibitors.

Clinical Studies

Both anastrozole and exemestane have been well studied in patients with metastatic breast cancer, and have demonstrated the ability to achieve objective responses and tumor stabilization in both pretreated patients as well as those with no prior hormonal therapy for metastatic disease. Table 1 summarizes the efficacy data from select trials comparing anastrozole and exemestane to tamoxifen in patients with no prior hormonal treatment for metastatic disease and to megestrol acetate or fulvestrant in patients who progressed after treatment with tamoxifen for metastatic disease.

Jonat et al compared two doses of anastrozole (1 mg and 10 mg) with megestrol acetate in 378 postmenopausal women with breast cancer who had received prior tamoxifen treatment and demonstrated measurable objective responses that ranged from 7%–13% with both doses of anastrozole in the subset of patients who had visceral only or mixed sites of disease including visceral.[20] These were comparable to the overall rate of complete and partial responses with either dose of anastrozole. Approximately 20% of the overall anastrozole treated population attained stable disease lasting longer than 6 months, but the rate of stable disease at visceral sites was not reported separately. A combined analysis of this trial and a trial by Buzdar et al[21] with an identical design and 40% of the combined population having visceral involvement, demonstrated objective responses at all sites of disease. The overall response rate and clinical benefit rate (CBR: CR+ PR+ SD ≥ 6 months) on both the anastrozole arms was approximately 10% and 30% respectively with the best responses seen in patients with soft tissue disease only.[22] Patients with any visceral involvement had a CBR of about 30% compared to 50% in patients without visceral involvement.[23]

Table 1. Efficacy data in subsets of MBC patients with visceral disease from select trials of Anastrozole and Exemestane.

Study regimen	Setting	Number with any visceral Involvement	RR in patients with any visceral Involvement	CBR in patients with any visceral Involvement
Anastrozole vs. Megestrol acetate[22]	Progressive disease on tamoxifen	124 vs. 113	7% vs. 8%	31% vs. 31%
Anastrozole vs. Fulvestrant[24]	Progressive disease on tamoxifen	190 vs. 191	13% vs. 15%	37% vs. 38%
Anastrazole vs. Tamoxifen[23]	No prior therapy for MBC	186 vs. 211	NR	49% vs. 46%
Exemestane vs. Megestrol acetate[25]	Progressive or relapsed disease on tamoxifen	207 vs. 239	13.5% vs.10.5%	NR
Exemestane[26]	Progressive or relapsed disease on tamoxifen	63	25%	41%
Exemestane vs. Tamoxifen[27]	No prior hormonal therapy for MBC	87 vs. 88	44% vs. 31%	NR
Exemestane vs. anastrozole[31*]	Progressive or relapsed disease on anti-estrogen therapy. Measurable visceral metastases	64 vs. 64	15% vs. 15%	38% vs. 32%
Exemestane vs. fulvestrant[43]	Progressive or relapsed disease on non-steroidal AIs	198 vs. 197	NR	27% vs. 29%

*Only randomized head to head comparison of exemestane and anastrozole in this setting. The data reported is based on the intention to treat analysis.
Abbreviations: RR, response rate; CBR, clinical benefit rate; MBC, metastatic breast cancer; NR, not reported.

Two randomized phase III trials have compared fulvestrant to anastrozole in the second line setting in postmenopausal women with advanced breast cancer. A combined analysis of these two trials demonstrated a CBR of 38% and 44% respectively with anastrozole treatment in the HR+ subset of patients with mixed sites of involvement including visceral and those with visceral involvement only. Median duration of clinical benefit was 8.6 months for both subsets.[23] An objective response rate of 19% in patients without visceral metastases and 13%–14% in patients with any or only visceral metastasis was reported.[24]

Similar data exist for exemestane in patients with visceral metastases. Objective response rates ranging from 13.5% to 25% in pretreated patients with visceral disease have been reported, with an additional 20%–25% of the overall population achieving stable disease for a CBR of about 40%–45%.[25,26]

While the above mentioned studies involve primarily pretreated patients, both exemestane and anastrozole have been evaluated in the first line setting as well. Paridaens et al compared exemestane to tamoxifen in the metastatic setting as first line hormonal therapy, with nearly half of the patients (47%) on study having visceral metastases. In this subset of patients, 44% obtained an objective response with exemestane compared to 31% with tamoxifen.[27] Anastrozole has also been compared to tamoxifen in the first line setting. Two individual randomized trials have demonstrated equal or better time to progression (TTP)[28,29] with anastrozole versus tamoxifen. A combined analysis of these two trials showed equivalence of anastrozole and tamoxifen for the protocol defined end point of TTP with an overall CBR with anastrozole of 57%. Objective response rates were not reported separately for the subset of patients with visceral disease. However, a higher likelihood of response was noted in patients with only soft tissue and/or lung metastases.[30] In a separate analysis evaluating the CBR in subsets of patients with or without visceral disease among the combined population, rates of 49% and 62% respectively with anastrozole were reported.[23]

So far, the data reviewed represent subgroup analyses from individual trials which differed in their design, methodology and proportion of patients with confirmed HR+ tumors. None of these trials were prospectively designed to evaluate the efficacy of aromatase inhibitors in patients with visceral disease, though a substantial proportion of patients in the individual studies had visceral involvement. The magnitude of benefit for these patients, though less than in patients with non-visceral disease, is consistently present with demonstrated objective responses and prolonged stabilization of disease.

For the reasons mentioned above, it is difficult to conclude efficacy differences between the type I and II aromatase inhibitors directly in this setting, though there might be a hint of somewhat greater activity of exemestane. This provided the rationale for evaluating the type I and type II aromatase inhibitors in a randomized head to head comparison trial in postmenopausal metastatic breast cancer patients with visceral metastases. Campos et al recently reported the results of this trial, which to our knowledge is the only direct comparison of exemestane to anastrozole in this setting.[31] The inclusion criteria for this study required post-menopausal women with at least one site of measurable visceral metastases, no prior hormonal therapies except antiestrogens in the adjuvant or metastatic setting, ≤1 line(s) of chemotherapy for metastatic disease, and confirmed HR+ tumors. The definition of visceral disease was amended from inclusion of liver, lung/pleura, and "deep nodes" to only liver and/or lung involvement. Patients were randomly assigned to receive standard dosing of exemestane 25 mg/day (Arm A) or anastrozole 1 mg/day (Arm B). The study was closed prematurely due to slow accrual with 130 of the planned 200 patients accrued. Of these, only 107 were deemed evaluable. Due to limited power, a formal statistical comparison for the primary end point of response rate at visceral sites was not performed. Efficacy measures were, however, reported for the individual treatment arms.

Overall, a response rate at visceral sites of 16% in the evaluable population and 15% in the intention to treat (ITT) population was reported in both arms. The authors also noted a similar CBR (CR+ PR+ SD > 180 days) in the visceral site(s) for Arm A (38%) and B (32%). Prolonged responses were observed with a median duration of response of 109 and 85 weeks respectively in the two arms. Though unable to establish efficacy differences between the two types of aromatase inhibitors, the study confirmed the activity and benefit of these therapies in patients with predominant visceral involvement with an observed median survival of 30–33 months in both study arms.

Safety

The safety and tolerability of aromatase inhibitors as a class has been evaluated in several trials of adjuvant and metastatic disease. Their side effect profile differs from that of tamoxifen which has an increased risk of thromboembolic phenomena, endometrial hyperplasia and cancer, vaginal bleeding, uterine polyps and vasomotor symptoms. When compared directly to tamoxifen in the adjuvant trials like ATAC and the Intergroup Exemestane Study (IES), both the AIs were noted to have a higher incidence of musculoskeletal symptoms including arthralgias and myalgias, bone loss including fractures at vertebral and non vertebral sites, and vaginal dryness, but a significantly lower incidence of venous thromboembolic events, uterine abnormalities and vasomotor symptoms.[32–34] We've taken the liberty of indirectly comparing the side effect profile of the type I and type II aromatase inhibitors because of the lack of large amount of safety data from direct comparisons. Table 2 summarizes the reported frequencies of the common adverse events (AEs) for exemestane and anastrozole from the IES and ATAC trials, the two largest published adjuvant therapy trials with comprehensive side effect reporting of these agents versus tamoxifen. There seem to be no significant differences between the two classes in the frequency of any AEs and serious adverse events (SAEs). The NCIC CTG MA-27 trial is a randomized trial directly comparing the efficacy and safety of exemestane and anastrozole in the adjuvant treatment of post menopausal breast cancer patients and will provide more safety data for these two drugs.

A small study evaluating markers of bone turn over in 162 post menopausal patients randomized to treatment with letrozole, anastrozole or exemestane in the adjuvant setting has been reported only in abstract form (Unpublished data McCaig FM et al. Abstract # 1145, SABCS 2008). There were no significant differences noted in any of the markers of bone resorption or formation between the steroidal and non steroidal aromatase inhibitors in this study.

In the randomized trial of metastatic disease by Campos et al,[31] the proportion of patients who experienced any adverse event on the two arms of the study was similar. The rate of SAEs was numerically higher in the anastrozole arm (17%) vs. the exemestane arm (9%), though only 1 SAE was considered to be related to anastrozole treatment. The most common treatment related AEs on both treatment arms were hot flushes and fatigue. The number of patients who discontinued treatment due to AE was not different between the two study arms.

In contrast to hormonal therapy, chemotherapy is commonly associated with one or more of the acute side effects of alopecia, nausea and vomiting, fatigue, anorexia, and myelosuppression. This is also often coupled with the requirement of an indwelling vascular access device for administration of chemotherapy, and the time and cost of infusional therapy. When these factors are considered in decision making for a patient with incurable disease, there are obvious advantages

Table 2. Reported percentage frequencies of AI related AEs for anastrozole and exemestane from the ATAC and IES trials.

Adverse events (AEs)	Anastrozole*	Exemestane*
Hot flushes^	35	41
Venous thromboembolic events^	2.8	1.2
Vaginal bleeding^	5.4	4.6
Uterine abnormalities^μ	3	1.5
Ischemic cardiovascular disease**	4.1	8
Fatigue**	19	22
Fractures¶	11	4.3
Osteopenia/osteoporosis¶	11	7
Arthralgias¶	36	19
Carpal Tunnel Syndrome¶	3	2.8

*Reported frequencies are in comparison to tamoxifen.
^AEs occurring with significantly lower frequency compared to tamoxifen.
**AEs with no difference in frequency compared to tamoxifen.
¶AEs occurring with significantly higher frequency compared to tamoxifen.
μUterine abnormalities include endometrial hyperplasia/neoplasms, and uterine polyps/fibroids.
Abbreviations: AEs, Adverse Events; ATAC, Arimidex, Tamoxifen Alone or in Combination; IES, Intergroup Exemestane Study.

to orally administered therapy that patients can take at home if the efficacy of treatment is not compromised.

Efficacy Differences among Aromatase Inhibitors

All third generation AIs are potent inhibitors of aromatase enzyme as demonstrated by measures of whole body aromatization.[17,18] The average inhibition with the third generation inhibitors is greater than 97 percent as opposed to 90 percent with aminoglutethimide. A dose dependant inhibition of aromatase activity in cultured fibroblasts from mammary adipose tissue has been observed with significantly lower IC50 for the third generation inhibitors compared to aminoglutethimide (10 µm for aminogluthemide vs. 15 nm for anastrozole vs. 5 nm for exemestane).[35] The differences among the third generation drugs are more subtle. Between the non-steroidal inhibitors letrozole and anastrozole, letrozole appears to be a more potent suppressor of breast cancer tissue and plasma estrogen levels compared with anastrozole[36]. This greater peripheral and intratumoral inhibition of estrogen and aromatase activity may translate to differences in clinical efficacy, but remains to be confirmed in head to head trials of these drugs such as the recently completed adjuvant Femara Anastrozole Clinical Evaluation (FACE) trial and the ongoing randomized comparison of anastrozole and exemestane in the NCIC CTG MA. 27 trial. Another comparative head-to-head trial in the metastatic setting is unlikely to be conducted and any efficacy differences in advanced disease will have to be extrapolated from results of the adjuvant trials or from indirect comparisons between trials of AIs versus other hormonal therapies as attempted in this review.

Patient Preference and Compliance

Compliance and adherence to oral therapy with tamoxifen and AIs is of major importance, especially in the adjuvant setting, given the reduction in mortality with these drugs for HR+ breast cancer. Studies looking at adherence over the entire adjuvant treatment period have shown varying rates of adherence. Partridge et al noted that between 19% and 28% of the women with early stage breast cancer on anastrozole had less than 80% adherence during the first year of therapy, and the adherence rate declined per year over a 36 month observation period.[37] Musculoskeletal symptoms resulting from, or worsening as a result of AI use are reported by patients as the most common reason for non-adherence and switching from one aromatase inhibitor to another.[38,39] Though reliable predictors for AI related arthralgias are lacking, studies have suggested that overweight but not obese patients[40] and ethnic minorities may be less prone to developing these symptoms.[41]

For patients with metastatic disease, these barriers for long term adherence to therapy may be less important. However, the influence on quality of life resulting from musculoskeletal and vasomotor symptoms remains relevant. As discussed previously, the generally manageable side effect profile of these drugs compared to the more significant chemotherapy related side effects make these agents a valuable tool in the treatment armamentarium for metastatic disease.

Place in Therapy

As noted throughout, third generation aromatase inhibitors have been evaluated in patients with HR+ MBC, including those with visceral metastases and they appear to be effective in inducing clinical benefit in a significant proportion of such patients. In patients with rapidly progressive disease, and those in a visceral crisis, where an expedited response is needed, aromatase inhibitors regardless of the type are not the ideal treatment. However, after a maximum response with chemotherapy has been obtained, endocrine therapy can help provide patients a chemotherapy free interval. In patients with isolated visceral metastases, slowly progressive disease, and/or those who are deemed unfit for chemotherapy, endocrine therapy can be a reasonable first line treatment. For patients who relapse on or within 1 year of adjuvant tamoxifen therapy, the NCCN guidelines recommend AIs as the initial endocrine therapy for relapsed disease. All three third generation AIs are endorsed as being equal in efficacy and safety in the current NCCN guidelines with no one drug being the preferred agent.[42]

There is evidence to show that patients who progress on non steroidal AIs can still derive benefit from the steroidal AI exemestane. Data from the randomized EFECT (The Evaluation of Exemestane versus Faslodex Clinical Trial) trial in patients with or without visceral metastases have recently been published.[43] The trial enrolled post menopausal patients with advanced breast cancer progressing on or recurring

after prior non steroidal AI therapy. Over half of the patients (57%) had visceral involvement. In this subset of patients, exemestane produced a CBR of 27%, similar to 29% with fulvestrant. The median duration of clinical benefit was 8 months and 10 months respectively for the two treatment arms. These data provide assurance that sequential hormonal therapy can help delay the use of chemotherapy in selected patients with visceral metastases with meaningful gains in quality of life.

Conclusions and Future Directions

The available evidence supports the role of type I and II AIs in the treatment of post menopausal patients with HR+ MBC, including those with visceral disease. Given the paucity of data from randomized head to head comparisons of these agents, we've presented an indirect comparison from trials evaluating them against other hormonal therapies in first and second line settings. Based on these comparisons and the only randomized data from Campos et al, there do not seem to be significant efficacy differences in patients with visceral metastases with either class of AIs. Importantly, though the likelihood of objective responses are lower in patients with visceral disease, the clinical benefit rates range from 40%–50% in the first line setting, and 30%–35% in the second line. In keeping with the goals of treatment in the metastatic setting with an emphasis on palliation of disease and maintaining a good quality of life, these drugs offer a less toxic alternative to chemotherapy. However, they remain underutilized in patients with visceral involvement due to fear of disease progression and the presumed higher efficacy of chemotherapy in such patients.

Regardless of the timing of use, resistance to endocrine therapies both in the adjuvant and metastatic setting is an increasingly recognized problem. Several mechanisms including up-regulation and cross talk with signaling pathways like the EGFR/HER2, Insulin like growth factor, PI3K-mTOR, VEGF etc. contribute to resistance to endocrine therapies. Novel strategies of combining endocrine treatments with other targeted therapies will further expand their role and prolong the treatment benefit afforded by them by circumventing or delaying resistance to these drugs. The results of two such trials of the combination of an AI with HER2 blockade in ER+, HER2+ MBC patients have been reported.

The TanDem trial evaluated a combination of anastrozole with trastuzumab versus anastrozole alone,[44] and the EGF30008 trial evaluated letrozole in combination with the dual EGFR/HER2 blocker lapatinib versus letrozole alone.[45] Both studies showed a longer TTP for the combination versus the AI alone. Other strategies being explored include combinations with anti VEGF agents, mTOR inhibitors, and HDAC inhibitors among others. The results of these trials and the head to head comparison studies in the adjuvant setting, including the biomarker sub-studies are eagerly awaited to further define their role in the treatment of HR+ breast cancer.

Disclosures

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References

1. Muss HB, et al. Megestrol acetate v tamoxifen in advanced breast cancer: a phase III trial of the Piedmont Oncology Association (POA). *Semin Oncol*. 1985;12(1 Suppl 1):55–61.
2. Pritchard KI, et al. Tamoxifen therapy in premenopausal patients with metastatic breast cancer. *Cancer Treat Rep*. 1980;64(6–7):787–96.
3. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687–717.
4. Dowsett M, et al. Meta-Analysis of Breast Cancer Outcomes in Adjuvant Trials of Aromatase Inhibitors versus tamoxifen. *J Clin Oncol*. 28(3): 509–18.
5. Greenberg PA, et al. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol*. 1996;14(8):2197–205.
6. Solomayer EF, et al. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Breast Cancer Res Treat*. 2000;59(3):271–8.
7. Vogel CL, et al. Survival after first recurrence of breast cancer. The Miami experience. *Cancer*. 1992;70(1):129–35.
8. Santen RJ, et al. Aminoglutethimide inhibits extraglandular estrogen production in postmenopausal women with breast carcinoma. *J Clin Endocrinol Metab*. 1978;47(6):1257–65.
9. Smith IE, et al. Aminoglutethimide in treatment of metastatic breast carcinoma. *Lancet*. 1978;2(8091):646–9.
10. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med*. 2003;348(24):2431–42.
11. Lamb HM, Adkins JC. Letrozole. A review of its use in postmenopausal women with advanced breast cancer. *Drugs*. 1998;56(6):1125–40.
12. Wiseman LR, Adkins JC. Anastrozole. A review of its use in the management of postmenopausal women with advanced breast cancer. *Drugs Aging*. 1998;13(4):321–32.
13. Lonning PE. Pharmacological profiles of exemestane and formestane, steroidal aromatase inhibitors used for treatment of postmenopausal breast cancer. *Breast Cancer Res Treat*. 1998;49 Suppl 1:S45–52; discussion S73–7.

14. Plourde PV, et al. ARIMIDEX: a new oral, once-a-day aromatase inhibitor. *J Steroid Biochem Mol Biol*. 1995;53(1–6):175–9.
15. Demers LM, et al. The efficacy of CGS 20267 in suppressing estrogen biosynthesis in patients with advanced stage breast cancer. *J Steroid Biochem Mol Biol*. 1993;44(4–6):687–91.
16. Zilembo N, et al. Endocrinological and clinical evaluation of exemestane, a new steroidal aromatase inhibitor. *Br J Cancer*. 1995;72(4):1007–12.
17. Geisler J, et al. Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. *J Clin Oncol*. 2002;20(3):751–7.
18. Geisler J, et al. In vivo inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients. *Clin Cancer Res*. 1998;4(9):2089–93.
19. Grimm SW, Dyroff MC. Inhibition of human drug metabolizing cytochromes P450 by anastrozole, a potent and selective inhibitor of aromatase. *Drug Metab Dispos*. 1997;25(5):598–602.
20. Jonat W, et al. A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. *Eur J Cancer*. 1996;32A(3):404–12.
21. Buzdar AU, et al. A phase III trial comparing anastrozole (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrol acetate in postmenopausal women with advanced breast carcinoma. Arimidex Study Group. *Cancer*. 1997;79(4):730–9.
22. Buzdar A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. *J Clin Oncol*. 1996;14(7):2000–11.
23. Howell A, Robertson JF, Vergote I. A review of the efficacy of anastrozole in postmenopausal women with advanced breast cancer with visceral metastases. *Breast Cancer Res Treat*. 2003;82(3):215–22.
24. Mauriac L, et al. Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials. *Eur J Cancer*. 2003;39(9):1228–33.
25. Kaufmann M, et al. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. The Exemestane Study Group. *J Clin Oncol*. 2000;18(7):1399–411.
26. Kvinnsland S, et al. High activity and tolerability demonstrated for exemestane in postmenopausal women with metastatic breast cancer who had previously failed on tamoxifen treatment. *Eur J Cancer*. 2000;36(8):976–82.
27. Paridaens RJ, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol*. 2008;26(30):4883–90.
28. Bonneterre J, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol*. 2000;18(22):3748–57.
29. Nabholtz JM, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol*. 2000;18(22):3758–67.
30. Bonneterre J, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer*. 2001;92(9):2247–58.
31. Campos SM, et al. A comparative study of exemestane versus anastrozole in patients with postmenopausal breast cancer with visceral metastases. *Clin Breast Cancer*. 2009;9(1):39–44.
32. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *The Lancet Oncology*. 2006;7(8):633–43.
33. Coombes RC, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet*. 2007;369(9561):559–70.
34. Howell A, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*. 2005;365(9453):60–2.
35. Miller WR. Biology of aromatase inhibitors: pharmacology/endocrinology within the breast. *Endocr Relat Cancer*. 1999;6(2):187–95.
36. Geisler J, et al. Letrozole is superior to anastrozole in suppressing breast cancer tissue and plasma estrogen levels. *Clin Cancer Res*. 2008;14(19): p. 6330–5.
37. Partridge AH, et al. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *J Clin Oncol*. 2008;26(4):556–62.
38. Schwartzberg LS, et al. Initial treatment and changes in adjuvant endocrine therapy for early stage breast cancer. *Breast*. 2009;18(2):78–83.
39. Hershman DL. Getting a grip on aromatase inhibitor-associated arthralgias. *J Clin Oncol*. 2008;26(19):3120–1.
40. Crew KD, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. *J Clin Oncol*. 2007;25(25):3877–83.
41. Moy B, et al. Clinical outcomes of ethnic minority women in MA.17: a trial of letrozole after 5 years of tamoxifen in postmenopausal women with early stage breast cancer. *Ann Oncol*. 2006;17(11):1637–43.
42. Carlson RW, et al. Breast cancer. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2009;7(2):122–92.
43. Chia S, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol*. 2008;26(10):1664–70.
44. Kaufman B, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol*. 2009;27(33):5529–37.
45. Johnston S, et al. Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor-Positive Metastatic Breast Cancer. *J Clin Oncol*. 2009;27(33):5538–46.